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CONTENTS

ABSTRACTS

Presidential Lecture

PL

Advancements and a Perspective of Surgical Treatments for Rheumatic Diseases

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Conflict of interest: None

Synovectomy used to be performed as a treatment of rheumatoid arthritis (RA) during the period of time when no effective medication was available. Although synovectomy achieved certain short-term effects, its long-term results were unsatisfactory due to a recurrence of symptoms or complications. Arthroscopy, which came into clinical use in 1959, eventually spread as an essential tool for diagnosis and treatment of joint diseases. Arthroscopic synovectomy has been widely used as a local treatment in cases in which disease activity is controlled by medication. For functional disorder due to joint destruction, arthroplasty, which flattens broken bone stumps, creates new articular facets, and rebuilds joints, has been performed. However, since RA is a progressive disease, the indication of this procedure has been limited. Nonetheless, since the progression of articular destruction can be suppressed by medication today, a satisfactory, long-term effect can still be expected when this procedures performed. Total hip arthroplasty has been spread widely around the world due to its satisfactory and long-term effects, after Charnley published in Lancet in 1961. Specifically, the combined use of a metal and ultra-high molecular weight polyethylene as a joint surface and the use of a bone cement as a fixing material has become the golden standard of artificial joints. This practice has also achieved satisfactory results on other joints. Although artificial joints started to accomplish stable, satisfactory, long-term results, how to prevent loosenings and handle infections and bone defects remain problems to be solved in the future. While arthrodesis has been performed for joints where stability has been considered more essential than mobility, cervical vertebra fixation has experienced problems, such as implant failure and nonunion. Magerl's method for atlantoaxial subluxation and pedicle screw or lateral mass screw fixations for subaxial subluxation have been used in recent years and have been achieving satisfactory results. Various osteotomies of the pelvis, femur and tibia have been performed for hip/knee osteoarthritis and aseptic necrosis of the femoral head among the younger population and have accomplished certain positive results. How to inherit this technique remains a big challenge for the future.

Representative Session

RS

Molecular Medicine of Mono-genic and Multi-genic Diseases: From Cytokine to Genomic & Cellular Medicine

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Conflict of interest: None

Biological drugs brought remarkable changes in treating Rheumatoid arthritis and other autoimmune diseases. Cytokines are biological protein drugs available only in minute quantity and their chemical and biological properties are clarified by recombinant DNA technology enabling the application of cytokines to medicine. In Part 1, I will talk about 1st stage biotech-revolution in 1970s triggered by Stanford University and bioventures in Silicon Valley, cytokine network elucidated by application of recombinant DNA technology to immunology, Immune regulation via cellular interaction of T, B and dendritic cells. I will also talk about translational research, the roles of bioventures and pharmaceutical industry in bringing novel discovery into frontier medicine. In the 2nd biotech-revolution from 1990s, genomic & system medicine approach become possible allowing us to characterize whole genome not limited to single gene at DNA, RNA, protein and metabolite levels. Also, the development of diagnosis and treatment of multi-gene diseases such as common diseases and cancer become an important agenda. Now, due to the availability of novel therapy and new drugs, patients suffering from common and/or serious chronic diseases can live much longer. Narrowing the gap between average life span and healthy life span by extending healthy life span become an important goal. This will help to reduce health care cost and medical expenses for aged people. To deal with multi-gene diseases, novel platform for drug development is necessary to confirm the efficacy and the safety of the combination therapy employing multiple drugs with different mechanism of action. In Part 2, I will talk about the technology revolution in IoT & AI areas and the paradigm shift of health and medicine. Part 1 Biotechnology and Cytokine Network 1. Ist Biotech-Revolution 2. From IFNs to Cytokine Network 3. Multi-potential Hematopoietic Stem Cell: Constitutive vs Inducible Hematopoiesis 4. Th1/Th2 Paradigm: Plasticity of T cells and Epigenomic Regulation 5. Cytokine Receptor & Signal Network 6. mDC & pDC: Two Types of Dendritic Cells and Immune Regulation 7. Drug Development for Advanced Medicine and Translational Research Part 2 Paradigm Shift of Health & Disease and Future Medicine 8. 2nd Biotech-Revolution 9. Mono- vs Multi-genic Diseases: Environmental & Epigenomic Regulation 10. Evolutionary Medicine and Agenda in Genomic Medicine 11. Average vs Healthy Life Span 12. Chronic Inflammation and Multi-genic Diseases: Tissue Repair Medicine & Cancer Immunotherapy 13. Management of Health and Medicine

Symposium

S1-1

Adaptation and positioning of the steroid therapy in RA latest treatments

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Conflict of interest: None

Based on the progress of therapeutic drugs such as biologics and the treatment concept of T2T (treat to target), the prognosis of rheumatoid arthritis (RA) has been improved by early diagnosis and treatment for clinical remission treatment target. On the other hand, the treatment choice of each rheumatologist is different because of various drugs, and the background or complication of patients. At the present, unsolved problems still exist in the medical treatment before and after the remission. One of them is the use of the steroid. The steroid is effective and a cheap medication for RA, so it is used for daily clinical practice. But the use is still a subject of debate among experts. There is a little difference in its use in European and American recommendation, and Japanese guidelines. The steroid is placed as a supporting drug of the RA treatment with a non-steroidal anti-inflammatory drug (NSAID). We cannot improve the arthritis of RA only with these drugs. However, we must often apply it appropriately for reducing arthralgia and protecting ADL in the daily life. Because the steroid has strong anti-arthritic and immunosuppressive effect, it can expect the improvement of a symptom and bone destruction temporarily. In addtion, there are a lot of adverse effects such as osteoporosis, infectious diseases, and GI tract disturbance by the combination of NSAID use even in small quantities. In addition, it is difficult to stop it when we use it once, and the long-term effect is not clarified. "When and how should we start and reduce the steroid?" The evidence is poor. But, in this symposium, I will discuss the risk and benefit of steroid therapy including the difference of its use in EULAR, ACR and JCR.

S1-2

Role of methotrexate as an anchor drug for the treatment of rheumatoid arthritis in the new biotherapeutic era

Yasuo Suzuki
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Conflict of interest: Yes

A recent paradigm shift of the treatment of RA is to aim for remission by the T2T strategy, using csDMARD as early as possible in the disease process. Methotrexate (MTX) has been recognized as the anchor drug at the end of the 1990s because of its long-term effectiveness, safety profile and widespread use in clinical practice. More than 10 years passed after the introduction of new drugs targeted to key molecules and cells involved in RA pathogenesis, role of MTX might be modified. In Japan, an increase in MTX dose up to 16mg/week was approved in 2011, and 7 biologics and a JAK inhibitor are now available. On the other hand, infection and LPD have been increasing probably due to long-term immunosuppression. Although it remained unclear what is the best dosing strategy for MTX, the suggestive evidences have been accumulated recently. The results of PMS showed that remission rate increased approximately 3 times by increasing MTX from 8mg to more than 10mg/week. In the C-OPERA study, a DB-RCT comparing MTX vs MTX plus certorizmab pegol for early RA, MTX was increased up to 16mg/week with a rapid dose escalation, and average MTX dose throughout the study period was 11.6mg/week in both groups. These evidences suggest that the therapeutic effect of MTX could be nearly maximum by increasing up to 12mg/week without safety concern. The recent systematic reviews showed combination of MTX and biologics for all classes was more efficacious than bio-monotherapy. In patients responding insufficiently to combination of MTX and biologics, the addition of the 3rd csDMARD such as igratimod could be a therpeutic option to not only achieve remission but also to reduce or discontinue biologics. In this symposium, I discussed the role of MTX in the new biotherapeutic era.

S1-3

Usefulness and limitations of the current biologic therapy

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Conflict of interest: Yes

Six biological agents targeting TNF and each one biological agent against IL-6 receptor and T cell co-stimulatory molecules are available for the treatment of RA in Japan. All agents accept the effectiveness in more than the half of patients with RA, and biological agents targeting TNF show the increased effectiveness by concomitant use of methotrexate. At the same time, any biological agents in any RA population never showed the remission rate exceeding 50%. This fact can be attributable to the restriction in the approved dosing regimen and the existence of patient population indeed requiring agents against novel molecular targets, both leading to insufficient coverage on variety of the RA patients. The limitation in the range of approved dosage may be due to the budget restriction in the drug development, which is insufficient for thorough examination of dose-response. Thus, rheumatologists have been doing a hard work for the adjustment of dosages or dosing intervals for each patient in the postmarketing phase. In addition, the difference in the expression amount of the target molecule and the subsequent difference in the agent dose for sufficient neutralization of the targeted molecule might be more important than the difference in the species of molecule to be targeted, because the expectation to the effectiveness of the remaining agents decreases for patients having repeatedly failed in prior biological agents. However, the increase in quantity of a biological agent by more than several times will not be acceptable if it is proportionally reflected to the treatment costs. In this respect, a prominent effectiveness of glucocorticoids in autoimmune diseases can be attributable to the fact that it is inexpensive even after the dose escalation by 100 times according to the diseases. In this talk, I am going to discuss the above-mentioned points with selected evidences in order to bridge over the following 2 lectures focusing on the agents under development.

S1-4

Perspective of RA treatment by new biological agents in clinical development

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Conflict of interest: Yes

Biological agents are positioned as an indispensable drug in rheumatoid arthritis (RA) treatment algorithm. The unique characteristics of the agents are made of proteins produced by the living and the targets by the agents are theoretically very clear, not acting on off-targets. At present, seven bio-original DMARDs in addition to one bio-similar products are commercialized in Japan, in which mechanism of action of those targets are inhibitions of TNF, IL-6 receptor, and T cell activation. I would like to introduce biological agents on new targets for RA patients, which are now going to late clinical development. Those include IL-6, GM-CSF/GM-CSF receptor, and RANKL. Biological agents targeting on IL-6 such as clazakizumab, olokizuma, and sirkumab may be reviewed by summarizing the publications. In particular, sirkumab, which may go into phase III clinical trials is highlighted and overviewed. Similarities and dis-similarities between IL-6 and IL-6 receptor as a target are discussed. GM-CSF and GM-CSF targets are similarly reviewed and mavrilimumab, targeting on GM-CSF receptor, may be overviewed. Denosumab, targeting on RANKL has been developed for RA in Japan and phase II trial (DRIVE study) as well as phase III study (DESIABLE study) would be overviewed. Finally, future perspective of these biological agents in late clinical development in the present RA treatment algorithm and personalization should be discussed.

S1-5

New perspective of kinase-targeting low molecular DMARDs for the treatment of RA

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Conflict of interest: Yes

RA is a systemic autoimmune disease characterized by synovial inflammation and joint destruction. However, sDMARDs such as MTX and bDMARDs have revolutionized treatment of RA. However, bDMARDs are limited to intravenous or subcutaneous uses and orally available small but strong products have been developed. The multiple cytokines and cell surface molecules bind to receptors, resulting in the activation of various signaling, including phosphorylation of kinase proteins. Janus kinase (JAK) plays pivotal roles in the pathological processes of RA. Tofacitinib, a small orally available product, inhibits phosphorylation of JAK1/JAK3. Six phase 3 studies revealed that tofacitinib was significantly effective than placebo in active RA, but its association with carcinogenicity and infections remains debated. Accordingly, multiple oral small products targeting kinases are emerging. Baricitinib is a Jak1/Jak2 inhibitor. Four phase 3 studies indicate oral baricitinib is more efficacious than placebo and adalimumab with or without MTX in patients with sDMARD-naïve, inadequately responsive to sDMARD (sDMARD-IR) and bDMARD-IR. The adverse effects were partly similar to tofacitnib. Filgotinib and ABT-494 are sDMARDs targeting JAK1 and showed similar efficacy and safety profiles as tofacitinib in phase 2 trials. Also, the JAK3 inhibitors decernotinib and peficitinib showed strong and rapid efficacy, comparable to tofacitinib in phase 2 trials. Oral kinase inhibitors targeting Syk and Btk are also under the development. Thus, small products targeting specific kinase could represent a valuable addition to the current therapies and these kinase inhibitors would take in the therapeutic armamentarium in RA and multiple autoimmune diseases. However, the commonly observed adverse events of them were related to infection, hematologic, hepatic and renal disorders. Major concerns regarding long-term safety should be clarified by post-marketing surveillance.

S2-1

Regulation of bone destruction by the adaptive immune system

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Conflict of interest: None

The immune and skeletal systems are closely related through a number of shared regulatory molecules including cytokines. Progressive joint destruction in rheumatoid arthritis (RA) is the most typical pathological conditions that depend on the interaction between the skeletal and immune systems. Large amounts of the inflammatory cytokines such as IL-6, IL-1 and TNF are released, and lymphocytes, synovial macrophages and synovial fibroblasts accumulate and proliferate in the inflamed tissues. These inflammatory cytokines promote not only the immune responses but also osteoclast differentiation and survival by inducing RANKL on synovial fibroblasts. As proven by the clinical efficacy of anti-cytokine therapies, it is apparent that the inflammatory cytokines are strongly associated with the pathogenesis of RA. However, since the autoimmune response is considered as the core of the progression of RA, elucidation of the mechanism how the adaptive immune systems affect bone is important for understanding the pathogenesis of RA. A unique effector helper T cell subset, Th17, has stimulatory effects on osteoclastogenesis and plays a key role in the pathogenesis of RA through IL-17. IL-17 not only induces RANKL on synovial fibroblasts but also activates local inflammation, leading to the inflammatory cytokine production. On the other hand, $Foxp3^{+}CD4^{+}$ Treg cells are a specialized T-cell subset that engages in the maintenance of immunological self-tolerance. Under arthritic conditions, a part of $Foxp3^{+}CD4^{+}$ T cells lose Foxp3 expression and undergo transdifferentiation into Th17 cells (called exFoxp3Th17). Notably, exFoxp3Th17 cells highly express RANKL and thus contribute to the pathogenesis of RA. Furthermore, recent studies revealed that the immune complex directly enhances osteoclastic bone resorption under inflammatory conditions such as RA. It is becoming clear that the adaptive immune systems exert direct deleterious effects on bone cells in RA.

S2-2

Inflammation and Osteoclastogenesis

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Conflict of interest: Yes

Patients with inflammatory arthritis diseases, such as rheumatoid arthritis (RA), exhibit continuous joint inflammation, a chronic inflammation, with joint destruction. In arthritis animal models, the joint erosion but not joint inflammation was reportedly blocked by inhibiting osteoclast differentiation or activity. In human, treatment with receptor activator of nuclear factor kappa B ligand (RANKL) was reported to block joint erosion but not disease activity in RA patients, suggesting that osteoclasts play a pivotal role for joint destruction but not joint inflammation. We found that signal transducer and activator of transcription 3 (Stat3) was required for both joint inflammation and erosion by osteoclast formation. I will discuss the inflammation and osteoclastogenesis.

S2-3

Involvement of RANKL-induced incomplete cytokinesis in polyploidization of osteoclasts: a novel mechanism of osteoclast polyploidization

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Conflict of interest: None

Polyploidy, in which a cell has more than the diploid complement of chromosomes, is a widespread physiological phenomenon observed especially in plants, fungi, and insects. Although it is less common in mammals, polyploidization occurs in selected tissues including the placenta, liver, heart, skeletal muscle, and bone marrow during normal development and aging. During developmental programs, cells obtain additional sets of chromosomes by various mechanisms, including endocycles, endomitosis, incomplete cytokinesis, and cell fusion. Endocycles, endomitosis, and incomplete cytokinesis are directly associated with the proliferative state of the cell. By contrast, cell fusion is entirely independent of cell proliferation. Osteoclasts are specialized polyploid cells that resorb bone. Upon stimulation with receptor activator of nuclear factor kappa-B ligand (RANKL), myeloid precursors commit to becoming polyploid, largely via cell fusion. Although generation of polyploid osteoclasts is thought to occur due to cell fusion, independently of cell proliferation, a relationship between cell proliferation and osteoclast differentiation has been pointed out. Here, we demonstrated that in addition to cell fusion, incomplete cytokinesis also plays a role in osteoclast polyploidization. Fluorescence *in situ* hybridization revealed that some of osteoclasts exhibited nuclear polyploidy (i.e., they contained nuclei with more than the diploid complement of chromosomes [> 2N]) *in vivo*, suggesting that cells that undergo incomplete cytokinesis are physiologically involved in formation of polyploid osteoclasts. Our findings reveal an unexpected pattern of cell division and fusion during the generation of polyploid osteoclasts.

S2-4

The regulation of hematopoietic stem cells by mesenchymal stem cells

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Conflict of interest: None

Somatic stem cells self-renew to maintain tissue homeostasis for the lifetime of organisms through tightly controlled proliferation and differentiation. Hematopoietic stem cells (HSCs) are essentially required for the hematopoietic homeostasis. Therefore, They do not only ensure lifelong replenishment of all blood lineages, but also keep their pool constant. Cell cycle quiescence is a critical feature contributing to stem cell maintenance. Recent studies have highlighted the importance of bone marrow microenvironments that regulate HSC functions (HSC niches).

In the HSC field, there has been a considerable interest and debate regarding whether or not quiescence and proliferation of HSCs is regulated by distinct niches. Previous reports suggest that quiescent HSCs reside near osteoblasts in the bone marrow whereas actively cycling HSCs are found near sinusoids. However, this popular concept has not been supported by rigorous analyses. To get more insight into the spatial localization of HSCs, we have developed a whole-mount staining technique that allows precise measurements of 3D distances of HSCs from structures and is amenable to computational simulation to define the significance of these interactions. This novel approach has allowed us to uncover two distinct types of vessels associated with quiescent and proliferating HSCs and to underscore the importance of arteriolar vessels for stem cell quiescence. In addition, we will introduce the groundwork for the characterization and identification of subsets of stromal cells that comprise the bone marrow niche and provide definitive data on the hierarchical organization of MSCs and precursors of stromal cells in the bone marrow.

S2-5

***In vivo* imaging of osteoclast dynamics**

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Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial joint inflammation and progressive cartilage/bone destruction. Arthritic bone destruction is considered to be mediated mainly by enhanced activation of osteoclasts at inflammatory sites. To prevent RA-associated bone destruction, it is important to understand the cellular dynamics of osteoclastic bone resorption *in vivo*. Because bone is the hardest tissue in the body, it is difficult and almost impossible to visualize the inner bone tissue in living animals. In the fields of bone and mineral research, cell morphology and structure in bone tissues can be analyzed by conventional methods such as micro-CT and histological analysis. These methods allow for the evaluation of cell shape and molecular expression, but cannot observe living osteoclast movement. Thus, how the bone-resorptive functions of mature osteoclasts are controlled *in vivo* remains unclear. To answer this question, we utilized an advanced imaging system to visualize living bone tissues with intravital multiphoton microscopy that we have originally established. By using this imaging system, we succeeded in visualizing the *in vivo* behavior of living mature osteoclasts on the bone surface, and identified different functional subsets of osteoclasts in terms of their motility and function, i.e., 'static - bone resorptive' and 'moving - non resorptive'. Treatment with recombinant RANKL or bisphosphonate changed the composition of these populations as well as the total number of mature osteoclasts. We also found that RANKL-bearing Th17 cells could control bone resorption of mature osteoclasts, demonstrating novel actions of Th17. Furthermore, we have established the practical imaging of bone destruction by osteoclasts in arthritic joints using intravital multiphoton microscopy. In this symposium, we show the latest data and also discuss the further application of intravital bone imaging.

S2-6

Osteoimmunology and arthritis

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Conflict of interest: Yes

Bone homeostasis is maintained with the balance of bone resorption by osteoclasts and formation by osteoblasts. Macrophage lineage cells differentiate into osteoclasts with RANKL produced by osteoblasts or osteocytes. RANKL was originally discovered as the factor expressed on T cells that promoted survival and activation of dendritic cells. IFN-gamma produced by Th1 cells inhibits RANKL-induced osteoclastogenesis. It is well known that the immune system greatly participates in osteoclastogenesis. The synovial tissue of rheumatoid arthritis is comprised of fibroblasts, macrophages and lymphocytes, and produces inflammatory cytokines such as TNF-alpha. These cytokines act on synovium itself to promote RANKL expression, which leads to bone destruction. At the same time, the expression of DKK-1 and sclerostin are decreased, those which inhibit Wnt signaling for osteoblast differentiation. It is thought that biologics work on immune cells or synovial fibroblasts and reduce both RANKL and DKK-1 expression. They indirectly inhibit bone destruction and also restore bone. Ankylosing spondylitis is characterized by the inflammation of sacroiliac joint and enthesis, where both bone destruction and formation are seen. If there is much TNF, enhanced expression of DKK-1 and sclerostin inhibit Wnt signaling. It is also thought that more transmembrane form and less soluble form of TNF result in more bone destruction and less formation. There is abundant TGF-beta near syndesmophytes and TGF-beta promotes the differentiation of the Th17 cell in collaboration with IL-6. When Th17 cell is dominant in local site, more IL-17, IL-22, and IL-23 are produced. IL-22 and IL-23 are known to promote the differentiation of osteoblasts by enhanced production of both Wnt and BMP. In autoimmune diseases, bone and immune system collaborate on forming the arthritis or enthesitis. I present the pathology of these diseases in touch with osteoimmunology.

S3-1

The physiological role of inflammasome-mediated immune responses

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Conflict of interest: None

IL-1β is a cytokine that is secreted by inflammasome activation and plays an important in host protection against pathogens, whereas its abnormal secretion results in autoinflammatory diseases. The suppressive regulatory mechanism of NLRP3 inflammasome is lost by mutations in patients with Cryopyrin (NLRP3)-associated periodic syndrome (CAPS). To understand the pathogenesis of CAPS, it is important to know how IL-1β secretion is regulated in response to inflammation or infection. In addition to danger signals that are required for inflammasome activation, the functional expression level of NLRP3 must be first upregulated through cell surface pattern recognition receptors such as Toll-like receptors by inflammatory molecules. The dual requirement for NLRP3 inflammasome activation means that each requirement can be filled separately by different bacteria within the same tissue environment. For example, during intestinal *Clostridium difficile* infection IL-1β secretion requires not only *Clostridium difficile* but also commensal Enterobacteriaceae species, which are responsible for host lethality and are the primary targets of IL-1β-mediated host responses in the mouse model. On the other hand, NLRP3 inflammsome activation and IL-1β secretion in the intestine are induced only by one commensal P. *mirabilis*, which have toxins and high pyrogenicity. Some intracellular bacteria, including *Salmonella* and *Legionella*, hide in host cells and avoid detection by cell surface detection, IL-1β secretion is induced by non-NLRP3 type inflammasomes such as NLRPC4. Once IL-1β is secreted at the infection site, IL-1β mediates local inflammatory responses such as neutrophil recruitment and induction of other cytokines (i.e. IL-22) that are important for systemic elimination of pathogens and pathobionts. The basal levels of IL-1β in non-infection state also induce chronic responses that impacts the inflammatory state. We believe that these new findings will advance our understanding of acute and chronic responses in autoinflamamtory diseases and contribute to development of new therapeutic approaches to treating autoimmune disease.

S3-2

Review in Familial Mediterranean fever - New insights into disease associated gene and cytokine/chemokine signaling

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Conflict of interest: None

Familial Mediterranean fever (FMF), the most common autoinflammatory hereditary disease, is characterized by recurrent attacks of fever with arthritis and serositis. The mutation of Mediterranean fever (*MEFV*) gene, which encodes pyrin, is closely associated with the pathogenesis of FMF. Although it has become apparent that FMF patients is not quite rare in Japan and that its survival rate is more than 90%, there is no fundamental treatment for this disease. Long-term treatment of oral colchicine is usually used among FMF patients. Even though it has been reported by case reports that IL-1 inhibitor, TNF inhibitor or IL-6 inhibitor is effective for the treatment of colchicine resistant FMF, the mechanism of the development of FMF has not been elucidated. Accordingly, it is required the identification of inflammatory cytokines involved in the development, the analysis of signal associated molecules which composed of inflamasome and discover of disease associated genes other than *MEFV* gene. Our research group has been addressing the formation of the FMF consortium, construction of bio-bank and analyzing the clinical information, genome DNA and serum from FMF patients. Also, we are going to search the new therapeutic targets in FMF. We recently found specific molecular interactions in patients with FMF based on multiple cytokines measurement. In addition, the active form of IL-1b is a valuable biomarker for monitoring disease activity in patients with FMF. We performed a comprehensive genome analysis to determine the entire nucleotide sequence of *MEFV* gene including the coding regions, the transcriptional regulatory regions, untranslated region and promoter region. We have been attempting to identify new disease-associated genes in all exon analysis using next-generation sequencer for the cases that can not be fully described in the mutation of the *MEFV* gene.

S3-3

Interferonopathy; dissecting SLE pathogenesis through the analyses of SLE-like Mendelian diseases

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Conflict of interest: None

Type I interferon (IFN) is a group of cytokines induced by outer stimuli such as viral infection. When induced, it activates a group of IFN-stimulated genes (ISGs). The association of SLE and ISGs detected by GWAS studies, and the overexpression of ISGs in SLE patients, both suggested type I IFN as a key molecule in SLE pathogenesis. A number of Mendelian diseases called “type I interferonopathy” is widely known, in that its genetically-determined type I IFN overproduction causes SLE-like phenotypes. Aicardi-Goutières syndrome (AGS) is an infantile-onset encephalopathy, which is characterized by developmental delay, intracranial calcification and CNS inflammation. AGS patients sometimes show SLE phenotypes, such as autoantibody production, low complement levels and chilblains, and indeed, some AGS patients fulfill the diagnostic criteria of SLE. Several genes engaged in nucleic acid metabolism are known to be responsible for AGS, in that their loss-of-function mutations result in the accumulation of nucleic acids and type I IFN overproduction. Our whole exome sequencing identified mutations in MDA5 (IFIH1 gene) in three AGS patients without mutations in known AGS genes. MDA5 is a cytosolic receptor of double-strand RNA, and we showed that these gain-of-function mutations in AGS patients spontaneously activate type I IFN signaling. Funabiki previously reported a mouse model of SLE due to an Ifih1 missense mutation (Funabiki et al, Immunity, 2014), which is in concordance with our results. Furthermore, Liu reported mutations in another upstream molecule of IFN pathway, STING (TMEM173 gene), is responsible for infantile-onset vasculitis and interstitial pneumonitis (Liu et al, NEJM, 2014), which they call SAVI (STING-Associated Vasculopathy of Infancy). In this talk, recent reports of interferonopathy and its mouse models aiming at the understanding of SLE pathogenesis will be discussed.

S3-4

Psoriasis with a genetic basis: DITRA and CAMPS

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Conflict of interest: None

I shall introduce 2 novel autoinflammatory diseases, interleukin-36 receptor antagonist (DITRA)- and caspase recruitment domain family, member 14-mediated psoriasis (CAMPS). Psoriasis is classified into 5 types: psoriasis vulgaris (PsV), psoriatic arthritis (PsA), psoriatic erythroderma, psoriasis guttate, and generalized pustular psoriasis (GPP). The cause underlying GPP was unknown. GPP is an incurable disease, with more than 1,900 patients registered in Japan. Because many GPP cases are adult-onset, it was not considered a monogenic autoinflammatory disease. However, we found that most GPP cases that are not accompanied by PsV are DITRA-mediated. *IL36RN* encodes interleukin-36 receptor antagonist (IL-36Ra), which antagonizes pro-inflammatory cytokines IL-36α, IL-36β, and IL-36γ in the skin. The inflammatory signal is considered to be activated to cause the DITRA-mediated lesion via IL-36 receptor due to lack of IL-36Ra antagonism against IL-36α, IL-36β, and IL-36γ. CAMPS is an autosomal dominant inherited disease due to *CARD14*. CAMPS phenotypes include PsV, PsA, GPP, or the psoriasis-related pityriasis rubra pilaris. CARD14 activates NF-κB in epidermal keratinocytes. However, the pathomechanism of the involvement of the *CARD14* mutation in CAMPS has not been elucidated, although some *CARD14* mutants have been proven as gain-of-function mutants in vitro.

S3-5

Disease modeling of autoinflammatory syndromes with patient derived iPS cells

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Conflict of interest: None

Induced pluripotent stem cells (iPSCs) is a pluripotent cell lines which can be established patients. iPSCs can be established from various somatic cells such as peripheral blood cells and skin fibroblasts. By differentiating patient-derived iPSCs into the responsible cell types, we are now able to obtain various patient-derived differentiated cells. Therefore, disease-associated iPSCs have been regarding as a promising tool to link the patients’ phenotypes to basic research, thereby contributing to the progress in medicine. The number of articles regarding the iPSC-based in vitro disease modeling is increasing explosively. Autoinflammatory syndromes are one of the disease entities characterized by the abnormal function of innate immunity. Most of autoinflammatory syndromes are accompanied by genetic alterations. We previously reported disease modeling of CINCA syndrome by using iPSCs derived from patients with somatic mosaicism of NLRP3. We consider iPSCs as a useful tool for understanding the pathophysiology of antoinflammatory syndromes, and for developing novel therapeutic approaches. In this presentation, we would like to introduce our efforts for establishing disease models of autoinflammatory syndromes.

S4-1

Current understandings of ankylosingspondylitis: from Japanese reports

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Conflict of interest: None

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease mainly affecting the axial joint and may lead to structural damage, syndesmophyte formation, ankylosis of spine, and finally impair the quality-of-life. AS develops in young age, with a peak age of onset around 20 years, and is highly associated with HLA-B27. HLA-B27 is

present in 90% of AS patients, and there is a clear correlation between the prevalence of AS and prevalence of HLA-B27. In Japan, prevalence of HLA-B27 is very low, about 0.5%, and this leads to the low prevalence of AS. Therefor, in Japan, clinical experience of AS is olso low, and there are some misdiagnosi, overdiagnosis, and overtreatment. In 2009, ASAS (Assesment of SpondyloArthritis international Society) develop the new classification criteria, and this is aimed early diagnosis and early treatment. In 2015, AS was approved as intractable disease defined by Japanese Ministry of Health, therefor AS patients can be administered expensive biological agents with low cost. But not all the AS patients needs this treatment. We must understand and diagnosis this disease correctly.

S4-2

Precise understanding of ASAS criteria, undifferentiated SpA and non-radiographic axial SpA

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Conflict of interest: None

The ASAS criteria for SpA have been frequently misinterpreted as diagnostic criteria. Patients will be easily diagnosed with SpA using a checklist of the ASAS criteria. However, individual patients should be diagnosed based on as the following: physician's judgment, excluding and/or differential diagnosis, case confirmation by other expert rheumatologists, confirmation over several months, and others procedures. uSpA is unclassified rather than early SpA. It is a generic term for patients who do not fit into the classic SpA disease classification. The main feature of uSpA patients exhibit is peripheral arthritis and not axial spondylitis. Male predominance, a high rate of HLA-B27-positive cases and an elevated level of serum CRP at the onset are clinical manifestations relevant to reactive arthritis. It has been postulated in US literature that most patients with uSpA have an unclear preceding history of infection. nr-axial SpA is implied as early AS and has been positioned in the target group to promote early treatment with TNF inhibitors. However, not all patients with nr-axial SpA progress to AS with radiographic sacroiliitis. Therefore, non-radiographic should not be regard as preradiographic. Furthermore, more females, a lower rate of HLA-B27-positive cases, and limited effect of biologics are characteristics of nr-axial SpA which are irrelevant to AS. Fibromyalgia is frequently misdiagnosed in Japan as well as overseas. It will be possible that the features of nr-axial SpA were affected by those of FM overdiagnosed by general physician. The concept of the nr-axial SpA is not fully and equally understood between the ASAS and the Spondyloarthritis Research and Treatment Network (SPARTAN) in the USA. Treatment with TNF inhibitors for nr-axial SpA in Europe have already been approved, but not by the FDA in the USA. It has been concluded by the FDA that the natural history of nr-axial SpA must be clarified in further investigation.

S4-3

Proper understanding of the significance of imaging

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Conflict of interest: None

In the diagnosis of ankylosing spondylitis (AS), it is important to demonstrate sacroiliitis (SII) by imaging. SII is classified into five stages in the modified NY criteria. However, it is difficult to diagnose SII in grade 1 and 2. Further, concordance rate (κ value) among readers is low. In the interpretation of the SII, less experienced readers tend to overdiagnose SII as compared to the experienced readers. When patients have inflammatory low back pain and there is no positive plain X-ray findings, if the AS is still suspected, MRI is effective in diagnosis of SII. In the MRI findings of SII, there are two categories: structural changes, inflammatory lesions. In the clinical practice, it is not often to demonstrate intensive BME by MRI. In the MRI diagnosis, by adding findings of structural changes, specificity of AS diagnosis is improved. Psoriatic arthritis (PsA) was classified into 5 types. However, there is an overlap in each type, and disease type also varies over time. Therefore, it is practical to classify into two types; peripheral arthritis and axial arthritis. PsA of hands and feet shows three patterns; DIP/PIP arthritis, Ray pattern, and RA like pattern. SII in PsA tends to be asymmetric, and intervertebral joint lesions are small as compared to those of AS lesion. Lumbar spine lesions are relatively infrequent, discontinuous, and asymmetrical. In PsA, MRI can depict joint lesions that are not clinically apparent. There are six parameters in the MRI findings; synovitis, erosion, bone marrow edema (BME), tenosynovitis, periarticular inflammation, bone proliferation. BME precedes erosion. Although MRI findings of early PsA are nonspecific, edema of enthesitis and diaphysis, and diffuse soft tissue edema are significantly frequent as compared to early RA.

S4-4

Psoriasis treatment modalities-topical, oral, phototherapy ands biologics

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Conflict of interest: Yes

Psoriasis is a chronic immune-mediated autoinflammatory skin disease. Risk factors and comorbidities commonly observed in patients with psoriasis include metabolic syndrome, cardiovascular disease, arthritis symptoms, and psychiatric illness. The estimated prevalence of psoriasis is 1% to 3% of the population worldwide, and the prevalence in Japan is 0.2%. Pathophysiologic mechanisms are related to aberrant immune responses, cell types, and proinflammatory mediators, such as tumor necrosis factor-a and interleukins (IL) 12, 23 and 17A. Biologics approved for the treatment of moderate-to-severe plaque psoriasis targeting these inflammatory mediators have improved the response rates associated with conventional oral agents, such as cyclosporine A, etretinate, and methotrexate. The "treat to target" recommendation is a PASI (psoriasis area and severity index) of 90. Phototherapy is also used to treat psoriasis. Ultraviolet light (UV) phototherapy using narrowband UVA (311-313 nm) is a well-established treatment for psoriasis. UV phototherapy has two primary modes of action: apoptosis induction and immune suppression. Narrowband UVB depletes pathogenic T cells by inducing apoptosis and regulatory T cells. Bath-psoralen plus ultraviolet light A (PUVA) therapy continues to be beneficial and used in the treatment of psoriasis due to its efficacy, safety profile, and low cost. Bath-PUVA therapy significantly reduces the number of Th17 cells and significantly increases regulatory T cell (Treg) function to almost normal levels, thus resolving the Th17 and Treg imbalance in patients with psoriasis, and induces activated Treg. These four treatment modalities: topical, oral, phototherapy, and biologics, are important and their application for treating and controlling psoriasis is relatively complex. Cooperation between rheumatologists and dermatologists is therefore essential for providing optimal care to patients with psoriasis.

S4-5

Psoriatic arthritis: clinical manifestations and the efficacy of biologics

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Conflict of interest: None

Psoriatic arthritis is a characteristic inflammatory arthritis associated with psoriasis. The recent studies shows that the disease burden of the psoriatic arthritis is comparable to those of rheumatoid arthritis and ankylosing spondylitis. The impact of psoriatic arthritis on physical activities and quality of life has been shown to be similar to rheumatoid arthritis. The successful introduction of biologics including TNF inhibitors dramatically changed the treatment of psoriatic arthritis and facilitated the development of the management recommendations for psoriatic arthritis. The three main drug classes for the treatment of psoriatic arthritis are NSAID, conventional synthetic (cs) DMARD and biological DMARD. TNF inhibitors have sufficient evidence for the efficacy on peripheral arthritis. The radiographic progression has been shown to be suppressed by TNF inhibitors. TNF inhibitors indicated to be effective in the treatment of enthesitis, dactylitis. Therefore, patients with predominant enthesitis or

dactylitis should be treated with biologics when NSAID or local therapy is ineffective. csDMARD has no evidence for the treatment of spondylitis. Some studies have shown the suppression of inflammation of spine by biological DMARD. However, the suppression of radiographic progression of psoriatic spondylitis has not been indicated although the assessment of the effectiveness of biological DMARD on the progression of spinal disease need longer time. At the moment, for psoriatic spondylitis, biological DMARD is recommended when use of NSAID with local therapy and/or rehabilitation shows inadequate response. The biological DMARDs to block IL-17 or IL-12/23 pathway have been shown to be effective to suppress disease activity of psoriatic arthritis. At the moment, those drugs should be used for patients with inadequate response to TNF inhibitors.

S4-6

Psoriatic arthritis: Medical care and complications in Japan

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Prevalence of Japanese patients with psoriasis (PSO) has been reported to be 0.34% in 2015 (K.Kubota et al BMJ 2015). At the same time, we have reported that there is a psoriatic arthritis (PsA) patients in 14.5% of patients with psoriasis (Ohara et al J.Rheumatol 2015). In Japan, there were about 63,000 patients with PsA. In recent years, since the biologics for PSO/PsA adopt Japanese insurance, the treatment of PSO/PsA got better. The recommendations from the Nature Review Rheumatology 2014, Once a diagnosis of PSO, you should take care of many symptoms of "Psoriatic Disease" (the skin and nails symptoms and joint symptoms and metabolic syndrome, cardiovascular disease …) Certainly the skin and joint symptoms of PSO/PsA are a dramatic improvement by biologics, but it is not yet fully possible to correspond about the "many complications" in the current situation. In this session, we would like to talk about epidemiology, clinical findings, the inter-department cooperation and the complications that should be noted.

S5-1

Progress in pathophysiology and treatment of pulmonary arterial hypertension associated with connective tissue diseases

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Conflict of interest: None

Connective tissue diseases (CTD) are frequently complicated by pulmonary hypertension (PH). Although right heart catheterization is gold standard for definitive diagnosis of PH, most rheumatologists find it difficult to perform, so useful screening methods have thus been sought. The most useful method is echocardiography. Exercise echocardiography is also being investigated in order to reduce false-negative results in this method, and approaches such as nailfold videocapillaroscopy and flow-mediated dilation are also being investigated. In addition, based on the fact that PH first develops after the effective pulmonary vascular bed becomes £1/3, 3D angiography using computed tomography is also being investigated. Because PH in systemic sclerosis (SSc) often develops gradually, yearly screening with tests such as echocardiography and pulmonary function tests is useful. Conversely, PH in systemic lupus erythematosus (SLE) and many cases of mixed connective tissue disease (MCTD) has an acute onset, which means that screening tests have a limited utility, and early tests must be performed following onset of the signs and findings of PH. PH in SSc is primarily caused by vascular stenosis, whereas PH in non-SSc diseases is thought to be primarily caused by pulmonary arteritis. Therefore, the main treatment is vasodilator agents for PH in SSc and high-dose steroid therapy and immunosuppressants for PH in non-SSc diseases. However, in the case of PH in SSc, venous lesions are often observed, so the use of vasodilator agents requires careful consideration. Even among CTD-associated PAH, which has a poorer prognosis than idiopathic pulmonary arterial hypertension, PH in SSc has a poorer prognosis than PH in non-SSc diseases, and few improvements in the prognosis of PH in SSc have been reported over time. In order to improve prognosis, it is considered necessary to achieve early diagnosis of PH and to elucidate its pathophysiology and provide appropriate treatment.

S5-2

Clinical characteristics and subsetting of interstitial lung disease associated with dermatomyositis

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Conflict of interest: None

Dermatomyositis (DM) is one of connective tissue disease characterized by proximal muscle weakness and typical skin manifestation. DM is sometimes accompanied by interstitial lung disease (ILD) and its diversity in clinical course, response to treatment, prognosis is well known. Correct evaluation and selection of appropriate treatment of ILD is important because it often affects the prognosis of DM. Chronic type of ILD in patients with DM has a good response in initial glucocorticoid treatment although it often relapses during glucocorticoid taper. On the other hand, patients who have no clinical muscle involvement termed clinically amyopathic dermatomyotisits (CADM), a clinical subtype of DM, have progressive type of ILD (rapidly progressive interstitial lung disease: RP-ILD). It is known that complicating RP-ILD in patients with DM has poor prognosis despite of intensive treatment with high-dose glucocorticoid and immunosuppressive agents. Autoantibodies that are found in patients with DM are well known to be useful for the classification of ILD. Major antibodies that are clarified to be associated with ILD and DM are anti-aminoacyl transfer RNA synthetase (ARS) antibody and anti-CADM-140/MDA5 antibody. Anti-ARS antibody is known to be associated with chronic clinical course of ILD whereas anti-CADM-140/MDA5 antibody is closely associated with acute or subacute type of ILD. Therefore, these antibodies are crucial for accurate diagnosis, determining therapy, predicting prognosis in patients with DM and ILD.

S5-3

Hematopoietic stem cell transplantation for diffuse cutaneous systemic scleroderma: theoretical back ground and clinical results

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Conflict of interest: None

Systemic scleroderma (SSc) is a systemic connective tissue disease characterized by skin sclerosis and vascular lesion. Autoimmunity is thought to be involved in the pathogenesis because autoantibodies to topoisomerase I and centromere are detected and are associated with diffuse and limited cutaneous type, respectively. Since five-year survival of severe diffuse cutaneous SSc is reported to be 50-60%, there were needs to develop effective treatment for these patients. In Europe and Unites states, on the basis of experimental data from animal models, hematopoietic stem cell transplantation (HSCT) was performed in more than 300 patients with SSc. van Laar JM and his colleagues reported that autologous HSCT (auto-HSCT) was superior to conventional intravenous cyclophosphamide (CY) in the long-term survival in their phase III randomized trial. We performed auto-HSCT in the treatment of 23 severe scleroderma patients as a phase I/II study. Peripheral blood stem cells (PBSCs) were mobilized with 4 g/m^2 of CY and G-CSF. After collecting PBSCs by apheresis, they were cryopreserved until autographting. All of the patients were treated with high-dose CY (200 mg/kg) and received auto-HSCT. Skin sclerosis was markedly improved within 6 months and the improvement was sustained for more than 60 months after HSCT. Vital capacity was gradually increased after HSCT. KL-6 and a titer of anti-Scl-70 were significantly decreased over a long period of time after HSCT. As toxicity, there were a variety of infections such as adenoviral hemorrhagic cystitis, sepsis, herpes zoster and cytomegaloviral antigenemia. Progression-free and overall 5-year survivals were 56% and 83%, respectively. In the analysis of T cell receptor (TCR) repertoire, CDR3 sizes of some TCR Vβ in SSc patients were oligoclonal or monoclonal, however, they restored diversity after auto-HSCT. In conclusion, auto-HSCT is effective and potentially improves the prognosis of severe SSc.

S5-4

Thrombotic microangiopathy in patients with rheumatic diseases

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Conflict of interest: None

Thrombotic microangiopathy (TMA) is a pathological condition characterized by microvascular occlusion by platelet thrombi, thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and renal dysfunction. Two phenotypes of TMA are hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). HUS can be divided into two categories; Shiga-toxin associated HUS (typical HUS) which presents with diarrhea and atypical HUS which occurs in various conditions such as complement activation or endothelial damage. TTP is defined by a severe deficiency of ADAMTS13 which can be hereditary or acquired as a result of inhibition of ADAMTS13 activity by autoantibodies. Systemic rheumatic disorders, such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), especially catastrophic APS (CAPS) and systemic sclerosis (SSc) can often cause TMA, aHUS or TMA like conditions. Since TMA is a life threatening condition, prompt diagnosis and management are necessary. Although plasma exchange (PEX) is used as a first line therapy for TTP, immunosuppressive therapy is also administrated in patients with PEX refractory TTP or aHUS after consideration of the disease activity of underlying diseases. In addition, rituximab or eculizumab (anti-C5 monoclonal antibody) are also considered in severe or refractory patients.

S5-5

Clinical manifestations and treatments of hemophagocytic syndrome associated with autoimmune disease

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Conflict of interest: None

Hemophagocytic syndrome (HPS) is characterized by macrophagic hemophagocytosis throughout the reticuloendothelial system, including bone marrow and spleen. HPS can be classified into either primary (genetic) or secondary (reactive) HPS. Several genetic diseases predispose to HPS, and secondary HPS occurs in association with underlying infectious disease, malignant disease or autoimmune disease. Autoimmune-associated hemophagocytic syndrome (AAHS) is a secondary HPS, which develops in association with underlying autoimmune disease. It occurs in association with a flare or activity of underlying autoimmune disease. SLE and AOSD are major underlying diseases for AAHS. Fever, lymphadenopathy, hepatomegaly and splenomegaly are found in approximately 90, 40, 40 and 50% of patients, respectively. Leukocytopenia, anemia and thrombocytopenia are in 80, 90 and 70%, respectively. Coagulopathy, liver dysfunction and hyperferritinemia can been seen, and approximately 20% show a normal or low value of serum ferritin. In patients underlying SLE, normal or low CRP value is characteristic. Patients underlying AOSD do not necessarily show leukocytopenia and thrombocytopenia, despite to prominent hemophagocytosis. The most commonly used therapy is corticosteroids, and 60% of the patients responded. Patients being refractory to corticosteroids are usually treated by cyclosporine, intravenous cyclophosphamide (IVCY) or intravenous immunoglobulin G, with IVCY being highly effective. Treatment with biologics, such as TNF alpha or IL-6 inhibitor, or anti-CD20 mAb, results in favorable effects in the majority of patients. So, proceeding directly from corticosteroids to biologics is promising. Recently we have shown that the mortality rate of AAHS is 13%. Male-sex, dermatomyositis and anemia (Hb<8 g/dl) are associated with mortality (Arthritis Rheumtol 66; 2297, 2014). We should elucidate the pathogenic mechanisms of AAHS and develop treatments aimed at the underlying pathologic process.

S5-6

Pathogenesis and evaluation of neuropsychiatric manifestations in connective tissue diseases

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Conflict of interest: None

Although neuropsychiatric systemic lupus erythematosus (NPSLE) is one of the recalcitrant manifestations of SLE, its pathogenesis remains unclear. The role of anti-neuronal antibodies in the pathogenesis of NPSLE has been appreciated since Bluestein et al demonstrated that IgG anti-neuronal antibodies were present in much higher concentrations in the cerebrospinal fluid (CSF) from patients with active NPSLE. Of interest, CSF IgG anti-neuronal antibodies were found to be significantly elevated in patients with diffuse psychiatric/neuropsychological syndromes (diffuse NPSLE) compared with neurologic syndromes (focal NPSLE) N-methyl-D-aspartate (NMDA) receptors are one of the glutamate receptor families and its stimulation has been shown to cause excitatory synaptic transmission in the central nervous system (CNS). DeGiorgio et al demonstrated that a subset of murine anti-DNA antibodies cross-reacts with a sequence within the NMDA receptor subunit NR2. Notably, the presence of such cross- reactive anti-DNA antibodies in the serum compartment alone could not result in brain damages, which also require a breakdown of blood-brain barrier (BBB) to allow such autoantibodies enter the CNS. Accordingly, we showed that CSF anti-NR2 antibodies, but not serum anti-NR2, were closely associated with diffuse NPSLE. In addition, we have also demonstrated that CSF anti-Sm antibodies, which can bind to neurons, were also associated with diffuse NP-SLE, especially acute confusional state (ACS). More importantly, these results demonstrate that the severity of BBB damages, but not the intrathecal synthesis of anti-NR2 or anti-Sm, plays a crucial role in the development of ACS. Although the precise mechanism of BBB damages remains to be elucidated, the role of C5a is now suspected.

S6-1

Defective PTEN regulation contributes to B cell hyperresponsiveness in systemic lupus erythematosus

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Conflict of interest: None

PTEN regulates normal signaling through the B cell receptor (BCR). In systemic lupus erythematosus (SLE), enhanced BCR signaling contributes to increased B cell activity, but the role of PTEN in human SLE has remained unclear. We performed fluorescence-activated cell sorting analysis in B cells from SLE patients and found that all SLE B cell subsets, except for memory B cells, showed decreased expression of PTEN compared with B cells from healthy controls. Moreover, the level of PTEN expression was inversely correlated with disease activity. We then explored the mechanisms governing PTEN regulation in SLE B cells. Notably, in normal but not SLE B cells, interleukin-21 (IL-21) induced PTEN expression and suppressed Akt phosphorylation induced by anti-immunoglobulin M and CD40L stimulation. However, this deficit was not primarily at the signaling or the transcriptional level, because IL-21-induced STAT3 (signal transducer and activator of transcription 3) phosphorylation was intact and IL-21 up-regulated PTEN mRNA in SLE B cells. Therefore, we examined the expression of candidate microRNAs (miRs) that could regulate PTEN: SLE B cells were found to express increased levels of miR-7, miR-21, and miR-22. These miRs down-regulated the expression of PTEN, and IL-21 stimulation increased the expression of miR-7 and miR-22 in both normal and SLE B cells. Indeed, a miR-7 antagomir corrected PTEN-related abnormalities in SLE B cells in a manner dependent on PTEN. Therefore, defective miR-7 regulation of PTEN contributes to B cell hyperresponsiveness in SLE and could be a new target of therapeutic intervention.

S6-2

Neutrophils in the pathogenesis of systemic autoimmune diseases

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Conflict of interest: None

The last decade has emphasized the role of innate immunity in the pathogenesis of systemic autoimmune diseases. In particular, a role for neutrophil dysregulation in loss of tolerance and organ damage in diseases like systemic lupus erythematosus, rheumatoid arthritis or ANCA-vasculitis has been proposed. These diseases present with enhanced propensity of neutrophils to form neutrophil extracellular traps (NETs),and this phenomenon may lead to the externalization of modified autoantigens that, in predisposed hosts, may promote immune stimulation. Furthermore, NETs are enriched with cytotoxic molecules that can damage endothelial cells, activate the inflammasome pathway and stimulate plasmacytoid DCs to synthesize type I IFNs. Externalization of modified nucleic acids by NETs is an additional immunostimulatory mechanism. Recent evidence indicates that in vivo inhibition of pathways implicated in NETosis can mitigate autoimmune features. As such, neutrophils may represent important therapeutic targets and better understanding of pathogenic neutrophil subsets will be key in designing specific therapies that can target immune dysregulation in individuals affected by these diseases.

S6-3

Treatment of experimental rheumatoid arthritis with toll like receptor ligands

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Conflict of interest: None

Rheumatoid arthritis (RA) is categorized as a disorder due to abnormal activation of adaptive immune responses. Recent studies indicate that innate immune activation plays a major role in triggering and perpetuating joint inflammation in RA patients. Varieties of endogenous ligands against innate immune sensors, namely toll like receptor (TLR) ligands, are identified as instigators of joint inflammation. Activation of TLR signaling pathways induces negative feedback pathways to prevent excessive inflammation in hosts, so-called "TLR tolerance". We hypothesized that induction of TLR tolerance would ameliorate joint inflammation in RA. Our laboratory has synthesized asmall molecule TLR7 ligand, 9-benzyl-8-hydroxy-2-(2-methoxyethoxy) adenine (SM360320, 1V136) (Chan et al, 2009) and its derivatives, and has investigated applications for treatment of autoimmune diseases. In vivo, chronic administration of low dose TLR7 ligand induced hyporesponsiveness following other TLR stimuli utilizing MyD88 adaptor protein. Our data indicated that repeated treatment with a low dose TLR7 ligand suppressed joint inflammation in the antibody induced arthritis model (Hayashi et al 2009). Repeated administration of a low dose TLR7 ligand induced negative feedback molecules, such as Interleukin 1 Receptor Associated Kinase (IRAK)-M and Src homology 2-containing inositol phosphatase-1 (SHIP)-1. This treatment regimen was also effective in other rodent models of human inflammatory disorders, such as multiple sclerosis, and chemically induced colitis. We also discovered novel small molecule TLR4 ligands through cell based high throughput screening, and demonstrated anti-inflammatory effects of the novel TLR4 ligands on the serum transfer arthritis model (Chan et al, 2012, Hayashi et al 2014). These findings suggest that manipulation of innate immune status by low-grade stimulation with TLR4 and TLR7 ligands may be a novel therapeutic approach for autoimmune inflammatory disorders.

S6-4

Th2 and eosinophil responses suppress inflammatory arthritis

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Conflict of interest: None

Th2 eosinophil immune responses are well known for mediating host defence against helminths. Herein, we describe a novel function of Th2-eosinophil responses in counteracting the development of arthritis. In two independent models of arthritis, *Nippostrongylus brasiliensis* infection led to Th2 and eosinophil accumulation in the joints associated with robust inhibition of arthritis and protection from bone loss. Mechanistically, this protective effect was dependent on IL-4/IL-13-induced STAT6 activation in hematopoietic cells. Furthermore, we showed that eosinophils play a central role in the modulation of arthritis by facilitating the recruitment of anti-inflammatory macrophages into arthritic joints. The presence of these pathways in human disease was confirmed by detection of GATA3 positive cells and eosinophils in the joints of rheumatoid arthritis patients. Taken together, these results demonstrate that helminth-induced activation of the Th2-eosinophil axis effectively mitigates the course of inflammatory arthritis.

S6-5

Pathogenic role of lysyl oxidase-like 2 in rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease characterized by the synovial hyperplasia, consisting of infiltrated immune cells and resident synovial fibroblasts (SF), and cartilage and bone destruction. Inflammatory cytokines from the immune cells induce intense proliferation of SF with the activated phenotype, producing inflammatory cytokines and matrix-degrading enzymes, and differentiating osteoclasts. Current anti-rheumatic drugs, which inhibit inflammatory cytokines and immune cells, do not necessarily introduce remission in all cases. We thus believe that SF should be another target for anti-rheumatic treatment. Lysyl oxidase-like (LOXL) 2 belongs to the lysyl oxidase family of secreted enzymes involved in collagen crosslinking. Recent studies revealed that LOXL2 is up-regulated and responsible for fibroblast activation and pathological extracellular matrix (ECM) formation in cancer and fibrotic diseases. These findings led us to assume that LOXL2 in RASF should plays crucial roles in the pathology of RA. RASF we isolated from the affected joints from RA patients expressed and secreted LOXL2. The level of LOXL2 secretion was augmented by TNF-α and IL-1β stimulation. The TNF-α and IL-1β stimulation induced the deposition of type I, III, IV and VI collagens around RASF. Knockdown of LOXL2 mRNA using lentiviral shRNA transduction and anti-LOXL2 antibody treatment attenuated the collagen deposition, demonstrating that LOXL2 should be involved in the ECM formation of RASF. In addition, the LOXL2 knockdown reduced proliferation and invasion of RASF in EdU incorporation and Matrigel invasion assays. Finally, administration of β-aminopropionitrile, an inhibitor of the LOX family enzymes, ameliorated collagen-induced arthritis of mice. Our findings revealed that LOXL2 should be involved in the ECM formation and the activation of RASF as a therapeutic target of RA.

S7-1

Medical partnership of clinical practice for rheumatoid arthritis: from University Hospital's viewpoint

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Conflict of interest: Yes

Corresponding rapid progress of elucidation of pathophysiological mechanism for rheumatoid arthritis (RA), RA treatment including methotrexate (MTX) and biologics has been changed. Alteration of consciousness and action of the lodgment institutions for research and education are prime tasks. Because Nagasaki that has isolated islands lacks sufficient rheumatologists, we started a public program for citizens and itinerate every 6 months. The program has lectures and question-and-answer session, in which we commentate individually. A medical partnership arose from uncertainty for great decrease of the rheumatologists in University hospital and reginal hospitals as of introduction of novel trainee doctors system. Since basic research was subject to criticism in local University department under the problems of human resources securement, increasing concerns for continuation of basic research activity most supported the implementation for the medical coalition. Consequently, we launched this partnership before a task force of RA and Allergy in the Ministry of Health, Labour and Welfare disclosed a coalition between primary care doctors and lodgment hospitals. After we sent prospectus to

facilities, we created of available medicines list and shared the information in our institution. After initial treatment was performed in University and achievement of low disease activity or remission was confirmed, we started the coalition. The fundamental principles of the partnership are double medical care with semiannual meetings with doctors of coalition facilities, in which mini-lectures and journal club are performed. Over 150 patients treated with MTX or biologics were in this partnership with 40 facilities over 5 years. A part of facilities utilize 'Ajisai net' that is a kind of cloud service system for medical data sharing. In 5 years, maintenance of DAS remission was observed without major adverse events, leading formulation of effective medical coalition system.

S7-2

From the situation of a medical practitioner (using Ajisai network)

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Conflict of interest: None

Although MTX and biological agents brought a marked effect in treatment of rheumatoid arthritis (RA), the use of them was limited to specialized institutions because of adverse events and complexity at the introduction. The department of immunology and rheumatology of Nagasaki university hospital started regular meetings for coalition between hospital and clinic to construct recycling-oriented local medical service system for treating RA patients in Nagasaki area in 2011. Clinics which specialized in general surgery as well as internal medicine were targeted, if they agreed. They are supported by the university hospital whenever adverse events occur. My surgery clinic also participated from the beginning and continued RA treatment after introduction of MTX and biological agents in reverse introduction system. At that time, Ajisai network (A-net) that was highly valued as the leading regional medical ICT network using VPN technology was already operated in Nagasaki city. My clinic using it registered all of RA patients. I could get almost all of electric medical records of the university hospital instantly and accurately. In this symposium I demonstrate the usefulness of A-net in RA coalition, presenting the cases. As hospital conclusion type medical care is changing to local conclusion type medical care, the reverse introductions in diseases such as RA that requires high specialty will also increase. Then the main theme of this meeting, "collaboration", becomes very important. Recently regional medical pathways are operated in several diseases, and A-net is also expected to be applied to electronic regional medical pathway for RA. Each participant could get a merit, that is, congestions of outpatients in the university hospital are relieved, patients could continue safe and secure care at clinics nearby, and clinics benefit of education and learning with this coalition. I think that we should continue the face-to-face meeting to keep good relationships hereafter.

S7-3

Hospital and clinic cooperation of the Akita Orthopedic Group on Rheumatoid Arthritis: from the standpoint of a local core hospital

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Conflict of interest: None

[Background] With advances in drug therapy, patients diagnosed and treated in the early stage of rheumatoid arthritis (RA) have shown remission. However, patients with unstable pathological conditions have difficulty repeatedly visiting distant RA hospitals and hence may receive insufficient treatment. To overcome these, we established the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) in 2010. AORA includes Department of Orthopedic Surgery of Akita University and its affiliated medical facilities (29 sites and 35 physicians in total). All the hospitals have a history of prescribing biologics. Board-certified rheumatism specialists playing a role as primary care physicians prevent patients from crowding the core hospital, and enable the patients to receive treatment at nearby medical institutions. We accumulated patient data and compared treatments provided by AORA members every year. [Objectives] We aimed to evaluate treatments received by patients at hospitals and clinics by using the AORA registry. [Subjects and methods] In all, 1665, 1843, 1987, and 2021 patients were registered in the AORA registry in 2012, 2013, 2014, and 2015, respectively. Patients were classified into hospital and clinic groups, and their profiles were compared. Treatment results were evaluated using the 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) and clinical disease activity index (CDAI). [Results] Age or disease period was not significantly different between groups. In all, 58% patients received treatment at hospitals, and 49%, 39%, and 23% of the overall population, hospital group, and clinic group received MTX. In 2015, the DAS28ESRs were 2.88, 2.82, and 2.90, and the CDAIs were 6.8, 6.3, and 6.5 in the patient groups, respectively, with no significant differences in both parameters.

S7-4

The Rheumatism Network in Japan

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Conflict of interest: None

With the introduction of biologics, the treatment options and outcomes for patients with rheumatoid arthritis (RA) have improved. The standard of care for RA has been well established by all organization of rheumatology. As the medical condition differs among cases, management requires caring for individual patient's needs. As treatments for RA improve, cooperation is needed among clinics and hospitals. There are too few rheumatologists to adequately care for RA patients in need of rheumatic disease expertise. When severe adverse effects would be occurred on the patients treated by biologics, they should be treated by the specialist who could treat them. The various medical staff, including doctors, nurses, physical therapists, occupational therapists, social workers, and other professionals, should work cooperatively to treat patients. The multidisciplinary team approach is necessary for management of RA patients. To be improved the treatment of RA, many organizations of the rheumatism network have been set up in many areas in Japan. Identifying common targets in the network may enhance collaboration. It is important that rheumatic disease specialists work more closely with primary care physicians to treat RA by using a team approach. The importance of clear role definition and communication between collaborators is emphasized. If such approaches in the Rheumatism Network are found to be effectives, RA management may be improved substantially.

S7-5

Construction of medical cooperation for rheumatoid arthritis and collagen vascular diseases in dense populated urban area

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Conflict of interest: None

[Introduction] Biological agents (BA) give a lot of benefits to RA

patients. On the other hand, as it has been reported, high-risk patients (HR), such as fulminant hepatitis (FH) and interstitial pneumonia (IP) have been increasing. It must be required to take immediate action and accurate treatment to those HR. Therefore, we established the High-risk Rheumatic arthritis and Colla-gen disease Network Center (HRRCN) in north Tokyo district in November 2011. **[Objective]** From HRRCN activities with our experiences, we evaluated whether it can be the practical mo-del of urban medical cooperation for RA. **[Results]** Initially 35 facilities with 38 physicians are registered in 2011, and now it is 44 with 65 in 2015. Nihon Univ. Itabashi Hosp. was the only HRRCN base hospital (BH) in 2011, and to expand the capacity of patient referrals and acceptances,added Teikyo Univ. Hosp. in 2012. We organized lectures and case conferences 3 times a year for not only physicians but for nurses and pharmacists to engage their cooperation. The numbers of the patient referrals to BH have been increasing as 7 cases in 2011, 14 cases in 2012, 15 cases in 2013, 42 cases in 2014, 26 cases in 2015, which consisted of hepatitis (2011: 72%, 2012: 43%, 2013: 13%, 2014: 5%, 2015: 0%), respiratory diseases (14%, 7%, 7%, 10%, 15%), systemic management (14%, 7%, 7%, 5%, 8%). **[Discussions**Developing knowledges and skills of clinical treatment and risk management through the lectures and case conferences are very important in order to strengthen the function of HRRCN. And these educational activities can be considered to contribute the decreasing trend of hepatitis and systemic management. To accept the HR immediately, there should need at least 2 BHs with high levels of mutual cooperatio. **[Conclusion]** HRRCN are fully functional to the RA treatment and HR. It is believed to be a model of medical cooperation in dense populated urban area.

S7-6

Merits and demerits of Hospital - clinic cooperation from practitioner's point of view

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Conflict of interest: None

There are some great advantages of medical cooperation in the field of rheumatology for practitioners. 1) Practitioners can seek advice from specialists when they determine diagnosis and treatment policy. This also appeals the close relationship between the hospital and clinic to patients. 2) Practitioners can learn state-of-the-art medical technology when they treat patients with specialists. This is a great opportunity for practitioners because new drugs, such as biologics and Jak inhibitors, appear one after another in this field. 3) Practitioners can send their patients to cooperative hospital when patients need hospital care. This is very important because rheumatic patients often have a number of complications. Cooperation between hospital and clinic has a number of medical merits but also has a serious managerial demerit. The problem is an increase of average cost per receipt of clinic. In usual medical cooperation, specialists in hospital perform costly treatment and scrutiny using advanced medical equipment. Practitioners perform routine outpatient care. In this case, the cost at hospitals becomes expensive. However it does not push up the cost at clinic. In rheumatology, specialists in the hospital introduce biologics to RA patients. Then they send the patients to clinic. Practitioners administer costly biologics to the patients in the daily practice. This system presses down on the cost at hospitals and pushes up the cost at clinic. When average cost per receipt is expensive, receipts are submitted to intensive investigation. In addition, practitioners regularly become to receive tutoring by local bureau of Health and Welfare. These are physical and mental burden for practitioners. High average cost per receipt will be disincentive of Hospital - clinic cooperation. However, specialists in hospitals are unfamiliar with insurance billing. I would like to pose problem of costly receipt as the first step for problem solving.

S8-1

Importance of X-ray imaging and treatment choice guided by biomarker evaluation after remission induction in RA

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Conflict of interest: Yes

Primary target in the T2T strategy is to induce sustained clinical remission that leads to prevent structural changes in joints and to minimize functional disability. Thus, evaluation of joint destruction is the most important outcome in RA treatment. X-ray is a conventional imaging method utilized for various bone and joint diseases. In RA, importance of X-ray imaging has been recognized as a useful tool for diagnosis as well as evaluation of therapeutic effect, since standardized scoring methods including van der Heijde's modified total Sharp score (vdH-mTSS) and Genant's modified total Sharp score have clearly revealed effect of biological DMARDs on joint destruction especially in several randomized clinical trials. Indeed, X-ray is not suitable for evaluating disease activity of the moment when comparing with ultrasonography (US) or MRI, since it requires time to develop a newly detectable radiographic change. However, X-ray is the first choice for regular structural evaluation in RA due to its benefits of economy, convenience, and ease for repetitive performance. Meanwhile, it has been reported that inhibition of joint destruction is not possible in a part of RA patients, even if they achieved and sustained in clinical remission defined by composite measures including DAS28. Active synovitis could be identified by US or MRI in patients in remission. Thus, clinical remission is required but insufficient for complete inhibition of joint destruction. When making a decision whether to continue or taper drugs in patients in remission, it is important to confirm no radiographic progression during the treatment for longitudinal outcome. Several biomarkers may help predicting or reflecting joint destruction, including MMP-3 for damage on cartilage, or ACPA/RF for identifying population at high risk. MBDA score may reflect biologically "true" activity. Combining X-ray with biomarkers may contribute to choose appropriate treatment in RA patients in clinical remission.

S8-2

Significance of musculoskeletal ultrasound in reduction and discontinuation of treatment after achieving clinical remission

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Conflict of interest: None

In late years, clinical remission has been the realistic goal by progress of the treatment including biological DMARDs (bDMARDs) in patients with rheumatoid arthritis (RA). Furthermore, the evidence regarding reduction or discontinuation of bDMARDs therapy after achieving clinical remission has been established, and the guidelines for the management of RA suggests reduction or discontinuation of bDMARDs therapy may be considered. However, a rate of remission continuation after reduction or discontinuation is not so high. It revealed that residual synovitis was frequently present in patients in clinical remission by the spread of musculoskeletal ultrasound (US). It was reported that residual synovitis, particularly power Doppler (PD) positive synovitis, was a risk of joint destruction progress and relapse. In our previous study, a rate of residual synovitis was low in patients treated with bDMARDs. Can US predict relapse after reduction or discontinuation of bDMARDs? Iwamoto et al. showed that patients with more than 3 of PD scores of 40 joints at discontinuation of bDMARDs was more likely to relapse within following six months. Naredo et al. showed that high DAS28 and that presence of PD positive synovitis at discontinuation were independent predictors of relapse. Therefore, if the discontinuation of bDMARDs was considered, low PD activity may be a requirement. We investigated the risk of relapse after discontinuation of bDMARDs within following 1 year in patients with maximum PD grade 1 or less. The non-relapse rate was 52.5%, which is relatively good results US-defined bone erosion was an independent predictor of relapse (OR 4.7). Marks et al. reported about reduction of TNF inhibitors in patients with clinical remission and US remission. The low DAS28 at TNF inhibitors initiation and RF negative was associated with remission maintenance.

S8-3

Evaluation of RA using whole-body MRI and treatment strategy after remission/LDA based on findings of conventional MRI

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Conflict of interest: Yes

Magnetic Resonance Imaging (MRI) has been established as a useful modality to evaluate synovitis, bone edema, and bone erosion in patients with rheumatoid arthritis (RA). We use whole-body MRI technique to validate effect of anti-rheumatic drugs. A total of consecutive 30 RA patients introduced biologics underwent contrast whole-body MRI before and one year after the initiation of TCZ. Hand joints and other joints (atlantoaxial, shoulder, hip, and knee joints) were evaluated according to RAMRIS and the modified RAMRIS, respectively. TCZ treatment led to improvement in whole-body synovitis score from baseline (mean ± S.D; 31.2 ± 14.6) to one year (23.2 ± 11.3), as well as in whole-body bone edema score from 11 [1-54] to 3 [0-43]. Erosion-score was improved in six patients. Whole-body synovitis score were identified as one of the poor prognostic factors for development of bone-erosion. ⊿RAMRIS synovitis score of hands did not correlate with ⊿synovitis score of other joints in whole-body MRI. Treatment strategy after remission is a new horizon but an emerging clinical issue. Especially, residual synovitis after remission still harbors blood flow and may contribute to continuous joint destruction. Here we evaluated hand X-ray, US and MRI for 24 weeks in 16 ex-active RA patients who achieved LDA. Among 116 joints positive for blood flow, 47 remained positive after 24 weeks. Positivity of the blood flow after achievement of LDA was related with structural damages ($P < 0.001$). Synovitis with osteitis before treatment positively predicted residual synovitis after achievement of LDA ($P<0.0001$). Conclusion: Imaging parameters before treatment, such as whole-body synovitis score /synovitis with bone edema evaluated by US/hand MRI may predict structural changes of the joints. Interaction between synovitis and bone lesion might be a sign of resistance to treatment.

S8-4

Assessing joint destruction in the knees of patients with rheumatoid arthritis by using a semi-automated software for magnetic resonance imaging

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Conflict of interest: None

Objective: To evaluate the prevention of knee joint destruction and clinical efficacy of methotrexate (MTX) plus etanercept (ETN) compared with MTX monotherapy in patients with rheumatoid arthritis (RA) by using semi-automated software for magnetic resonance imaging (MRI) scan analysis. Methods: This study enrolled patients with active moderate to severe RA, who displayed inadequate response to oral MTX at screening. Patients were assigned to receive either MTX plus ETN or MTX monotherapy (≥ 10 mg/week). The primary endpoint was the quantitative knee cartilage volume using our developed software for MRI scan analysis. Results: A total of 18 female patients were enrolled in this study and allocated to the MTX + ETN group (n = 9) or the MTX monotherapy group (n = 9). At 52 weeks, the quantitative knee cartilage volume was significantly reduced compared with baseline in both the groups (MTX plus ETN group: 2.3 ± 2.3 cm^3; MTX monotherapy group: 2.4 ± 1.6 cm^3); however, the difference was not significant. Furthermore, we conducted subgroup analyses considering the upper quartile (n = 4) of the knee synovial membrane volume at baseline vs. the lower-three quartiles (n = 14). At 52 weeks, the knee cartilage loss was significantly higher in patients in the upper quartile (-5.0 ± 2.6 cm^3 vs. -1.5 ± 0.7 cm^3 in the lower-three quartiles, $p = 0.008$). Conclusion: The semi-automated software for MRI scan analysis can reveal useful and potentially clinically important information about the characteristics of knee joint destruction in patients with RA.

S8-5

Mode of action of biological agents revealed by advanced imaging technology

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Conflict of interest: Yes

Recent development of diverse biological agents has been revolutionizing the clinical practices for treating RA. Nevertheless the actual modes of mechanism have been still elusive how each biologics act on specific target cell types and exert their respectively characteristic pharmacological effects. The presenter has so far originally established the system for visualizing inside of living bone tissues and joints by exploiting intravital two-photon microscopy, and elucidated cellular mechanisms on bone destruction by osteoclasts. Here I introduce the recent data showing the practical mode of actions of different biologics on inflammatory bone destruction in vivo, and, based on these fundamental data, discuss the future perspective on biological treatment of RA.

S9-1

Relationship between HTLV-I infection and Sjögren's syndrome

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Conflict of interest: None

Disease contribution rate of HTLV-I against Sjögren's syndrome (SS) is high as 17.6% with odds ratio 3.1. Complication rate of SS toward HTLV-I-associated myelopathy (HAM) is also high. Because there is no evidence to show direct effect of HTLV-I infection toward SS although infiltration of HTLV-I-infected lymphocytes in labial salivary glands (LSGs) in HTLV-I asymptomatic carrier, we examined infection of HTLV-I toward salivary glands epithelial cells (SGECs) and expression of relevant molecules in primary SS after evaluation of ectopic germinal center formation in LSGs. American-European Consensus Group classification criteria proven clinical reevaluation as a historical cohort showed 26.5% of SS was HTLV-I-seropositive and 38.5% of HAM patients complicated SS with low frequency of autoantibodies. HAM patients complicated SS also lacked both ectopic GC and CXCL13/follicular dendritic cells. HTLV-I-related proteins were detected at 72-96 co-culture. HTLV-I-related proteins and cytokeratin-double positive SGECs were 7.8 ± 1.3 %. HTLV-I proviral DNA was detected at 48 hour co-culture by *in situ* PCR by using HTLV-I pX region primers. ICAM-1, RANTES or interferon gamma-induced protein 10kDa (IP-10/CXCL10) were observed in supernatant co-cultured with HCT-5 by antibody array and ELISA and these molecules were detected on HTLV-I-infected SGECs. However, no increase of these molecules was observed in supernatant co-cultured with Jurkat. Pro-apoptotic molecules such as cytochrome C and anti-apoptotic molecules including HO-2, HSP-27 were detected in SGEC lysate co-cultured with HCT-5, although no apoptosis determined by TUNEL staining was observed. SS is apt to complicate HAM with low frequency of autoantibodies that is partly explained by low frequency of ectopic GC. Although HTLV-I-infected CD4+T cells are main cause of inflammation, HTLV-I-infected SGECs with up-regulation of associated molecules were partly related to pathogenesis of HTLV-I-associated SS.

S9-2

Medical care for HTLV-1 positive patients with rheumatoid arthritis

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Conflict of interest: None

Human T-lymphotropic virus type 1 (HTLV-1) is a causative agent of adult T-cell leukemia (ATL). HTLV-1 infection has been also considered

to be related to chronic inflammatory diseases. It is still determining whether HTLV-1 infection directly contributes to the development of rheumatoid arthritis (RA). More than one million HTLV-1 positive people is estimated to exist in Japan; therefore, whether the DMARDs treatment is as safe and effective in HTLV-1 positive RA patients as in HTLV-1 negative patients is an important clinical question (CQ). The research to clarify these CQs has been performed. Several cases of ATL among RA patients treated with biologics were reported; however, there has been no evidence that DMARDs (biologics) treatment increases the risk of ATL thus far. We reported that HTLV-1 positive patients with RA had greater resistance to anti-TNF treatment than HTLV-1 negative patients; however, a larger scale study is necessary to give a conclusive answer. The inflammatory response of RA synovial cells was shown to be enhanced by the co-culture with HTLV-1 positive cells. We did a nation-wide questionnaire survey to the rheumatologists and received requests for more information about HTLV-1 infection and medical care for RA. Therefore, an instruction for the rheumatologists to see the HTLV-1 positive RA patients in daily clinical practice has been made, supported by Japanese Ministry of Health, Labour and Welfare and AMED. It is necessary to continue the research about HTLV-1 positive patients with RA and to improve this instruction.

S9-3

Rheumatic diseases and nontuberculous mycobacteriosis

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Conflict of interest: Yes

While wide distribution of biologics for many difficult inflammatory diseases including rheumatoid arthritis has dramatically improved their clinical courses, an accumulating data revealed their complications including infections. Among them infectious diseases due to nontuberculous mycobacteria (NTM) have recently gathered much attention since the lack of availability of effective treatment except *M.kansasii*. On the basis of dramatic report from USA by Winthrop, et al. in 2009 showing extremely high mortality among patients complicated with NTM diseases under anti-TNFa therapy, NTM diseases have originally been contraindication for biologics use, especially anti-TNFa agents. In Japan however, an analysis of accumulated clinical RA cases using biologics under coexistence with NTM diseases have demonstrated their favorable clinical course. Consequently in 2014, it was allowed to use biologics for RA patients with NTM diseases under careful evaluation and follow-up. The other important aspect of NTM diseases is that RA itself often presents pulmonary manifestations which are often indistinguishable from NTM lung disease. Recent epidemiological investigation by research group of Japanese Ministry of Health, Labor and Welfare, using domestic diagnostic criteria on the basis of ATS/IDSA (American Thoracic Society / Infectious Diseases Society of America) statement in 2007, has demonstrated an obvious increase of prevalence of pulmonary infectious diseases due to NTM species (14.7/100,000), predominantly *M.avium* complex, exceeding that of culture confirmed tuberculosis. Taken together it is important to up-to-date current information regarding management of NTM diseases and rheumatic diseases with NTM from all aspects including epidemiology, diagnosis and treatment. It is also pursued to develop optimal use of biologics for RA patients with NTM diseases.

S9-4

Varicella and singles in rheumatic diseases

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Conflict of interest: None

Varicella-zoster virus (VZV) is a DNA virus belonging to alpha-herpesviridae and causes varicella at the primary infection. VZV vaccine is safe and effective in healthy children and currently included in the national regular vaccination program of Japan. Primary VZV infection causes severe and often fatal varicella in immunocompromised hosts particularly under the treatment with corticosteroid (CS) or immunosuppressants (IS). On the other hand, infection of vaccine-strain virus is a matter of concern in the immunocompromised hosts. Accordingly, Pediatric Rheumatology Association of Japan recommends;(1) any live-attenuated vaccine should be withheld in patients receiving high-dose CS, high-dose IS or biologics;(2) VZV vaccine should be considered in sensitive patients ideally 3 weeks or longer before the commencement of IS, CS, or biologics;(3) live-attenuated vaccines may be considered in patients receiving low-dose CS and/or IS, if indicated, as a clinical trial under the approval by Institutional Review Board. Following the primary infection, VZV latently infects in the dorsal root ganglia and causes singles in immunocompromised status such as aging and under immunosuppressive therapy, which often results in postherpetic neuralgia. Because exposure to the virus such as contact with varicella patients boost VZV-specific immunity in latently infected individuals, widespread use of VZV vaccine in children may increase the risk of singles in adults. Singles vaccine is recommended in persons over 60-year-old including patients with rheumatic diseases receiving low-dose CS and/or IS in the US. However, singles vaccine is, to date, not available in Japan and often substituted by off-label use of VZV vaccine. Furthermore, inoculation of singles vaccine before the use of TNF-blockers is still controversial. Nation-wide study is necessary to establish vaccine guideline suitable for Japanese patients with rheumatic diseases.

S9-5

Paramyxovirus as the cause of Paget's bone disease

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Conflict of interest: None

Paget's disease (PD) is characterized by abnormal osteoclasts (OCL) that secrete high IL-6 levels and induce exuberant bone formation. OCLs are increased in number and size and express a "pagetic phenotype" that distinguishes them from normal OCLs. OCL precursors from many PD patients express measles virus nucleocapsid protein (MVNP) and are hypersensitive to 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3). The increased 1,25-(OH)2D3 sensitivity is mediated by transcription initiation factor TFIID subunit 12 (TAF12), a co-activator of vitamin D receptor, mediated transcription, TAF12 is present at much higher levels in MVNP-expressing OCL precursors than normals. Genetic and environmental factors contribute to the pathogenesis of PD. The most frequent mutations linked to PD are in the SQSTM1/p62 gene, in particular p62P392L, which is found in 30% of hereditary PD patients and 10% of sporadic cases, but mutations like p62P392L appear insufficient to induce PD. Because MVNP and the p62P392L mutation are implicated in PD, marrows from 12 PD patients harboring p62P392L and eight normals were tested for MVNP expression and pagetic OCL formation. Eight out of twelve patients expressed MVNP and formed pagetic OCL in vitro, which were inhibited by antisense-MVNP. Four out of twelve patients lacked MVNP and formed normal OCL that were hyper-responsive to RANKL but unaffected by antisense-MVNP. Similarly, mice expressing only p62P394L formed normal OCL, while mice expressing MVNP in OCL, with or without p62P394L, developed pagetic OCL and expressed high IL-6 levels dependent on p38MAPK activation. IL-6 deficiency in MVNP mice abrogated pagetic OCL development in vitro. These results suggest that p62P392L and IL-6 induction by MVNP play key roles in PD.

S9-6

EBV infection and rheumatic disease

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Conflict of interest: Yes

Epstein-Barr virus (EBV) infects human B lymphocyte and approximately 100 % of adult man is inapparent infection. But it's known that EBV reactivation as s result of the immunosuppressed causes a number of autoimmune disease. There was a significant higher of anti EBV antibody in patients with systemic lupus erythematosus (SLE) compared to

controls and patients with high titer of anti nucleoid antibody (ANA) is more high of EBV-VCA IgG, EA IgG. EBV infection is associated with pathogenesis of SLE. At Sjögren Syndrome (SS), EBV antigen and gene are detected by lymphoid structures in the salivary glands and infiltrated B lymphocyte and EBV infection appears to contribute to local growth and differentiation of disease-specific autoreactive B cells. At rheumatoid arthritis (RA), there are two problems associated with EBV incection. EBV reactivation may be involved in the onset of RA. We detected EBER and LMP-1 in the synovium of RA patients and cloned the signaling lymphocytic-activation molecule (SLAM) associated protein (SAP) gene, which activates CTL for EBV. One reason for reduced protection against EBV in RA patients is abnormal SAP function. Expression of LMP-1 on synovial cells suppresses SAP, activates EBV, and induces synovitis in RA patients. Furthermore, using humanized mice, we show that this mice causes erosive arthritis infected to EBV. EBV reactivation and persistent infection cause MTX-associated lymphoproliferative disorder (MTX-LPD), which not only includes immunopathy associated with autoimmune diseases such as RA but also LPD due to EBV reactivation and persistent infection subsequent to immunosuppression by MTX. One more attention, EBV-associated LPD is observed in patients treated tofacitinib, which was anti rheumatic drug of JAK inhibitor than cyclosporine. EBV cause pathogensis of rheumatic disease and reactivation of EBV and changes in pathology should be monitored carefully during immunosuppressive therapy.

S10-1

Timing of hand surgery in RA

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Conflict of interest: None

Rheumatoid arthritis (RA) commonly occurs in the wrists or the phalangeal joints, with progressive symptoms. As the deformity and bone destruction in the upper extremities progresses, there is impairment of activities of daily living (ADL), so it is important to administer suitable treatment at the appropriate time. However, a wide variety of tissues are impaired, such as bone, cartilage, ligaments, tendons, articular capsule, and skin. Functional activities are also impaired, affecting pinching and grasping movements, writing and face washing. This has resulted in mixed outcomes of surgical treatment of RA affecting the upper extremities. There have been recent advancements in early diagnosis and pharmaceutical therapy, and through the efforts of hand surgeons, there has been a gradual improvement in surgical outcomes when treating RA of the hand. There have also been major qualitative and quantitative changes in the surgical treatment of RA. Changes include the surgical indication and procedure, and the number of cases per surgical site. Arthroplasty of the lower limbs, such as total hip arthroplasty, is decreasing, but surgery of the upper limbs is increasing. These procedures have made it possible to control this disease state, and are associated with patients' increased functional awareness and motivation for treatment. Despite diagnosis and treatment being performed in accordance with guidelines, the deformities of the upper extremities, and particularly the hand, as well as the functional impairment, are seen to worsen over time. Thus, treatment should be administered as early as possible, with the objective of functional reconstruction where possible while preventing worsening of upper limb function. To perform surgical treatment at an early stage, surgeons require thorough knowledge of the upper limb anatomical structure and deformities, and how to select the appropriate surgical technique, depending on the disability.

S10-2

Problem of adjacent joint in the upper limb surgery

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Conflict of interest: None

In recent year, with progress of the RA medical treatment, a control of the disease activity improves, and activities of daily living (ADL) and the quality of life (QOL) that the patients hope become higher. The surgical treatment for the destructive joint is effective in the improvement of ADL and QOL. In case with the multiple destruction of lower limb joints, it is principal to perform surgery earlier for central joints such as hip and knee joints. Therefore, the indication of surgery is relatively clear in lower limb joints compared with upper limb. Whereas, in the case with the multiple destruction of upper limb, surgical indication and timing are unclear because the surgical procedures are complicated. Souter conducted the systematic consideration about the timing of the upper limb surgery in RA about 20 years ago, there is still not a major change in the basic way of thinking. We orthopaedic surgeon pay more attention to not only the improvement of individual joint functions, but also an adjacent articular condition, and it is necessary to strive the surgical cure that was targeted improvements of the entire upper extremity. I will consider about the upper limb surgery in RA in consideration of the adjacent joint disorder based on our cases.

S10-3

Timing of total hip/knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are common procedures for treating damaged large joints in patients with rheumatoid arthritis (RA). The incidence of THA and TKA tends to decrease probably due to more aggressive drug therapy. However, surgical treatment, such as THA and TKA, should be indispensable for treatment of RA even in the biologic era. Our cohort study showed that the cumulative incidence of total joint arthroplasty in patients treated with TNF inhibitors was approximately 10% at 5 years after initiation of agent. Additionally, multivariate analysis revealed that concomitant MTX independently predicted total joint arthroplasty (HR: 0.36, 95% CI: 0.20 to 0.65). In other words, the patients, who are discourage from receiving sufficient drug therapy, are more likely to require total joint arthroplasty due to the progression of joint destruction. Japan College of Rheumatology recommends THA and TKA to the patients with advanced joint destruction. However, the surgical indication and the timing of surgery have not been established. Therefore, we performed a multicenter prospective cohort study to establish the concrete index of timing of THA and TKA in the patients with RA. The study showed the following results: 1) range of motion (ROM) and index of activity speed [Time Up and Go test (TUG)] were significantly associated with HAQ-DI, 2) preoperative ROM had a significant effect on postoperative ROM, 3) preoperative ROM had a significant effect on postoperative TUG. Accordingly, preoperative ROM and TUG could be a concrete index that decides the timing of leg surgery. Today, orthopedic surgeons need to perform the surgeries that offer higher patient satisfaction. It is important to predict postoperative physical function using a concrete index and share information with patients before surgery.

S10-4

Foot and ankle surgery against RA cases by correcting the displacement of loading axis

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Conflict of interest: None

Patients with rheumatoid arthritis (RA) often suffer from destructive

changes of the ankle joint and valgus hindfoot simultaneously. For the treatment of end-stage osteoarthritis (OA), low tibial osteotomy (LTO) is widely performed as a novel procedure. In this procedure, corrective osteotomy is performed at the distal tibia to correct the displacement of weight-bearing line. Then, it is plausible to understand that correction even in hindfoot could also improve the displacement of weight-bearing line passing the ankle joint. Thus, first, we selected hindfoot correction to preserve the ankle joint mobility, and then ankle pain has been observed. In recent years, we often experienced the cases which could be escaped from the additional ankle joint surgery after subtalar realignment. At the same time, we had also experienced the cases that hallux valgus (HV) deformity was improved after hindfoot realignment. On the other hand, there were cases with the progression of valgus hindfoot showing the recurrence of HV deformity after forefoot surgery. Taken together, correcting of the displacement of the loading axis not only between the hip joint and hindfoot, but also between hindfoot and forefoot is very important against comprehensive RA foot deformity.

S10-5

Perioperative managements for deep vein thrombosis and pulmonary thromboembolism in rheumatoid arthritis patients

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Conflict of interest: None

Treatment of rheumatoid arthritis (RA) progressed dramatically with the appearance of biological DMARDs. Operations on the hip or knee joints have decreased. However, total knee arthroplasty (TKA), total hip arthroplasty are defined to carry a high risk of pulmonary thromboembolism (PE) or deep vein thrombosis (DVT). Many reports have also found that patients with RA are exposed to a high risk of venous thromboembolism (VTE). More than half of patients who undergo TKA are said to develop DVT, with most remaining asymptomatic. To avoid fatal PE, we must treat DVT because once PE arises due to DVT, treatment is difficult. From the analysis of symptomatic VTE, according to the latest American college of chest physicians (ACCP) guidelines, anticoagulant therapy with antigoagulant drugs or aspirin are recommended equally (Grade 1B), and in cases with a high risk of bleeding, use of intermittent pneumatic compression or avoidance of anticoagulant drug are recommended (Grade 2C). Many reports have described ultrasonography as useful in checking for DVT, but have also reported that this method is more useful for the proximal type than for the distal type. Phlebography of the lower extremity is invasive if contrast agent is to be used. As identification of DVT using a blood test would be simpler, measurement of D-dimer levels is common. A negative result can be used to exclude the presence of thrombus, but abnormal D-dimer levels do not always indicate the existence of thrombus. On the other hand, soluble fibrin monomer complex (SFMC) levels have been reported as a new DVT marker and reflect the hypercoagulable state under which thrombin forms in the blood. No methods are available to prevent or predict DVT completely. The merits and risks of anti-coagulation therapy need to be taken into consideration on a case-by-case basis. Once PE develops, diagnosis needs to be made as soon as possible, and patients should be treated using an appropriate multidisciplinary approach.

S10-6

Management of Surgical Site Infection in Rheumatoid Arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a joint destructive disorder that affects the entire body and leads to functional disability. Recent advances in medication such as biological DMARD (bDMARD) have reduced the disease activity and joint destruction in most patients with RA. However, the need for surgical treatment has not declined despite the improvements in medications. RA has a high risk of operative complications, especially surgical site infection (SSI). This complication can be devastating for patients and may require repeated surgical intervention. Some reports have identified the risk factors for SSI such as older age, longer duration of disease, and use of steroid or bDMARD. However, the definition of SSI was not consistent among reports and the percentage of patients who experience deep SSI is not high and the most published results are from retrospective studies. There remains controversy about the specific risk factors for SSI in patients with RA.We conducted a prospective observational study in an RA cohort to investigate the ratio of SSI and to identify the independent risk factors for SSI in patients with RA. A total of 530 orthopedic surgeries from 2004 to 2012 were analyzed. The multivariate analysis models showed that having prosthetic replacement surgery, the presence of diabetes mellitus, and the preoperative use of a bDMARD were independent risk factors for SSI. I would like to discuss it whether DMARD is a risk factor of SSI, perioperative discontinuation of DMARD, prophylaxis, and treatment of SSI in this simposium.

S11-1

Hematological disorders, especially lymphoproliferative disorders associated with Sjogren's syndrome

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Conflict of interest: None

Although Sjogren's syndrome (SjS) is an organ-specific autoimmune disorder often associate with xerophthalmia and xerostomia, as a generalized autoimmune disease it manifests as various symptoms in general organs. Moreover, various blood count abnormalities, including anemia, leukocytopenia and thrombocytopenia, leukemia and myelodysplastic syndrome have been reported in patients with SjS. In patients with SjS, the incidence of lymphoma is higher than in patients with other collagen or autoimmune diseases. In these patients, polyclonal B-cell proliferation progressed to oligo- and monoclonal B-cell expansions, then lymphomas developed. Histological findings of salivary glands in SjS are called lymphoepithelial sialadenitis including lymphoepithelial lesion which is a histological finding of epithelial destruction due to lymphocytic infiltration, monocytoid B-cells and marginal zone B-cells. Although T-cell infiltration is dominant at early stage of lesion in SjS, at later stage B-cell is dominant, then some cells acquire monoclonality causing MALT lymphoma. A germinal center-like structure in labial salivary gland biopsy might be a prognostic factor of lymphomagenesis in patients with SjS. Patients with SjS have a high incidence of complication with not only MALT lymphoma, but other lymphomas. In our examination, MALT lymphoma in the salivary glands developed from oligo- to monoclonal expansion in labial salivary gland tissue. In contrast, clones different from the salivary gland clone, expanded in patients with extra-glandular lymphoma, therefore, clonal selection may have been caused by sustained generalized B-cell expansion. Although the standard treatment of MALT lymphoma is radiotherapy, xerostomia in patients with lymphoma associated with SjS might be worsened by radiation, thus chemotherapy including rituximab should be considered.

S11-2

Renal involvement in primary Sjogren syndrome

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Conflict of interest: None

The kidney is one of the major target organs in primary Sjogren's syndrome (pSS). EULAR Sjogren's Syndrome Disease Activity Index regards kidney involvement as being as important as that of muscle, lung, and central and peripheral nerve with a high weighting factor. The most representative kidney lesion is tubulointerstitial nephritis (TIN), and its diverse clinical picture includes renal tubular acidosis (RTA), renal concentrating defects or diabetes insipidus, nephrocalcinosis, osteomalacia,

and Fanconi's syndrome. The frequency of kidney involvement is usually reported to be less than 10%, but it ranges from 0.3% to 33.5% according to factors such as differences in ethnicity. TIN is often accompanied by RTA. Most of RTA in pSS is distal type with hypercalciuria and hypokalemia and a morning urine pH > 5.5. Clinically, periodic paralysis due to hypokalemia is a representative feature. Plasma cell-rich TIN with patchy distribution is the most common histopathological finding. Sometimes tubulitis and tubular atrophy are seen in the advanced stage. One of the important differential diagnoses is IgG4-related TIN. These two diseases are differentiated based on differences in regional lesion distribution, characteristic fibrosis, and the results of IgG4-immunostaining. Glomerular lesions can occur in pSS. Membranoproliferative glomerulonephritis with cryoglobulinemia and membranous nephropathy are two major glomerular lesions. Rarely, cases with anti-neutrophil cytoplasmic antibody associated vasculitis have also been reported. In cases with glomerular lesions, a differential diagnosis with overlap of other autoimmune disease such as lupus nephritis is needed. The response to corticosteroid therapy for TIN is generally good with the initial dose of 30-60 mg/day of prednisolone, and the renal prognosis in not poor.

S11-3

Neurological manifestations in Sjögren's syndrome from the perspective of the neurologists

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Conflict of interest: Yes

Extraglandular manifestations of Sjögren's syndrome (SS)are due to involvement of virtually every organ including the musculoskeletal system, kidneys, lungs, and the central or peripheral nervous system. The prevalence of neurologic involvement in patients with SS remains unclear owing to conflicting results in the published series, with numbers ranging from 2% to over 60%. The diagnosis of SS with neurologic involvement is sometimes difficult, because the timing of neurological manifestation during the course of SS has also been debated. We are going to present an overview of the current state of neulorogical manifestations in SS from the viewpoint of clinical practice. Nervous system and immune network have a high order of complexity. SS is like other systemic autoimmune diseases, characterized by a large number of autoantigens and autoantibodies and infiltration of glandular tissue by predominantly lymphocytes. Although autoreactive T cells are involved in the pathogenesis of SS, the subject of this seminar is the humoral autoimmune response, especially autoantibodies and their target. Before the discovery of anti-aquaporin-4 (AQP4) antibody, SS was reported to have a variety of effects on the central nervous system, including myelopathy, encephalopathy and MS/NMO-like manifestations. Therefore, it remains to be elucidated whether SS myelitis is exclusively induced by anti-AQP4 antibodies and whether all brain lesions show atypical NMO-like features. Kondo et al. reported on two Japanese patients with SS, who also developed chronically progressive dysautonomia. They showed an elevated titer of ganglionic acetylcholine receptor (gAChR) antibodies. This case indicated that anti-gAChR antibodies are relevant to SS. Thus, the detection of autoantibodies associated with the gAChR, which mediates fast synaptic transmission in all peripheral ganglia in the peripheral nervous system, shows promise in the search for SS biomarkers.

S11-4

Muscular and articular manifestations of Sjögren's syndrome: Recent progress in management

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Conflict of interest: Yes

Muscular and articular involvements are common features among extra-glandular manifestations of Sjögren's syndrome (SS). Recent studies revealed that articular manifestations (AM), arthritis, and myositis were detected in 53%, 16%, and 3% of primary SS (pSS), respectively. We discuss the recent progress in 1) clinical features, 2) laboratory and imaging findings, 3) differential diagnosis, 4) deals in EULAR SS Disease Activity Index (ESSDAI), and 5) treatments for muscular and articular involvements of SS. 1) Arthritis was predominantly reported as symmetrical, and in PIP, MCP, and wrists joints. Muscular weakness and myalgia are common muscular symptoms. 2) Radiologically, arthritis of SS was commonly classified as non-erosive. Positivity for anti-CCP antibody in pSS was 7%, which associated with AM. A recent study showed that muscular biopsy confirmed myositis in 46% of examined pSS, in addition to elevated CK and abnormal electromyography and MRI. 3) Differential diagnosis of anti-CCP antibody positive pSS from RA with secondary SS (sSS), and pSS with definite myositis from polymyositis with sSS should be concerned. 4) For AM, synovitis in ≧6/28 joints is defined as high activity with 6 points. For muscular involvements, highly active myositis with weakness or elevated CK is defined as high activity with 18 points. 5) NSAID is effective for mild AM, however, steroid and DMARD (MTX and SASP) are used for active arthritis. Although hydroxychloroquine (HCQ) is frequently used in overseas, a recent RCT (JOQUER trial) did not confirm the effectiveness of HCQ. Among biologics, TNF inhibitors and rituximab have not been shown to be effective for AM in RCT. On the other hand, belimumab improved AM in the pilot study. Moreover, we showed effectiveness of abatacept for AM of sSS with RA in multicenter prospective trial (ROSE trial). Although steroid and immunosuppressant are effective for muscular involvements, IVIG and rituximab might be considered for intractable cases.

S11-5

Respiratory complications of Sjögren's syndrome

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Conflict of interest: Yes

Sjögren's syndrome (SS) is a chronic inflammatory disorder characterized by diminished lacrimal and salivary gland function associated with lymphocytic infiltration of exocrine glands. The pathogenesis of SS includes multiple genetic and nongenetic interacting factors. There is involvement of innate and adaptive immunity, as well as neuroendocrine and neuropathic processes on the pathogenesis of SS. In addition, infection of HTLV-I causes SS-like syndromes, but there are no convincing evidences for retroviruses itself as a causal agent in the pathogenesis of SS in Caucasian populations, and the role of retroviruses remains to be elucidated. In addition to causing dry eyes and dry mouth, SS can affect extraglandular organ systems including the lung. Respiratory complications of SS include airway mucosal disorders, a variety of interstitial lung diseases (ILDs), non-Hodgkin lymphomas, pleural thickening or effusion, and, rarely, thromboembolic disease or pulmonary hypertension. SS-associated ILD is most common in patients who have both glandular and extraglandular manifestations. The proportion of patients with SS who develop ILD is estimated to be 10-20%. The symptoms and signs of SS-associated ILD depend on the type and severity of lung parenchymal and lower airway involvements. The most common type of primary SS-associated ILD is nonspecific interstitial pneumonia (NSIP), followed by usual interstitial pneumonia (UIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP). High resolution computed tomography (HRCT) findings include bronchial wall thickening, bronchiectasis, centrilobular nodules, irregular interlobular thickening, ground-glass attenuation, subpleural honeycombing, thin-walled cysts, and branching linear shadow. In this presentation, I will talk about the clinical summary of respiratory complications of SS, including the results of our retrospective analyzes of the characteristics of HRCT in SS patients diagnosed by lip biopsy.

S11-6

Sjögren's Syndrome and Digestive System involvements

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Conflict of interest: None

Sjögren's Syndrome (SS) is a chronic autoimmune disorder primarily characterized by lymphocyte-mediated-destruction of the exocrine glands, resulting in dry eye and dry mouth. The inflammatory process can affect any extraglandular organ. Therefore, in addition to the common dryness signs and symptoms, systemic manifestations may occur. ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index) is a clinical index that measures disease activity in SS, and includes 12 domains (organ systems). However, digestive organs are not included in evaluation points of ESSDAI. Because the exocrine glands are disordered in SS, the digestive system, which has a great deal of exocrine glands, is vulnerable to injuries due to SS. In fact, many SS associated manifestations have been reported, and clinicians often encounter digestive symptoms and abnormalities in digestive system examinations in daily clinical practice for SS. SS associated digestive system involvements consist of various pathologies in every organ. However, precise pathologic analysis of these manifestation in SS has not been done sufficiently. Therefore, it is difficult to understand digestive system involvements in SS appropriately. This lecture will review digestive system manifestations in SS, such as gastrointestinal tract, liver, biliary duct and pancreas, with previous research reports. In SS associated digestive disorders, there are more research reports about involvements of liver, biliary duct and pancreas than those about gastrointestinal tract involvements. However, in practical clinic, digestive complaints of SS patients are gastrointestinal symptoms mainly. I will mention our investigation of gastrointestinal symptoms in SS patients. In addition, we previously reported that salivary epidermal growth factor (EGF), contribute to wound healing in oral cavity and gastrointestinal tract, decreased in SS. I will describe the association between digestive disorders and salivary EGF.

S12-1

AA amyloidosis in experimental aspects

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Conflict of interest: None

1. in vitro fibril formation In human AA amyloidosis, the amino terminal 2/3 portion of serum amyloid A (SAA) exist in the deposits. When partial SAA peptides are used, an amino terminal segment and a middle portion can make fibril, but a carboxyl terminus cannot. Culture experiment using human peripheral monocytes and rSAA isotype revealed that SAA1.3 generates fibrils more than other isotypes do, consistent with a genetic background of this disease. 2. Murine experimental amyloidosis (1) Time course of AA amyloidoisis: AA amyloidosis can be made in mouse by administrating inflammatory stimuli. When a single stimuli and AEF (Amyloid enhancing factor) are given, amyloid deposits appear in spleen at day 2, and then maturate up to day 30 even though SAA reach a normal level. Around day 30, the deposits almost disappears, consistent with the clinical observation that amyloid can be reduced by successful suppression of inflammatory activity. (2) Inhibition of onset: Anti-inflammatory regimes, which suppress SAA elevation, can inhibit AA amyloidosis. However, tacrolimus is effective too although it does not affect SAA levels, suggesting the contribution of factors other than high SAA to AA amyloidogenesis. (3) AEF: The extracts from amyloidotic organs can dramatically reduce the term for the amyloid depositions. Not only AEF works as a seed for the amyloid, but also it enhances the SAA response during amyloidogenesis. Animal experiments indicate that AEF is transmissible so that AA amyloidosis may be expanded in a small community. (3) Metabolic features of SAA: Mouse SAA1, which is a sole SAA isotype generating fibrils, is cleared from plasma faster than non-amyloidogenic isotype. Instability in plasma may be a feature common to amyloidogenic precursors. We revealed that human amyloidogenic SAA is dissociated from HDL, the plasma acceptor of SAA, more efficiently than other isotypes.

S12-2

Immune functions of serum amyloid A in inflammatory disorders

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Conflict of interest: None

Serum amyloid A (SAA) is a highly conserved, acute-phase protein synthesized predominantly by the liver. During acute inflammation, serum SAA levels may rise up to 1000-fold. The increase of SAA level was seen earlier than the other inflammatory markers, such as CRP, immediately after acute inflammation, and its significance was demonstrated as a more sensitive inflammatory marker. SAA has been considered to have a key role in the pathogenesis of amyloid A-type amyloidosis. Sustained high serum levels of SAA is necessary precondition for the development of AA amyloidosis, and tight control of SAA (<8mg/ml) prevents the occurrence of AA amyloidosis. SAA exhibits significant immunological activity by binding and activating cell-surface receptors, including Toll-like receptor (TLR) 2 and TLR4, formyl peptide receptor-like 1 (FPRL-1). We investigated whether it may also participate in the pathogenesis of chronic inflammatory diseases, including rheumatoid arthritis. SAA activated the inflammatory cells to secrete IL-6, therefore, SAA/IL-6 mediated positive feedback loop may perpetuate the inflammatory cascades. We focus on the recent findings implicating SAA in the regulation of in the inflammatory cascades, including inflammasome, and its effect on the inflammatory genes expressions and epigenetic modulation.

S12-3

Pathogenesis and risk factors of AA amyloidosis and coping strategy of gastrointestinal disorders in AA amyloidosis

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Conflict of interest: None

1. Pathogenesis and risk factors of AA amyloidosis (AAA): SAA, the precursor of AA protein, is highly amplified in the liver under the stimulation of inflammatory cytokine such as IL-6, TNFα. Continuance of longstanding high level of SAA is the most critical risk factor of the onset and the prognosis of AAA. The SAA gene products, SAA1 and SAA2 are both elevated with acute inflammation and are therefore named acute-phase SAA. More than 90% of the precursor proteins of AA protein are derived from SAA1. SAA1 has several allelic variants, in which the exon 3 polymorphism generates three common isoforms in the Japanese population. This polymorphism contributes to the susceptibility of the Japanese to RA-associated AAA; *SAA1.3* is a risk factor for AA amyloidosis, while *SAA1.1* acts as a defense. In animal model studies, elevated SAA was detected in ageing mice and organ extracts from aged mice had amyloid enhancing factor activity that accelerated experimental SAA production. We examined the contributions of ageing to the induction of AAA in RA in our large cohort and identified ageing as an independent risk factor for the formation of AAA complicating RA. Coping strategy of gastrointestinal (GI) disorders in AAA: When patients with rheumatic diseases show GI symptoms such as intractable diarrhea, abdominal fullness, anorexia and et al., we must strongly suspect the presence of AAA and should actively conduct GI biopsy. Massive deposits of AA protein on GI tissue causes impaired peristalsis, malabsorption, protein losing, hypoalbuminemia, nausea, vomiting and diarrhea. In cases of severe GI disorders such as intractable diarrhea and paralytic ileus, Intravenous hyperalimentation treatment and anti-IL-6 or anti-TNF or middle dose of corticosteroid therapy are favorable regimens because of rest of GI tract and the ability of strong suppression of SAA value. And case of GI perforation due to ischemic colitis needs life-saving operation.

S12-4

Coping with renal AA amyloidoisis

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Conflict of interest: None

The AA amyloidosis is found in approximately 5% of rheumatoid arthritis (RA). Amyloid A (AA) which is metabolites of serum amyloid A (SAA) is deposited in the gastrointestinal (GI) tract and the kidney. Renal amyloidosis causes proteinuria, and it leads to renal failure. The diagnosis is made by tissue biopsy such as GI, rectal, and renal biopsies. The diagnosis of the renal amyloidosis is made by renal biopsy, but the renal biopsy is highly associated with GI biopsy about amyloid deposition and often copes as renal amyloidosis when amyloid is detected by GI biopsy. It had been focused on therapy with biologics as potential agents for the treatment of AA amyloidosis in RA through strong suppression of SAA. As for the biologics, an excellent effect on amyloidosis was reported regardless of a mechanism, but the IL-6 receptor antibody could expect a strong effect from the mechanism of action. The patient survival was improved by use of the biologics and it could be possible to delay dialysis initiation. Whereas we need attention for dialysis initiation, because multiple organ failure has already existed in patients with the renal failure. In these patients, gender, long-lasting inflammation with RA, together with low level of serum protein, were associated with a decrease in muscle volume. This might in part explain why serum creatinine levels were not elevated when compared to the creatinine clearance levels in these patients. Therefore it is necessary to consider earlier initiation of dialysis treatment than renal failure due to other diseases. To avoid a trouble at initiation, programmed initiation was effective for the preparations for shunts. The use of biologics of the normal quantity after hemodialysis initiation decreased disease activity of RA, but could not confirm the superiority about survival for the moment. Whereas it is necessary to reduce SAA to prevent extension of other organ damage and it should be used it even if the biological dosage reduces it.

S12-5

Development in the treatment of AA amyloidosis secondary to rheumatoid arthritis

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Conflict of interest: None

Amyloidosis is an uncommon disorder characterized by the deposition of extracellular amyloid fibrils in various tissues, which causes multiple organ dysfunction. Reactive amyloid A (AA) amyloidosis is one of the most severe complications of several chronic disorders, particularly rheumatoid arthritis (RA). AA amyloidosis is a serious, potentially life-threatening disorder caused by deposition in organs of AA fibrils, which derive from the circulatory acute-phase reactant, serum amyloid A protein (SAA).Both treatment and understanding of the roles of cytokines in RA have resulted in considerable progress. Remarkable advances have been made recently, which not only provides insight into pathophysiology of the disease but also helps to discover new therapies to fight the deadly disease. The introduction of disease-modifying anti-rheumatic drugs focusing inflammatory mediators revolutionized the treatment of RA. Targeting key components of the immune system allows efficient suppression of the pathological inflammatory cascade that leads to RA symptoms and subsequent joint destruction. Also, specific treatment of AA amyloidosis caused by RA aims to stop SAA production. This notion of approach to treatment of AA amyloidosis is the most common and best-studied therapy interferes with the synthesis of SAA, with the goal of preventing further AA fibril formation.Next approach targets AA amyloid deposits directly, by destabilizing AA fibrils so that they can no longer maintain their structural configuration. Treatment with hexanoyl bis (D-proline) efficiently depletes serum amyloid P component (SAP) from the plasma but leaves some SAP in amyloid deposits that can be specifically targeted by therapeutic anti-SAP antibodies. Also, eprodisate which binds to glycosaminoglycan-binding sites on AA fibrils and in principle can destabilize them in tissues, thereby causing regression of AA amyloidosis.

S12-6

Genetic risk factors for AA amyloidosis

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Conflict of interest: None

Amyloid A (AA) amyloidosis complicates secondary to chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel diseases, and several hereditary periodic fever syndrome (HPFs). Prolonged SAA elevation by primary inflammatory diseases is critical but not sufficient for the development of amyloidosis. Genetic factors seem to be involved in the pathogenesis and would relate to the primary diseases and to the SAA metabolism. Acute phase SAA1 produced in the liver by the stimuli of inflammatory cytokines, is a predominant precursor to AA. The presence of 2 SNPs within exon 3 of the *SAA1* gene, 2995C/T and 3010C/T, define 3 haplotypes; *SAA1.1*, *SAA1.3*, and *SAA1.5* alleles. Linkage between *SAA1.3* allele and susceptibility to AA amyloidosis in Japanese RA patients has been shown, while the *SAA1.1* allele was a risk factor in Caucasoid population. The only difference between the SAA1.1 and SAA1.3 proteins is a single amino acid change from Val to Ala, thus, it is unlikely that the discrepancy between 2 different ethnic groups can be explained by differences in SAA1 protein secondary structures. The -13C/T SNP in the 5'-flanking region of SAA1 was strongly associated with amyloidosis and -13T allele was closely linked to *SAA1.3* and *SAA1.5* haplotypes in Japanese, while -13T was linked to *SAA1.1* rather than *SAA1.5* in the Caucasian. These strongly suggest that the -13T allele, but not the 2995C allele is directly associated with the risk of amyloidosis. The genetic risk factor of the primary disease like HLA-DR4 in RA, would also be risk for the development of amyloidosis. The various mutations that cause HPFs such as FMF and TRAPS, are the risk for amyloidosis in HPFs, and could also induce considerable inflammation in other inflammatory condition. Mutations of *MEFV* or *TNFRSF1A* genes are reported in a few cases with AA-amyloidosis secondary to chronic inflammation, however, the association between these genes and amyloidosis in RA has not been demonstrated so far.

S12-7

Discussion about diagnosis and treatment of AA amyloidosis complicated RA from the point of practical and clinical medicine

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Conflict of interest: None

The incidence of clinically overt AA amyloidosis complicated RA has been reduced recently. But some patients have serious diseases with a significant mortality due to end-stage renal failure or severe infection. Therefore, the management of AA amyloidosis complicated RA is still an important research issue. We have reported that the survival rate of patients with AA amyloidosis diagnosed in the 2000s has improved due to dramatic advances in treatment of active RA, and the average value of serum creatinine at the beginning of biological treatment was significantly lower in the treatment continue group compared to the stop group. In our series of 74 patients with AA amyloidosis complicated RA, only 6 cases (one diagnosed in 1998 and the others in 2000s) have survived more than 10 years at December 2015. Two of 6 patients are treated with dialysis due to end-stage renal disease (ESRD). In the remaining 4 cases any one of biologics has been continued and their clinical courses are good without the deterioration of kidney function. All 4 patients have serum SAA concentration within the reference range (<10mg/L) and amyloid deposits in their gastro-intestinal mucosal tissues disappeared. Their urine abnormalities and disease activities have been controlled well. We administered biological agents including tocilizumab (TCZ, n=10), etanercept (ETN, n=4), infliximab (IFX, n=2), abatacept (ABT, n=1) or adalimumab (ADA, n=1) to patients with AA amyloidosis complicated RA until December 2015. But treatment with TCZ, ETN or IFX was discontinued or switched to other biologics in half of them. There were no cases whose treatment with ABT or ADA was stopped. AA amyloidosis led to renal death or ESRD in 3 of 4 patients who completely gave up treatment with biologics. For a progressive improvement in survival period, strategies for early diagnosis and treatment of AA amyloidosis and perfect removal of amyloid deposits from gastro-intestinal tissues should be needed.

S13-1

Collaboration between internal medicine and surgery in the treatment of musculoskeletal diseases

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Conflict of interest: None

Collaboration between internal medicine/Rheumatology and Orthopeadic surgery is included in all guidelines and qualifier indicators for the treatment of arthritis and musculoskeletal diseases. These criteria are most frequently issued by professional organizations but their use is also supported by payors, patient organizations and Healthcare care inspectors. In The Netherlands all rheumatology groups have regular and structured meetings and joint consultations with orthopeadic surgeons and frequently these patients are seen jointly. The standard of arthritis care in Holland announced that if a patient with arthritis have residual pain despite 3 month of adequate conservative treatment, such a patient should also be seen by the orthopeadic surgeons. Two decades ago orthopeadic surgeons performer all operations. At this moment there are surgeons specialized in various parts of the locomotor apparatus. Despite that it is felt to be necessary that one surgeon is the conductor. Given the success of pharmacological treatment, the number of operations in arthritic patients decreases. Therefore concentrations towards centre for arthritic surgery are mandatory. Rheumatologists and orthopaedric surgeons also tightly collaborate in medical education of future doctors. Together they also formed a special society: Netherlands Society of Rheumatology and Arthritis surgery (NERASS with 200 members). Paramedical professionals can also join NERASS such as physician assistants, Hand therapists and Podotherapists. In the presentation indications for surgery including pain, function, inflammation and deformations will be discussed.

S13-2

The review of changes of surgical treatment for patients with rheumatoid arthritis in Japan and other countries

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Conflict of interest: None

In patients with rheumatoid arthritis (RA), chronic synovitis causes joint destruction. Recently, introduction of strong therapeutic reagents such as methotrexate in the last decades of 20th century and biologic agents in the early 21th century has changed the realistic goal of RA treatment to remission or near-remission. This change seems to contribute to avoidance or delay of surgical intervention. Several reports on trend of RA-related surgeries has been published from different countries. As many researchers and clinicians estimated, most of the papers concluded that the rate of patients receiving RA-related surgeries, as represented by total joint replacement for large joints, had been declining or at least relatively declining when compared with osteoarthritis-related surgeries. There are a few reports mentioning the changes in the operative procedures. They say that widespread application of strong drug therapy has changed the purpose of surgical intervention from gaining minimal activity of daily life to achieving high quality of life. In the symposium presentation, we will review and discuss these recent reports on trends of RA-related surgeries. In addition, we will report and discuss the trend of the rates of the surgery and type of surgical procedures in a nationwide observational cohort database of rheumatic diseases in Japan [National Database of Rheumatic Diseases by iR-net in Japan (NinJa)].

S13-3

Our approach to correct RA-patients using selective surgical procedures

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Conflict of interest: None

Although we observe a profound amelioration concerning the handicap of patients suffering from RA within the last fifteen years due to improved medical therapy we are nevertheless still confronted with progressive deterioration of the daily living activities regarding the upper extremities in general as well as the function of wrist and hand in particular. Generally speaking we have to differentiate between functional loss and the deformities in particular patients.Not every deformity needs to be corrected surgically if it does not interfere with the overall function of the hand.Special attention is directed to grip and pinch ability within the personal daily living activities (ADL) of a given patient. This includes a complete evaluation of the upper extremity function since only a normal function of elbow and shoulder joints permits the correct use of the hands within a given space. We tend to treat any functionally disorder of the elbow or shoulder joints prior to the surgical management of the hand. Concerning the hands the functional stability of the wrist remains a prerequisite for an adequate function of the whole hand. For instance it makes no sense to correct ulnar deviated fingers for patients with unstable,radially deviated wrist joints.It makes no sense to treat finger deformities for patients having a stiff elbow joint in extension like not seldom in JRA patients. In that case we have to mobilise the elbow first by implanting a Total Joint Replacement before the treatment of the finger deformities. Having a stable elbow and wrist joint we draw our attention to the functional impairment of the thumb and fingers.In case of ulnar deviated fingers we have also to consider and sometimes to stabilise the fourth and fifth CMC joints.Swan neck deformities need often a stabilization of the MCP-joints and flexor tendon synovectomy in addition to tendon reconstruction. Generally speaking the surgical treatment of hand deformities remains stage related, meaning that flexible deformities are subject to soft tissue reconstruction and are surgically more demanding than stiff deformities which require more often arthrodesis or arthroplasty. Since the improvements medical treatment using target related biologicals RA patients involving not only the median but also frequently the radial and ulnar nerve.Electroneurographic studies of our RA patients have been showing that every third patient showed abnormalities sometimes associated with paresis of extensor or flexor tendons or intrinsic muscles of the hand.Surgical exploration and decompression may improve these symptoms.

S13-4

Latest treatment of hand surgery in rheumatoid arthritis in Japan

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Conflict of interest: None

With the use of methotrexate and bDMARD or a recently appeared tsDMARD, uncontrollable synovitis in the past has been soothed in the patients with rheumatoid arthritis (RA). In the real clinical practice, more than 50% of the patients are in remission. However, some patients are still difficult to reach remission due to problems such as infection, respiratory disease, diabetes mellitus, aging and economic burden. In the patient with clinical remission, smoldering synovitis so called “silent destructor” is often detected by ultrasonograpy or by synovial histology in the small joints of the hand. In recent years, over use with “no pain” increases the risk of deformity, osteoarthrosis, tendon rupture and entrapment neuropathy. Highly motivated patients, who concern about the appearance of the hand, hope to get a higher level of activities of daily living (ADL) and quality of life (QOL). A prospective cohort study was performed for the purpose of knowing whether rheumatoid hand surgery affects the patient’s QOL and mentality as well as upper extremity function. A primary hand surgery was scheduled in 119 patients with RA. Synovectomy and Darrach procedure, radiolunate arthrodesis, reconstruction of the extensor tendons, arthroplasty at the metacarpophalangeal (MP) using Swanson implant, fusion at the proximal interphalangeal (PIP) joint, suspensionplasty at the carpometacarpal (CM) joint of the thumb (Thompson method) were frequently performed. As a result, J-HAQ (physical function & QOL), EuroQOL-5D (QOL), Beck Depression Inventory-II (BDI-II:depression,mentality) at 6 months and at 12 months after surgery improved significantly compared to those just before surgery ($p<0.01$). Disease activity score 28- C reactive protein 4 (DAS28-CRP (4)) decreased significantly ($p<0.01$). Latest hand surgery

on tight medical control is possible to raise QOL and to lead mental remission for the patient with RA.

S13-5

Foot and ankle surgical intervention aiming at higher level of quality of life for the patient with rheumatoid arthritis

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Conflict of interest: None

Although surgical intervention for rheumatoid arthritis is declining due to the better pharmacological treatment options, the foot is still the most important reason for walking disability in rheumatoid diseases. As the foot is not included in the DAS-28, about half of the clinicians don't check the feet on a regular basis and as the diagnosis "remission" is often based on the DAS-28 score many patients in remission still have active arthritis in their feet. For the forefoot we can observe a shift toward more joint preserving surgical options as before resection arthroplasty was the mainstay of the treatment. I'll discuss the different treatment options for forefoot reconstruction and their results from literature. For the hindfoot the triple fusion is still the most performed surgical intervention and this operation gives good results, especially in rheumatoid patients. For the ankle there is still debate whether to implant a total ankle replacement or to do an ankle fusion. In my lecture I'll give an overview of the literature on ankle arthritis and my treatment algorithm. Because rheumatoid patients in the current time have less damage to other joints they are also not het "low demanding patients" as they were before. This also influences the way we look at our results, 20 years ago we were satisfied when we kept patients ambulatory, nowadays we almost treat them as patients without a disability and expect better functional results. When we focus on the outcome we also have to take this in to account and have to use different outcome measures. Although there are more than 50 different scoring systems for the foot and ankle, only few have been validated and officially translated in different languages which makes it difficult to compare results from different international institutes.

S13-6

Latest treatment of foot and ankle surgeries in rheumatoid arthritis in Japan

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Conflict of interest: None

Over the past decade the advance in the pharmacotherapy of rheumatoid arthritis (RA) has bestowed great benefits on not only the early RA patients but also the established RA patients with joint damage and irreversible disability. The reduced disease activity could diminish the fragility in bone and soft tissue resulted in easy handling in delicate surgery. The remission or low disease activity of RA also could create an incentive for patients to demand further functional or cosmetic recovery and the better quality of life. So, while the paradigm in treatment of RA was changing into earlier introduction of pharmacotherapy and tight control, there was also the great changes both in the procedure and indication of surgical intervention in Japan. Now we are aiming to the goal that RA patients still have normal skeletal function 20-30 years hence, through the application of specialist skills both in pharmacotherapy and orthopedic surgery. With respect to walking ability, I give much attention to three principles. First, surgical intervention should be indicated considering the progressive decline in skeletal function due to aging. Second, surgical intervention should be indicated earlier as possible in the case with multiple damages in lower legs and spine. Finally, osteotomy or arthrodesis in hind-, or mid-foot where the post-operative rest is required should be indicated before the immobility-induced sarcopenia is critical. The improvements in foot and ankle surgeries in RA are focused on following three points. The first one is to correct the malalignment in lower leg or foot in multi-joint damaged RA patients. The second is to preserve the organ and tissue that is required for the better function. MTP joint preserving forefoot surgery is an example in this case. The third is early detection of foot problems and timely interventions by multi or transdisciplinary foot care team. These improvements in Japan might be the reason why RA foot surgeries increase in number.

S14-1

Rheumatoid factor and anti-CCP antibody: The role in early diagnosis

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Conflict of interest: None

Recent advance of medical treatment has markedly improved the outcome of rheumatoid arthritis (RA). However, there is an emerging problem regarding medical cost, and establishing scheme for diagnose RA is warranted. In Japan, rheumatoid factor (RF) has been used for screening test in routine health check-up, but little is known about usefulness of the screening test for RA in general population. St. Luke's Center for Preventive Medicine is attached to St. Luke's International Hospital, and all medical records of them were shared each other and available as an electric medical record. Basic health checkup consists of questionnaire regarding past medical history and daily life, physical examination, and blood test. Since 2003, RF has been a part of routine blood tests, and all the people who have health checkup are tested RF routinely. During November 2013 to August 2014, all the female who had health checkup at St. Luke's Center for Preventive Medicine were offered ACPA test in addition to the routine blood tests described above. During the study period, 13094 women underwent medical checkup, and 11758 women mean aged 51.2 ±11.5 years-old had ACPA test in addition to their regular examination. Among 11758 tests, the number of the seropositive patients for RF and ACPA are 1271 (10.8%) and 154 (1.3%), respectively. In seropositive patients, 98 were positive for both of RF and ACPA. One hundred fifty-five screening seropositive patients were refereed to our clinic, and five of them were diagnosed as RA at initial visit. In addition, 6 patients developed RA during follow-up. Overall, the positive predictive value of screening RF, ACPA are 0.09% and 1.8%, respectively.

S14-2

Usefulness of ultrasonography in the diagnosis of rheumatoid arthritis

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Conflict of interest: Yes

The usefulness of ultrasonography (US) in the diagnosis of rheumatoid arthritis (RA) has been often reported, especially in early diagnosis and differential diagnosis of RA. By using US, physicians can detect subclinical joint inflammation even in patients without obvious swelling or positive inflammatory findings. Such kinds of subclinical inflammation detected by US might improve the accuracy of early diagnosis of RA. Moreover, US assessment might be useful in the diagnosis of early RA in patients with seronegative inflammatory arthritis. Although subclinical inflammation is frequently found in metacarpophalangeal (MCP) and radio-carpal joints, subclinical inflammation in fifth metatarsophalangeal (MTP) joints has been considered quite specific for RA. Thus, US examination in MTP joints should be considered for early diagnosis of RA. There are some specific findings to make differential diagnosis easier in

the other inflammatory arthritis like spondyloarthritis (SpA) including psoriatic arthritis or ankyloses spondylitis. New bone formation on the inflammatory site or enthesitis is specific for SpA. US can also demonstrate a relevant diagnostic potential in crystal arthropathies. In crystal arthropathies, US can identify so-called "double contour sign" which is homogenous linear deposition of crystal aggregates on the chondrosynovial interface of the hyaline cartilage as highly evocative signs of gout. Also US can detect calcium pyrophosphate dihydrate (CPPD) crystal deposition as hyperechoic linear spots not generating acoustic shadowing located within the hyaline cartilage layer especially in femoral hyaline cartilage. The main advantages of US, with respect to other imaging modalities, include low running costs, absence of radiation, multiple imaging capability, real-time scanning and easily to use. US has huge utility comparing with traditional methods for diagnosis such as clinical examination, laboratory test and conventional radiography.

S14-3

Differentiating early rheumatoid arthritis from other inflammatory arthritides

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Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic, autoimmune polyarthritis whose main site of inflammation resides in synovium. Early diagnosis and therapeutic intervention is of paramount importance, which is the consensus among rheumatologists. Many clinical conditions including infectious diseases and rheumatic diseases may mimic early RA. Of note, the recent advances of therapeutic options of spondyloarthritis (SpA), such as psoriatic arthritis, has revealed the similarities and differences between RA and SpA. Although TNF inhibitors have shown effectiveness both for RA and SpA, IL-6 receptor antagonist may not work well for SpA, and the efficacy of anti-IL-17A antibody for RA seems to be somewhat limited. As seen above, to make an accurate diagnosis of early arthritis may influence the therapeutic strategy itself, in particular the choice of biologic DMARDs. The chronic inflammation of SpA consists not only from synovitis, but also tenosynovitis and enthesitis. Its radiographic change is differ from RA in that SpA shows "osteoproliferative" change as well as bone erosion and joint space narrowing. In Japan, the prevalence of polymyalgia rheumatica (PMR) has increased because of the aging of the population. PMR is an idiopathic, seronegative, polybursitis which responds well to medium-dose glucocorticoid. PMR itself won't cause irreversible joint destruction, but peripheral arthritis due to PMR is not uncommon, which must be differentiated from late-onset RA. In this session, practical ways of differentiating early RA from inflammatory arthritis due to other conditions will be addressed.

S14-4

Assessment of disease activity and health-related quality of life in daily practice

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Conflict of interest: None

A 'window of opportunity', to halt irreversible damage from occurring through early diagnosis and concomitant start of conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy, is open during the first two years from the onset of rheumatoid arthritis (RA) but closed if the initiation of the csDMARD is delayed. The 2010 treat-to-target recommendation (T2T), treatment to target by measuring disease activity every 1-3 months during active disease and adjusting therapy accordingly to reach remission or low disease activity, is proven to be effective not only in early RA patients whose 'window of opportunity' is open but also in established RA patients whose 'window of opportunity' is closed. This T2T strategy is reflected in the EULAR recommendation (2013), the JCR guideline (2014), and the ACR recommendation (2015). The use of validated composite measures of disease activity which include joint assessments is recommended in the T2T and EULAR recommendation, whereas RAPID3, consisting of three major patient-reported outcomes (pain, function, and patient global assessment), is also accepted in the ACR recommendation, where routine functional assessment by HAQ or MDHAQ (The mHAQ, still commonly used in Japan, is excluded due to the floor effect). The T2T 2014 recommendation emphasized that the choice of disease composite measure of disease activity and the target value should be influenced by comorbidities, patient factors, and drug-related risks. However, it did not state the specific methods. In this lecture, referring to the opinions of the developer of DAS (Dr. Riel), SDAI (Dr. Smolen), and RAPID3 (Dr. Pincus) and our data, the effective choice of the composite measures in daily practice will be discussed. The SF36 is a validated tool to assess health-related quality of life (HRQoL) in clinical trials but not suitable for daily practice. I will introduce the use of MDHAQ questionnaire to address HRQoL in daily practice.

S14-5

Treatment strategy for rheumatoid arthritis patients in whom methotrexate is contraindicated

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Conflict of interest: Yes

Methotrexate is the anchor drug in the current treatment strategy for rheumatoid arthritis (RA). Global standard of the RA treatment is first early diagnosis and second methotrexate therapy for all patients if not contraindicated. However, we have some patients in whom MTX is contraindicated due to their comorbidity such as pulmonary, renal, or hepatic dysfunction. Worldwide guidelines for RA treatment recommend a monotherapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); salazosulfapyridine, bucilamine, tacrolimus, and iguratimod are primarily used in Japan. If a monotherapy is insufficient, a combination therapy of cs DMARDs or biological DMARDs (bDMARDs) is applicable. Concomitantly used MTX is well known to be important when the patients are treated with bDMARDs. The effects of concomitantly used MTX is first augmentation of bDMARDs efficacy and second suppression of the immunogenicity of bDMARDs; production of anti-bDMARDs antibody and subsequent secondary failure of bDMARDs. It has been reported that MTX mainly suppress the serum IL-6 concentration. Thus, the anti-TNF agents fatefully require the anti-IL-6 effect of MTX to demonstrate their maximum efficacy. In contrast, since the non-TNF agents (tocilizumab and abatacept) do not require MTX very much, these agents would be good treatment option for the patients without concomitant MTX. We demonstrated that there was no significant difference in the incidence rate of secondary failure between patients with and without concomitant MTX treated with etanercept or non-TNF agents. Our results suggested the low immunogenicity of these agents. We can expect the long-term retention of the low-immunogenicity bDMARDs without concomitant MTX. It is always expected to do our best to achieve the treatment goal, clinical remission, even in the RA patients with contraindication for MTX by using csDMARDs, non-TNF bDMARDs, low-immunogenicity bDMARDs, or combination of these agents.

S14-6

The impact of concept-based clinical training on the quality of care for RA patients in the US

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Conflict of interest: None

This session will review rheumatology practice in the US, with particular attention to 1) how US rheumatologists are trained and develop conceptual framework to solve a clinical problem and 2) how such training affects the quality of care for patients with rheumatoid arthritis (RA) and other immune-mediated diseases. The major objective of rheumatology fellowship training is to learn the method of clinical problem solving rather than proficient application of "diagnostic criteria". Specifically, fellows learn how to recognize subtle but important clinical cues, inte-

grate relevant data to establish the foundation of clinical assessment, and develop reasoning skills to justify their clinical decisions. What is emphasized in the diagnosis of RA is that arthritis is solely a manifestation of a variety of immuno-pathological processes and that there are no definitive disease-defining markers of RA. With this key principle in mind, fellows are trained to develop skills to carefully rule out numerous RA mimics. To better demonstrate how such a practical method is taught in the US, this session will include a brief review of systematic approach to a patient with arthralgia. The latter half of the lecture will discuss the currently accepted standard RA treatment as well as how US rheumatologists approach a question where there is not enough guidance by definitive scholarly evidence. The ultimate goal is to clarify what needs to be done to improve the quality of care for RA patients through interactive discussion with the audience.

S15-1

Diagnosis of and criteria for initiation of pharmacological treatment of osteoporosis

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Conflict of interest: None

For the diagnosis of osteoporosis, a medical interview, physical examination, diagnostic imaging, and blood and urine examinations (including measurement of bone metabolic markers) should be conducted first. Then, bone assessment must be conducted with bone mass measurement and spinal radiography. Based on this information, diseases causing low bone mass or secondary osteoporosis should be excluded, and then an accurate diagnosis of primary osteoporosis should be made based on the diagnostic criteria. As for secondary osteoporosis, outside glucocorticoid-induced osteoporosis, no diagnostic criteria or any criteria for the initiation of medical treatment have been established, which has caused the diagnosis criteria for primary osteoporosis to be used instead. However, it is necessary to keep in mind that the diagnostic criteria for primary osteoporosis are not intended for secondary osteoporosis. Primary osteoporosis is diagnosed on the presence of a fragility fracture in either the lumbar spine or the proximal femur, the presence of an other fragility fracture and a bone mineral density (BMD) below 80% of young adult mean (YAM). If there is no fragility fracture, osteoporosis is diagnosed by the BMD equal to or below either 70% or -2.5SD of YAM. Based on new knowledge about risk factors and the consideration about using FRAX, the criteria for initiating pharmacological treatment to prevent fragility fracture was established by Japanese 2015 Guidelines for Prevention and Treatment of Osteoporosis. Addition to the subjects diagnosed primary osteoporosis, the subjects who's BMD is above 70% to below 80% of YAM were recommended to initiate pharmacological treatment, if they have family history of proximal femoral fractures, or the 10-year probability of major osteoporotic fractures is equal or above 15% by using FRAX.

S15-2

Clinical efficacy of bisphosphonate

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Conflict of interest: Yes

Bisphosphonate (BP) is the first line drug for the treatment of osteoporosis. New drugs such as weekly, monthly, intravenous, and jelly type bisphosphonates have been developed. In Japan, etidronate, alendronate, risedronate, minodronate, and ibandronate are available for the treatment of osteoporosis. Such nitrogen-containing bisphosphonates improve BMD well (>6% for lumbar BMD, >3% total hip BMD) and reduce vertebral fracture from 36 to 62%. Non-vertebral and hip fractures can be also reduced by some bisphosphonates. Ibandronate was included in new "Guideline for Prevention and Treatment of Osteoporosis" as a new bisphosphonate. And the recommendations for each drug were reconsidered according to the previous clinical studies. Major adverse events in bisphosphonates are osteonecrosis of the jaw and atypical femoral fracture. Although their incidence rates are very low, "Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment" was published by a Task Force of ASBMR in 2015 for appropriate use of bisphosphonates. In this symposium, changes in the new guideline will be discussed and new bisphosphonates that become available in 2016 will be presented.

S15-3

The clinical effectiveness of denosumab

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Conflict of interest: Yes

Osteoclasts are differentiated from monocyte/macrophage-lineage precursor cells in the presence of receptor activator of NF-kB (RANKL) and macrophage colony-stimulating factor, and play essential roles in bone resorption. It is now widely accepted that RANKL-RANK pathways play essential roles in the pathologic bone resorption such as osteoporosis, rheumatoid arthritis and cancer bone metastasis. Denosumabfully is a human IgG2 monoclonal antibody that neutralizes RANKL and potently suppresses osteoclast development. In a study of postmenopausal osteoporosis patients (FREEDOM), denosumab significantly reduced the risk of new vertebral fractures at 3 years by 68%, non-vertebral fractures by 20% and hip fractures by 40% relative to placebo. To examine the anti-fracture efficacy and safety of denosumab (60 mg subcutaneous injection every 6 months [Q6M]) in Japanese patients with primary osteoporosis, a randomized, double-blind, placebo-controlled trial with an open-label referential arm was conducted (DIRECT trial). Denosumab reduced the risk of new or worsening vertebral fracture, with incidences of 3.6% in the denosumab group and 10.3% in the placebo group in 24 months without increasing the risk of adverse events of interest. These results suggest that anti-RANKL therapy is effective in reducing osteoporosis fractures.

S15-4

Efficacy of Teriparatide

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Conflict of interest: Yes

Teriparatide is a polypeptide hormone that contains the 1-34 amino acid fragment of recombinant human parathyroid hormone. A once-daily teriparatide composed by genetic modification was marketed in Japan in 2010, and once-weekly teriparatide acetate developed in Japan was marketed in 2011. Both teriparatides are bone anabolic agent that increases bone mineral density (BMD) especially in lumbar spine and reduce vertebral fracture incidence. However, there are differences regard to amount of dosage, interval of administration, total period of treatment, injection method, change of bone turnover markers. Daily teriparatide increased bone turnover and resulted a rapid initial increase in serum P1NP levels within 1 month after treatment, followed by an increase in serum CTX levels. It was observed that BMD increase of lumbar spine was significantly correlated with change of bone turnover marker. The highest correlation was between P1NP absolute change at 1 month and % change of lumber spine BMD at 12 month. Baseline PINP concentration was also a useful predictor of lumbar spine BMD absolute increase. On the other hand, after weekly teriparatide injection, serum osteocalcin decreased at 24 h and urinary NTX was significantly increased transiently and then decreased at 24 h. After 24 weeks, serum osteocalcin increased significantly, and bone resorption markers decreased or remained the same. In other words, the bone turnover markers cannot explain an increase in bone turnover for weekly teriparatide. Daily teriparatide significantly increased BMD at the lumbar spine by 13.4%, and at the total hip by 3.7% at 24 month in Japanese subjects, and also reduced the risk of new vertebral fracture with a relative risk of 0.35 in fracture prevention trial (median duration of observation, 21 months). At 72 weeks, weekly teriparatide increased BMD by 6.4% at the lumbar spine and 3.0% at the total hip, and reduced the risk of new vertebral fractures with a relative risk of

0.20.

S15-5

Importance of cooperation between physicians and dentists for prevention of antiresorptive agent-related osteonecrosis of the jaws

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Conflict of interest: Yes

The first report regarding an increased incidence of osteonecrosis of the jaw (ONJ) in oncology patients treated with intravenous bisphosphonates (BPs) was published by Marx in 2003. The first peer-reviewed article describing ONJ in both oncology and osteoporosis patients was published by Ruggiero and colleagues in 2004. Since minor oral surgery like tooth extraction was reported to be one of risk factors for ONJ, this has led to confusion among physicians, dentists, and patients, especially in osteoporosis treatment. Recently, ONJ has been identified in BP-naïve patients receiving denosumab (Dmab). ONJ is defined as (1) exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider;(2) exposure to an antiresorptive agent; and (3) no history of radiation therapy to the craniofacial region. The pathophysiology of ONJ is not well understood. International consensus paper published in 2015 provided 4 main pathophysiologies: infection; suppression of bone turnover; antiangiogenic properties; genetic predisposition. Of these, the most convincing one is infection. In fact, magnetic resonance imaging reveal signal of "inflammation" but not "osteonecrosis" in patients with ONJ. At the viewpoint of this, oral health care is the best way to reduce the incidence of ONJ in patients treated with BPs. Position paper in Japan as well as United States recommends the drug holiday before tooth extraction in patients treated with BPs; however, we recently reported that ONJ occurred even in patients who completed drug holiday before tooth extraction. Additionally, we observed lesser cooperation between physicians and dentists in osteoporosis treatment. Although ONJ recently tends to decrease over the world, it is likely that lesser cooperation between physicians and dentists may result in an increased incidence of ONJ in Japan.

S15-6

Osteoporosis in Japanese patients with rheumatoid arthritis

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Conflict of interest: None

Patients with rheumatoid arthritis (RA) are at high risk for developing fractures. Japanese patients with RA are 2-fold more likely than the general population to develop osteoporosis. Previous studies have reported that patients with RA, compared with controls, have an increased risk of fracture, which is most marked at the hip and spine. Thus, RA is one of the risk factors in the World Health Organization Fracture Risk Assessment Tool (FRAX®). In Japanese patients with RA, older age, female sex, disability, daily prednisolone dose, history of total knee replacement, and low bone mineral density are reported as significant risk factors for fractures which may differ depending on the skeletal site. Previous reports have indicated that serum 25 (OH) D levels were significantly lower in RA patients than in controls, and more than 70% of Japanese female patients with RA were vitamin D deficient (< 20 ng/mL). Despite the positive impact of biologics, fracture risk appears not to differ between RA patients treated or not treated with biologics. In Japanese patients with RA, as reported for patients of other ethnicities, a substantial gap exists between fracture risk and the initiation of osteoporosis treatment. Thus, Japanese rheumatologists should not only treat to reduce disease activity using methotrexate and biologics, but also consider medications for RA patients with osteoporosis to reduce their fracture risk. When treating osteoporosis in Japanese female patients with RA, attention should be given to reducing vitamin D deficiencies in order to improve bone mineral density. Bone loss in RA is attributable to the abnormal activation of osteoclasts, and one third of RA patients receive glucocorticoids. However, antiresorptives such as bisphosphonates and denosumab are suitable medications for osteoporosis in patients with RA. Active vitamin D3 use may also contribute to reducing the risk for new vertebral fractures in Japanese patients with RA.

S16-1

Biologic DMARDs in rheumatoid arthritis

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Conflict of interest: None

Biologic DMARDs have been available for over 20 years and it is therefore appropriate to review their effectiveness and safety. When first used, it was by no means obvious how effective these drugs would be. The study that changed everything was the ATTRACT study which showed for the first time a dramatic effect of TNFi (with MTX) on radiographic progression. A number of key insights have been observed over the last several years, the most important is the differential response according to the time of treatment. In particular, the increased response to early TNF blockade is dramatic. Ideally biomarkers should be developed for predicting response, and one of the agents that is ideal for biomarker use is that of rituximab which is an anti-CD20 which works by B-cell depletion. By studying high sensitivity B-cell assays it has been possible to analyse how important different aspects of therapy have been, and in particular the effect of rapid depletion on duration of response. This has been now confirmed both in proof of concept studies and with other agents that act by B-cell depletion. Abatacept has been shown to be as effective as TNF inhibition in early disease but its unique mode of action high in the immunological cascade suggests it may be most effective when used early and there are some data to support its use. Recent data in sero-negative patients and its less effective results in rituximab failures are described. Tocilizumab an agent first developed in Japan has been successful both as IV and subcutaneous and more recently excellent results have been achieved with early use. Its unique mode of action has particular effectiveness in patients who are sero-negative with an adult onset Still's phenotype. The major interest in recent times has been that of remission induction and subsequent dose reduction or dose cessation. There are now a number of studies which have addressed this question and a degree of consensus has emerged.

S16-2

Challenges in diagnosis and treatment of early rheumatoid arthritis

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Conflict of interest: None

The outlook for most patients with rheumatoid arthritis has greatly improved. Newer therapies, resulting in better suppression of disease activity than many classical DMARDs, helped to set new goals in achieving optimal low disease activity with a minimal delay. Targeted therapy using composite scores is introduced in daily practice, and new definitions of remission aim to pinpoint the target. Radiological damage progression becomes clinically irrelevant when inflammation is well suppressed. After intensive initial dosing, many patients will be able to taper and (temporary) discontinue antirheumatic drugs and drug free remission is becoming a realistic treatment target. However, remission can be a target easily to miss even if inflammation is suppressed. During the window of opportunity, the start of treatment may prevent chronicity of arthritis associated with development of damage and a need for chronic medication. To make optimal use of this, strategies to rapidly see and diagnose new patients are needed. The first manifestation of disease may be Clinically Suspect Arthralgia (CSA). How this can be recognized is still the subject of research. MRI may help distinguish non-inflammatory arthralgia from early phases of RA, and may offer the opportunity to start preventive therapy, as results from the Leiden CSA cohort show. Which would be the best treatment to use, and for how long, based on which outcome

evaluations, is yet to be discovered. Earlier diagnosis and earlier treatment will have an impact on the balance between benefits and negative effects of our intervention, between the risk of overtreatment and undertreatment. Given the results of recent trials in early arthritis, to alleviate symptoms and improve function where no more inflammation can be found may be the biggest challenge to come.

S16-3

Treat-to-Target: Japanese evidence

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Conflict of interest: Yes

The treatment of Rheumatoid Arthritis (RA) has been progressed in recent twenty years. However, there have been enormous gaps between the recent monitoring methods, treatment guidelines, new drugs, and the outcome in daily clinical practice. In order to overcome such gaps, treat to target strategy for managing Rheumatoid Arthritis (RA) has developed to standardize the medical treatment, which promotes better outcome of RA as a whole. Thus, Treat-to-Target recommendations were first announced in 2010 and it set the definition of treatment target, namely remission or at least low disease activity, assessment of disease activity by composite measures, regular adaptation of therapy, accounting for individual patient aspects such as risks and co-morbidity, and shared decision between patients and rheumatologists. In Japan, Goal study group was established to promote the Treat-to-Target recommendations to rheumatology community and started in 2011 and hosted more than 100 regional and 3 nation-wide meeting, recruiting 1500 rheumatologists until 2013. The web-based questionnaires were surveyed in 2012 on 301 rheumatologists, showing that the understanding and perception of the overarching principles and recommendations were excellent, but the implementation of several items were not so. For example, 44% answered that they were not discussing treatment strategies with all of their patients, and among them approximately half reasoned that it was because some patients did not understand or could not make decisions. The majority also cited the lack of time as a reason of not being able to implement T2T recommendations. One of such barriers to implement Treat-to-Target, only 23% of the rheumatologists monitored health-assessment questionnaires (HAQ). In order to provide deep insight into the recommendations and promote outcome measures by HAQ in Treat-to-Target in Japan, the goal study group initiated HAQ survey in RA patients, who will start methotrexate in 2013 to 2014. We summarized the date for 478 patients and discuss the data. Now, the second round HAQ survey has started to compare the patient characteristics, outcome, and so on. By considering these activities for Treat-to-Target in Japan, we would try to make a future perspective in the managing RA in Japan.

S16-4

Contributions of imaging for rheumatoid arthritis

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Conflict of interest: None

Efficient methods for diagnosis, monitoring, and prognostication are essential in rheumatoid arthritis (RA). Conventional radiography has been the cornerstone of imaging in RA for decades, but data on the additional value of ultrasonography and magnetic resonance imaging are accumulating rapidly, fueling their increasing use in RA. This talk focuses on the clinical applications of these imaging modalities.

S16-5

Influence of comorbidity in the prognosis of rheumatoid arthritis

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Conflict of interest: None

[Background] Recent progress of drug therapy successfully improved the outcome of patients with rheumatoid arthritis (RA), however, presence of comorbidity limits the therapeutic options, and resulted in the poor outcome of patients. Thus, it is important to understand the impact of each comorbidity on the treatment pattern and the outcomes of RA patients. [Methods] Using the prospective cohort study IORRA in October 2013, we conducted a cross-sectional analysis on disease activity, functional impairment and treatment by comorbidity:(1) coronary artery disease (CAD), (2) cerebral hemorrhage/cerebral infarction/subarachnoid hemorrhage (stroke), (3) hypertension, (4) heart failure, (5) interstitial pneumonia (IP), (6) chronic obstructive pulmonary disease (COPD), (7) gastrointestinal hemorrhage (GI), (8) hepatic dysfunction, (9) cancer, (10) depression, (11) diabetes, (12) fracture. [Results] Among 5,837 patients with RA (mean age, 60.9 y; RA duration, 14.8 y; females, 85.5%; DAS28, 2.6; J-HAQ score, 0.59; patients with MTX / corticosteroid / biologics, 77.4% / 33.2% / 18.8%), the most common comorbidity was hypertension (19.3%), followed by COPD (4.7%), GI (4.5%), diabetes (4.4%), fracture (4.0%) and IP (2.8%). Mean DAS28 was the highest in patients with IP (3.2) and cancer (3.0). Mean J-HAQ was the highest in those with fracture (1.04) and IP (1.01). MTX was administered at the lowest in patients with IP (47.6%) and heart failure (55.3%). Corticosteroids was given at the highest in IP (68.1%) and lowest in diabetes (36.3%). Patients receiving biologics was the highest in IP (25.9%) and depression (21.8%), and lowest in cancer (12.5%). [Conclusions] Although the therapeutic options are limited by the presence of comorbidities, current RA therapy provides adequate control of the disease activity. Thus, management of comorbidities are important for the better outcome of RA patients in the daily practice.

S17-1

Molecular mechanisms controlling nucleic acid sensing and responses by Toll-like receptors

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Conflict of interest: Yes

Toll-like receptors (TLRs) sense microbial invasion and mount defense responses. Nucleic acid (NA) is one of the principal TLR ligands. TLR7/8 and TLR9 are localized in endolysosomes and sense single strand RNA (ssRNA) and ssDNA, respectively. Cytoplasmic NA sensors respond to double strand DNA (dsDNA) and dsRNA. Self-derived NAs are continuously degraded by nucleases. Impaired degradation leads to accumulation of NAs and activation of NA sensors. For example, the lack of DNase II, the lysosomal DNase, is reported to activate the cytoplasmic DNA-sensing pathway, leading to arthritis. DNase II, on the other hand, has a role in processing dsDNA into short ssDNA fragment, to which TLR9 responds. ssRNA sensors TLR7 and 8 are reported to respond to self-derived RNA and cause SLE and arthritis, respectively, in mouse models. The structure of human TLR8 shows that TLR8 binds to uridine and dinucleotide. Moreover, uridine enhances TLR8 responses to ssRNA. TLR7 response to ssRNA is enhanced by Guanosine instead of Uridine. These results indicate that TLR7 and 8 responses are dependent on RNA metabolites such as Uridine and Guanosine. Taken together, NA metabolism has a key role in controlling TLR responses to NAs.

S17-2

Innate lymphoid cells and inflammation

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Conflict of interest: Yes

Innate lymphoid cells are classified into three groups, ILC1, ILC2 and ILC3s based on their ability to produce distinct sets of cytokines. We have identified a previously unidentified lymphocyte population producing large amounts of type 2 cytokines, which we named Natural helper (NH) cells. We identified NH cells in lymphoid clusters in adipose tissues, which we termed fat-associated lymphoid cluster (FALC). NH cells produce Th2 cytokines constitutively without any stimulation, and sup-

port the self-renewal of B1 cells and IgA production by B cells. Stimulation by IL-33 or helminth infection activates NH cells to produce large amounts of IL-5 and IL-13, which induce eosinophilia and goblet cell hyperplasia, both of which play an important role in anti-helminth immunity and pathophysiology of allergic diseases. NH cells are now considered to be a member of group 2 innate lymphoid cells (ILC2s) that are tissue-resident lymphoid cells present in various tissues. We have shown that NH cells are involved in the steroid resistance of allergic airway inflammation. In addition, we have identified interferon-a/b, interferon-g and IL-27 as negative regulators of NH cell functions *in vivo*. We will present our recent work on the role of NH cells in allergic inflammation.

S17-3

Mucosal Multi-ecosystem for the Control of Symbiosis and Diseases

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Conflict of interest: None

Digestive tract is continuously exposed to infinite beneficial and harmful antigens including commensal and pathogenic microbe via the large mucosal epithelium. The intestinal mucosal surface is thus equipped with multi-complexed but harmonized biological components including commensal microbiota, epithelial-mesenchymal cells and mucosal immunocompetent cells which form “Mucosal Multi-ecosystem” for the establishment of beneficial symbiosis condition as well as cooperative defense force. As an example, our study identified that commensal bacteria, *Alcaligenes* species can create “intra-tissue co-habitation niche” in Peyer’s patches (PPs), an example of commanding tissue for the induction and regulation of mucosal immunity. Innate lymphoid cells (ILCs) have been shown to play critical role by the cooperative interaction with epithelial cells for the creation of intra-tissue co-habitation. Further, ILCs have been shown to regulate epithelial cell glycosylation [e.g., fucosyltransferase 2 (Fut2) mediated fucosylation] for the creation of healthy gut microbiota and providing protective barrier against gut pathogens. The other form of innate immunity-associated cells, mast cells (MCs) expressing P2X7 purinoceptor are also involved in the maintenance or disruption of healthy gut environment via the extracellular ATP and P2X7 cascade. Based on our knowledge of “Mucosal Multi-ecosystem”, appropriate delivery of vaccine or neutralizing antibody to the mucosal surface lead to the control of infectious diseases and inflammation. Cross fertilization of our knowledge in mucosal immunity and agriculture science resulted in the development rice transgenic (Tg) vaccine system, “MucoRice”. The MucoRice rice expressing vaccine or naoantibody has been shown to provide appropriate protective immunity against intestinal pathogens. The MucoRice system is thus an attractive and next generation of oral vaccine for the control of various diseases.

S17-4

Cytokines in Rheumatic Diseases

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Conflict of interest: None

Autoimmunity is caused by T cells and/or antibodies specific to self-antigens. However, innate immune cells such as gd T cells have no such specificity. Therefore, it is an enigma how these innate immune cells participate in the development of tissue-specific autoimmune diseases. Here, we show that gd T cells cause tissue-specific inflammation in collaboration with tissue-specific T cells. Previously, we showed that IL-1 receptor antagonist (IL-1Ra)-deficient mice (*Il1rn*$^{-/-}$) mice spontaneously develop arthritis which is highly dependent on IL-17. IL-17 in the affected joints was mainly produced in gd T cells and specific antibody-mediated depletion of either gd T cells or CD4^{+} T cells suppressed the development of arthritis. Transfer of gd T cells together with CD4^{+} T cells from *Il1rn*$^{-/-}$ mouse lymph nodes induced arthritis in *scid/scid* mice, while gd T cells or CD4^{+} T cells alone did not, indicating collaboration between gd T cells and CD4^{+} T cells is required for the development of arthritis. We showed that CD4^{+} T cells induce CCL2 in joints, while IL-17-producing gd T cells express CCR2, suggesting CCL2-CCR2 interaction is important for the recruitment of gd T cells to the joints. These CCR2^{+} gd T cells in *Il-1rn*$^{-/-}$ mice, which mostly belong to the Vg6^{+} subset, highly expressed IL-1R, resulting in these gd T cells highly sensitive to IL-1b to produce IL-17. Our findings suggest a pathogenic mechanism in which excess IL-1 signaling induced by a defect of IL-1Ra induces a CD4^{+} T cell-dependent autoimmune arthritis in a gd T cell-dependent manner.

S17-5

B-cell mediated suppressive function in autoimmune inflammation

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Conflict of interest: Yes

Previously, it has been thought that a most important role of B cells is to make antibodies and eradicate invading pathogens. But, in addition to such activating inflammation, new evidence is emerging that B cells mediate inhibitory functions on Dendritic cells and T cells by producing IL-10 and that generating antibodies, modified by sialylation on their Fc part, mediate anti-inflammatory functions. Therefore, B cells and generated antibodies are now thought to execute suppressive functions during autoimmune inflammation, thereby providing new aspect into novel intervention for autoimmune diseases. Here, we show our recent progress of such suppressive roles of B cells and generating antibodies.

S17-6

Inhibitory cytokine-mediated B cell regulation by CD4+CD25-LAG3+ regulatory T cells

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Conflict of interest: Yes

Autoreactive B cells and autoantibody play a crucial role in the pathogenesis of autoimmune diseases. Although CD4+CD25+Foxp3+ regulatory T cells (CD25^{+} Treg) are associated with the suppression of autoantibody production, the disease phenotype of Foxp3-mutated IPEX patients is quite different from that of systemic autoimmune diseases. Previously, we identified an IL-10-producing CD4+CD25-Foxp3- regulatory T cells (Treg) population that expresses both lymphocyte activation gene-3 (LAG3) and early growth response gene-2 (Egr2). We revealed that CD4+CD25-LAG3+ Treg (LAG3+Treg) suppress antibody production and exhibit therapeutic activity in lupus-prone MRL/lpr mice in a TGF-beta3-dependent manner. T cell-specific Egr2/Egr3-deficient mice exhibited enhanced development of germinal center B cells and lupus-like disease due to reduced TGF-beta3 production. LTBP3, a structural extracellular matrix protein induced by Egr2/Egr3, was required for the production of TGF-beta3. Interestingly, although TGF-beta3 as well as TGF-beta1 paradoxically promoted B cell antibody production under stimulation with TLR agonists, TGF-beta1/3 and IL-10 synergistically regulated TLR-induced B cell responses both in vitro and in vivo. In MRL/lpr mice with increased serum concentration of IL-10, administration of TGF-beta3 with expression vector ameliorated lupus-like disease. In contrast to TGF-beta1 that shows pro-fibrotic effect, TGF-beta3 was reported to exhibit anti-fibrotic effect in wound healing. Therefore, induction of LAG3+Treg and TGF-beta3 may be a hopeful approach to treat autoantibody-mediated autoimmune diseases.

S18-1

Issues of infectious diseases in patients with rheumatoid arthritis

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Conflict of interest: Yes

Patients with rheumatoid arthritis (RA) have about twice higher risk for infection than non-RA individuals. Previous studies identified risk factors of infection in patients with RA. Infections with elevated risk in these patients are lower respiratory infection, skin and soft tissue infection, sepsis, infectious arthritis, and osteomyelitis. Various data are available for the risk of antirheumatic drug for infection, especially methotrexate and biologics. We reported that the use of methotrexate over 8mg/week and the use of infliximab or etanercept were significant risk factors of serious infection in Japanese patients with RA using the database of the REAL study. A meta-analysis with 70 articles revealed that the use of a TNF inhibitor in patients with RA significantly increased risk for overall opportunistic infection, mycobacterium infection, and overall viral infection. Damage of host in infectious disease is a function of response of host to microorganism. Too weak or too strong response of host to the microorganism may lead to severe organ damage or death. When a patient with RA develops severe infection, it is a common practice to discontinue immunosuppressants or biologics, and start treatment with appropriate agents against a pathological microorganism. Anecdotal reports showed that some patients with RA who developed tuberculosis or Cryptococcal pneumonia during treatment with a TNF inhibitor deteriorated despite cessation of a TNF inhibitor and commencing appropriate drugs for *M. tuberculosis* or *Cryptococcus spp.* Emerging evidence indicated that immune reconstitution inflammatory syndrome (IRIS) accounts for clinical courses of such cases. Continuing immunosuppressive treatment in patients with RA after reactivation of hepatitis B virus is recommended to prevent severe liver injury by IRIS. I will overview infections in patients with RA in the light of IRIS in this symposium.

S18-2

Fulminant cases of tuberculosis or hepatitis B virus infection in RA patients receiving biologics therapy

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Conflict of interest: Yes

Treatment with biologic agents has now established a major place in rheumatoid arthritis (RA) and several other rheumatic diseases. Meanwhile, adverse reactions such as respiratory infections including tuberculosis (TB), bacterial pneumonia and Pneumocystis pneumonia, and reactivation of hepatitis B virus infection have been emerged as the major obstacles for safe accomplishment of these therapy. Effective strategies of prevention and empirical treatment have been established, with considerable success. However, despite these effort, sporadic TB cases continue to occur until now, and even more importantly, more than ten deceased cases have been reported in Japan, in spite of proper anti-TB treatment. Through the analysis of some of these cases, immune reconstitution inflammatory syndrome have been postulated as a provable mechanism. Abrupt stopping of immunosuppressive drugs such as corticosteroids, MTX and biologic agent may cause elevated immune response against existing pathogen and may intensify inflammation, sometimes to fatal degree, which can only be controlled with proper use of immunosuppressive drugs. This phenomenon have been recognized widely in various situation with pharmaceutical immunomodulation in non-HIV infected patients, including TNF blocking therapy and TB. In Japan, several case reports showed this paradoxical exacerbation do occur in RA patients after the initiation of TB chemotherapy with discontinuation of biologics, all of which was controlled with appropriate use of corticosteroids. Reactivation of HVB may progress to fulminant hepatitis with poor prognosis. Physicians must beware the risk of IRIS and be cautious of withdrawal of biologics therapy even at the occurrence of infectious episodes.

S18-3

What is Immune Reconstitution Syndrome? Its clinical and immunological significance

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Conflict of interest: None

The immune reconstitution syndrome (IRS) is an increasingly recognized disease concept and is observed with a broad-spectrum of immunosuppressive therapy-related opportunistic infectious diseases and severe drug eruptions complicated by viral reactivations. Clinical illness consistent with IRS includes tuberculosis, herpes zoster, herpes simples, cytomegalovirus infections and sarcoidosis: thus, the manifestations of this syndrome and diverse and depend on the tissue burden of the preexisting infectious agents during the immumosuppressive state, the nature of the immune system being restored, and underlying diseases of the hosts. Although IRS has originally been reported to occur in the setting of HIV infection, it has become clear that the development of IRS can also be in HIV-negative hosts receiving immunosuppressive agents, such as prednisolone and tumor necrosis factor alfa inhibitors, upon their reduction and withdrawal. Drug-induced hypersensitivity syndrome, a life-threatening multiorgan system reaction, is another manifestation of the newly observed IRS. Clinical recognition of the IRS is especially important in improving the outcome for diseases with an otherwise life-threatening progenosis. Clinicians should be aware of the implications of IRS and recognize that relieving the symptoms and signs of immune recovery by anti-inflammatory therapies needs to be balanced with anti-microbial therapies aiming at reducing the amplitude and duration of tissue burden of preexisting microbes.

S18-4

Tuberculosis during anti-TNF therapy: The clinical characteristics of immune reconstitutions inflammatory syndrome due to discontinuation of anti-TNF therapy

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Conflict of interest: None

Anti-tumor necrosis factor (TNF) therapy increases the risk of tuberculosis (TB). Discontinuing anti-TNF therapy during treatment for TB sometimes results in the reconstitution of immune system and may contribute to “paradoxical worsening”. This phenomenon, known as immune reconstitution inflammatory syndrome (IRIS), is well recognized in human immunodeficiency virus (HIV) patients treated with anti-TB and anti-HIV therapy. To the best of our knowledge, there are 17 reported cases in which the patients developed TB during anti-TNF therapy and experience IRIS after discontinuing anti-TNF therapy and receiving anti-TB therapy. Most of all patients with IRIS had disseminated TB at the time of a diagnosis. The clinical manifestation of IRIS was various. The time from discontinuation of anti-TNF therapy to the onset of IRIS tended to be longer under infliximab therapy than under adalimumab therapy. Regarding the management of IRIS, half of the above patients required new treatment with or an increased dose of corticosteroids. However, two of the patients were resistant to high-dose corticosteroids and required the readministration of anti-TNF therapy for life threatening IRIS. This indicates that anti-TNF therapy inhibits an excessive inflammatory response and thus improves IRIS more effectively and safely than corticosteroid at the time of TB therapy. Moreover, it is suggested that continuing anti-TNF therapy may have the potential to prevent IRIS and accelerate therapeutic response to TB in patients who develop TB during the course of anti-TNF therapy. We herein describe the cases of patients who developed TB during the course of anti-TNF therapy and experienced IRIS after discontinuation of anti-TNF therapy.

S18-5

Development of Acute Liver Failure Due to Viral Reactivation in Patients with Resolved Hepatitis B Virus (HBV) Infection during Immunosuppressive Therapies

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Conflict of interest: Yes

HBV itself is not toxic against hepatocytes. Liver injuries develop as a result of immune response against hepatocytes on which HBV-related

antigens are expressed. Clinical courses of patients with HBV infection are classified into immune tolerant, eradication and surveillance stages. Patients with HBV infection during the immune surveillance stage in whom serum HBs-antigen disappeared are diagnosed as having previously resolved HBV (prHBV) infection. Thus, patients with prHBV infection are classified into 2 types; those after horizontal HBV infection during adulthood in whom viremia resolves transiently and those after vertical HBV infection during babyhood in whom viremia persists until senescence. In both patients, liver injuries do not occur, since HBV proliferates minimally since nucleoside mutations occur during the immune eradication stage. During immunosuppressive therapies, however, minor HCV strains possibly showing active proliferation may appear in the sera, and liver injuries might develop. Hepatitis aggravates due to imbalance of immune reaction in patients with HBV infection leading to development of fulminant hepatitis. In patients with transient HBV infection, massive liver necrosis develops as a result of microcirculatory disturbance due to sinusoidal fibrin deposition, when hepatic macrophages activates in necrotic areas followed by a second attack as LPS. In contrast, in patients developing *de novo* hepatitis B, liver injuries persist for a long-period during immunosuppressive therapies, and sub-massive liver necrosis might develop when hepatitis exacerbates due to imbalance of immune reactions. These patients generally shows fatal outcome when antiviral therapy is initiated following onset of hepatic encephalopathy. In the present paper, the mechanisms involved in development of acute liver failure are discussed in relation to recent status of patients manifesting *de novo* hepatitis B during immunosuppressive therapies.

S19-1

The Fact about the interpretation and scoring of large joints with ARASHI scoring system

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Conflict of interest: None

Treatment of RA has made dramatic progress by the clinical application of biologic. In particular, the biologic is significantly different from the csDMARDs is that having the joint preserving effect. Joint preserving effect is evaluated in small joints of hands and feet with m-TSS.But, it gives directly loss and dysfunction with ADL and QOL is the large joints of the limbs, I think X-ray evaluation of this site is more important. Conventionally, large joints are evaluated by the Larsen grade and have been used for selection of surgical indications and procedures in the RA surgery, However, it has a problem in the evaluation of the efficacy of biologic. Because it has a width in a single grade, and includes a variety of lesions. So, detailed changes in the grade are ignored. Furthermore, it is assumed progression of joint destruction and not intended to repair the joint being confirmed by X-ray in the case of using a biologic. So, ARASHI study group has proposed ARASHI score that is relatively simple and detailed large joint evaluation system. ARASHI score evaluates the front simple X-ray of the 10 joints (Shoulder, elbow, hand, knee, ankle). It reflects the improvement effect of biologic, and is a highly reproducible method. ARASHI score consists of ARASHI status score (ASS) for evaluating one time and ARASHI change score (ACS) for comparing the two time points. Both ASS and ACS evaluates 10 joints. ASS evaluates the four items, 1) joint space narrowing, 2) bone erosion, 3) bone destruction, 4) joint stabilization, ACS evaluates the 5 items that were added to the 5) bone atrophy. ASS evaluates the 1 joint at 0~16 points, and 10 joints at 0~160 points. On the other hand, ACS becomes a negative score if there is improvement. So it evaluates the 1 joint at -11~16 points, and 10 joints at -110~160 points. I tried to actually doing, I realized the difficulty of scoring 2)bone erosion and 3)bone destruction. In this symposium, I outline ARSHI score with specific example.

S19-2

Comparison between ARASHI score and modified Total Sharp Score in the evaluation of large joints destruction in patients with rheumatoid arthritis under disease control of biologic disease modifying antirheumatic drugs

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Conflict of interest: None

Treatment of rheumatoid arthritis (RA) has improved over the past decade with the modification of treatment strategy and recent application of biologic agents (Bio). It has been revealed that the treatment by Bio achieved not only improvement of clinical symptom, but also inhibition of the progression of joint destruction in small joints of hand and foot. However, there are little evidences of inhibition of the progression of the large joint destruction with the treatment by Bio. ARASHI score, which is composed of ARASHI Status Score (ASS) and ARASHI Change Score (ACS), had been newly developed to evaluate the progression of the large joint destruction as well as remodeling. The current study was aimed to investigate the correlation among the ARASHI score, modified total sharp score (mTSS), and other clinical parameters, and to clarify the patients' parameters leading to large joint destructions in patients with RA under disease control by Bio. 75 patients with RA under disease control by Bio were available for the current study. Average disease duration was11.7 year. They were examined for serum level of C-reactive protein (CRP), mHAQ, DAS28-CRP, SDAI, CDAI, mTSS, ACS, and ASS at the beginning of the study. The amount of change of CRP, mHAQ, DAS28-CRP, SDAI, CDAI, and mTSS were defined as ΔCRP, ΔmHAQ, ΔDAS28-CRP, ΔSDAI, ΔCDAI, and ΔmTSS, respectively. There was no significant correlation between the ACS and ΔmTSS. There were no significant correlations betweenΔmTSS and other clinical parameters, whereas ACS was significantly correlated with ΔCRP, ΔmHAQ, ΔDAS28-CRP, ΔSDAI, and ΔCDAI. Our results suggested that sufficient suppression of the disease activity is important for the large joints to prevent the progression of joint destruction among long-standing RA patients under control by Bio. The destruction of large joints did not correlate with that of the small joints of hands and feet among these patients group.

S19-3

Radiographic evaluation of large joint damage in patients with rheumatoid arthritis using total ARASHI scoring method

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Conflict of interest: None

Backgrounds: Structural impairment of large joints in patients with rheumatoid arthritis (RA) is strongly associated with functional disabilities. Although evaluation methods of large joint damage were limited, the ARASHI study group has recently devised new radiographic scoring system. **Objectives**: To evaluate the radiographic damage of 10 large joints (bilateral shoulder, elbow, hip, knee and ankle joints) in patients with RA using the ARASHI score, and to explore factors that predict the progression of large joint damage. **Methods**: We have prospectively examined

72 patients with RA. Radiographic findings of large joints, excluding the joints with history of surgical intervention, were evaluated at baseline using the ARASHI status score and at 1 year using the ARASHI change score. Total ARASHI status score and change score were calculated from scores of all 10 large joints in each patient. We measured CRP, MMP-3 DAS28-ESR, SDAI, CDAI and HAQ-DI at baseline and at 1 year, and then compared differences of these clinical features between total ARASHI change score < 1 (non-progression) group and change score ≤ 1 (progression) group. **Results**: The mean total ARASHI status score of all 10 large joints in 64 patients was 8.38 (0-58) at baseline. The total ARASHI change score showed joint remodeling in 20 patients (27.8%) and progression of joint damage in 22 patients (30.6%) at 1 year. The age, disease duration, CRP, MMP-3, disease activity, HAQ-DI and total ARASHI status score at baseline. The mean MMP-3 value at 1 year in progression group was significantly higher that in non-progression group (154.2 ng/ml vs 80.46 ng/ml, $P < 0.05$). **Conclusions**: We evaluated the radiographic damage of all 10 large joints in each patient with RA using total ARASHI score. Our results showed that decrement of serum MMP-3 level was associated with the inhibition of large joint damage in RA.

S19-4

Effects of tocilizumab on inhibition of large joints destruction in patients with rheumatoid arthritis

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Conflict of interest: Yes

Medication of rheumatoid arthritis (RA) is improved. Although data of small joints destruction is increase using evaluation by mainly modified total Sharp score in many randomized clinical trials, clinical data of large joints destruction is lacking when using new drugs. Data before bDMARDs era showed that bone erosion (ERO) in large joints were seen in 70% of RA cases and in 69% of RA cases without ERO in hand and feet (Drossaers-Bakker). In Japanese data, destruction of 4 large joints in early 5 years were observed in RA patients with large joints involvement who needed total knee arthroplasty (Oishi). It was reported that improvement of pulse Doppler of large joints tended to be delayed compared with that of small joints in ultrasonography examination (Harman). It was reported that early medication using cDMARDs (Moura), anti-TNF drugs (Seki), and biological DMARDs (Nakajima) could delayed progression of destruction in large joints. Concomitant MTX with anti-TNF drugs was suggested to inhibit large joint destruction compare with anti-TNF monotherapy (Asai). Tocilizumab (TCZ) may be one of the promising options to inhibit the progression of large joints due to strong effect to reduce joint inflammation. 22 RA cases who continued TCZ treatment during 2 years were used in the present study. SHS was used for evaluation of small joints and ARASHI score (Kaneko) was used for evaluation of large joints of lower extremities. Delta SHS of baseline, 0-1 year and 1-2 year was 11.3, 3.2 and 1.2, respectively.Mean ARASHI score of lower extremities in 0-2 year was -0.8. In analysis using 125 joints during 2 years, 12.8% were improved, 84.0% were unchanged and 4 3.2% were worsened. The rates of concomitant MTX were decreased from 69.6% at baseline to 26.1% at 2 year. No joint surgeries were performed in this observation period. TCZ was suggested to be one of the options to inhibit large joints destruction despite of small cases in this study.

S19-5

Evaluation of synovitis at the large joint using ultrasonography and histological findings

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Conflict of interest: None

Background: After starting to use biological DMARDs (bDMARD), the number of small joint (SJ) arthroplasty increased as compared with large joint (LJ) at our rheumatic center. Additionally, ultrasonography (US) for the examination of the affected joints widely utilized and it became a tool by which the rheumatologist should learn to diagnose RA and to evaluate disease activity. **Purpose:** To clarify relationship among systemic disease activity, local disease activity using US and synovial histopathological evaluation, we examined serum CRP, MMP-3 and DAS28, and US at the surgical site before surgery. After surgery, histopathological examination of the gathered synovium at the surgical site was performed. **Patients & methods:** Between March, 2011 and September, 2015, 668 joints underwent surgical treatment and synovial biopsies were performed. There were 152 LJs including 8 shoulders, 60 elbows and 84 knees, and 516 SJs including185 fingers, 118 toes, 192 wrists and 21 ankles. Male: female ratio was 1:7. The bDMARD (IFX20, ETN62, ADA17, TCZ44, ABT16, CZP4, GLM13) was used in 176 cases. Maximum power Doppler (PD) signal grade of US was determined ranging from 0 to 3. They were compared with serum CRP, MMP-3, DAS28 and local disease activity using histopathological evaluation using Rooney score (RS). **Results:** Systemic disease activity correlated with local PD signal intensity both in LJs and SJs. Also, total RS and its item score excepting "proliferating blood vessels" correlated well with PD signal intensity. Systemic disease activity, local synovial proliferation and lymphocyte infiltration were more severe in LJs than in SJs. Though sensitivity of synovitis at LJs lower than at SJs, there was not a significant difference in PD signal intensity and RS between at LJs and at SJs. RS reflected systemic disease activity more in LJs than in SJs. **Conclusion:** US is an excellent tool to reflect local synovitis as well as systemic disease activity both in LJs and SJs.

S19-6

Sonographic assessment of large joints in rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is characterized by destructive synovial inflammation which causes functional impairment. Musculoskeletal ultrasonography allows accurate assessment of synovitis by directly visualizing the thickening and hyperemesis of synovial tissues and thus plays important roles in the diagnosis and monitoring of RA. The image resolution and the sensitivity to detect synovial with ultrasound tend to be suboptimal in the large joints as compared to those in the small joints. In addition, because the area that can be visualized in a single image with a generally used transducer is limited, scanning technique which capture captures the whole synovial lesions in the large joints can be more complex. Therefore, quantitative/semi-quantitative methods to evaluate synovitis are less established in the large joints than in the small joints. Furthermore, the radiographic methods that sensitively capture the change in structural damage are also less established in the large joints than in the small joints, making studies to demonstrate a utility of ultrasonography to predict radiographic progression in the large joints difficult. However, because the influence of the large joints on physical function is more profound than that of the small joints, there is urgent need for the feasible and accurate assessment of the large joints. In this presentation, the current status and prospective of the sonographic assessment of large joints will be discussed.

S20-1

Rheumatoid Arthritis and Healthcare Costs - International Comparison - Impact of DMARD combination therapies on Healthcare economy -

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Conflict of interest: None

With the introduction of biological agents (BA), the medical costs of Rheumatoid Arthritis have risen considerably. In 2014, all 7 BAs sold in Japan ranked among the world's top 50 most expensive drugs and the 3 BAs are within top 4, yet BA selling price in Japan is relatively low. Then why BA treatment costs high and is hard to achieve in Japan? This is because insurance system differs among countries. Generally BA is expen-

sive and mainly used in the advanced countries. OECD countries excluding the U.S. maintain medical cost through public healthcare insurance. There are essentially two major types of healthcare system: Beveridge (funded by taxation) and Bismarck (saving-type funded by payroll contributions). Currently a combination of the two is also popular. In Western Europe, medical cost is covered by British-type consumer tax, patients can receive treatment almost for free and BA penetration rate is high. In Australia, the self-pay ratio is 15% and BA is less popular than Western Europe. Among advanced countries, only Japan and Korea have 30% self-pay ratio basically, yet 10% is applied to those with RF positive in Korea. In the U.S., the largest BA market, lacks universal healthcare basically (The poor and disabled are covered by public insurance, though) and there is a growing public concern about healthcare costs. However, drug companies often take some measures to reduce patient's self-pay cost, thus the actual self-pay is around a few thousand yen per month and the lower price encourages more BA use in the U.S. In Japan, based on 30% self-pay ratio, around 400,000-500,000 yen per year is necessary for BA therapy, which costs 20 to 25 times more than csDMARD. Recently European countries where patients can receive medical treatment without self-pay have released guidelines and recommended csDMARD therapy before moving to BA to control price escalation. Japan also needs healthcare cost control. I will report csDMARD triple therapy results in Japan.

S20-2

Issues with the medical fee system in RA treatment

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Conflict of interest: None

With the advances in RA treatment, the costs for treatment also has skyrocketed. Improvement in disease activity commensurate with the high costs is essential for the patient to be convinced to take up such treatment. Over the years, the RA treatment community has chosen the treatment that either has remarkable efficacy or convenience, justifying the high costs. But in reality, this has led to a completely different problem - that of medical fee receipts All medical fee receipts undergo strict scrutiny for the suitability and validity of the treatment involved. But variations do arise in these scrutinies, based on several factors. In spite of efforts to standardize these scrutinies like holding pan region conferences in the case of orthopedic surgeons, instances of varying judgement on individual cases often arise. In 2015 working Group of the Japan Congress of Rheumatology undertook a survey of the trustees of this congress, regarding the doubts surrounding medical insurance. This survey revealed several doubts, notable ones being, Interval for MMP-3 blood work, Second test for anti CCP antibody, Doppler fees for ultrasound scans, MTX usage, Biologics usage and the fee calculation for surgery. We would like to thank everyone for their contribution. The Social Insurance Working Group shall strive to provide detailed response to all the doubts that were unearthed in this survey.Institutions where large number of RA patients are treated often receive corrective guidance from local bureau of health and welfare due to the average invoice medical fee points being high. The guideline from the Insurance division of MHLW stipulates issuing corrective guidance to all institutions falling in the top 8% of those which overshoots the average invoiced medical fee by a certain margin. This is also a distraction for RA treaters. Specific measures are not highlighted in this summary, but will be addressed in the presentation slides.

S20-3

Health care system in Japan and RA medical economics in NinJa

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Conflict of interest: Yes

National medical care expenditure in Japan increased year by year, and it reached finally more than 40 trillion yen (314,700 per person) in fiscal 2013. Japanese government is promoting the use of generic drugs as part of the medical cost containment, but its market share (56% by 2015 preliminary) in Japan is still much lower than in USA (92%) and in Germany (83%). NinJa (National Database of Rheumatic Diseases by iR-net in Japan) showed that the disease activity decreased year by year, the remission rate of DAS28-ESR dramatically increased from 12.7%(NinJa2003) to 39.3%(NinJa2014), and the rate of RA-related surgery decreased from 7.7% to 4.9%. The usage rate of MTX increased from 36.7% to 63.8%, biologics from 0.5% to 26.8%, tacrolimus from 0 to 10.8%, and annual costs of anti-rheumatic drug per patient gained from approximately 30,000 to 485,000. However, the usage rate of csDMARD other than MTX has maintained after decreasing from 60.6% to 37.0%(NinJa2009), which means the necessity of csDMARD as its monotherapy and combination therapy with MTX for RA. In addition, the dose reduction and the extension of dosing interval of biologics are progressing, and the use of Biosimilar will be promoted in the future. Now getting a powerful therapeutic tool "biologics", rheumatologists must determine the therapeutic strategy for each patient considering the expense of the patient and the cost effectiveness including negative amount due to adverse events. However, many doctors are not familiar with the underlying health care systems, such as programs for intractable diseases, disability pension, physical disability certificate, expensive health care system, and so on. In this symposium, as well as to organize the knowledge of the health care system needed to RA care, I want to think about RA medical economics on the basis of the data of NinJa.

S20-4

Health Economic Issues Associated with Rheumatoid Arthritis and Cost-Effectiveness of Biologics

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Conflict of interest: None

The introduction of biologics has resulted in significant advances in the treatment of rheumatoid arthritis (RA). Analyses of the IORRA, a prospective cohort study of Japanese patients with RA that has been ongoing at the Institute of Rheumatology, Tokyo Women's Medical University since 2000, have also provided evidence for improvement in the outcomes of patients with RA over time. On the other hand, the progress in RA therapy may be associated with a further increase in medical costs, placing a heavy burden on society as well as patients. RA is a chronic condition with long-term impact, which makes not only direct costs but also indirect costs a large part of the disease burden. However, few studies have been conducted to assess the health economic aspects of RA in Japan. We have investigated the direct costs and loss of work in Japanese patients with RA based on the IORRA cohort. Our studies have clearly shown that the economic burden on patients with RA has grown year by year and that direct and indirect costs associated with RA increase with the progression of functional impairment and reduction in quality of life. This means that stopping the progression of joint damage through early and appropriate treatment of RA may, for example, eliminate the need for joint surgery, prevent patients from becoming bedridden or requiring nursing care, and restore the ability to work, potentially decreasing both direct and indirect lifetime medical costs. A pharmacoeconomic study evaluates both the clinical benefits and the economic efficiency of a drug to determine whether it is worth the cost. Cost-utility analysis is mainly used to assess the cost-effectiveness of biologics in the treatment of RA. A simulation analysis based on routine clinical practice data from the IORRA has demonstrated that cost-effectiveness in patients receiving biologics is well within the acceptable range compared with that in patients receiving the "anchor drug" methotrexate.

S20-5

Health economic evaluation in clinical plactice guideline of rheumatoid arthritis

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Conflict of interest: None

Health economic aspects of biologic DMARDs would be as important as their efficacies and safety, as they are so efficacious and so expensive, especially for establishing clinical practice guideline. Cost-effec-

tiveness of clinical strategies were already referred to in foreign guidelines, like the ACR's one in 2015 and the EULAR's one in 2013. Although no original cost-effectiveness evaluation were conducted, importance of consideration for the impact of high-cost biologic DMARDs to public health care system were repeatedly emphasized, especially in the EULAR guideline. Biologic DMARDs are assessed by various HTA agencies throughout the world for the purpose of coverage decision and/or reimbursement price modification. In general, HTA agencies are likely to set stricter criteria for indication of biologic DMARDs than clinical practice guidelines would do. For example, NICE (National Institute for Care Excellence) recommends the use of biologic DMARDs only if patients' DAS score is above 5.1 and they have treated two or more conventional DMARDs. Not only the condition of initial indication but also that of continuous usage, are more stricter than those in the EULAR guideline. CADTH in Canada and PBAC in Australia also set similar criteria for biologic DMARDs. HTA would be incorporated to Japanese health care reimbursement system since Apr. 2016, while it is provisional phase. Currently, several drug which met certain criteria are designated by the government and manufactures are required to submit health economic data. Data would be reviewed by external group and appraised by the governmental decision making body. Results would be reflected to next price revision, enacted from Apr. 2018. Fortunately enough, there already be domestic data sources/cohorts, which would be useful for conducting health economic analyses of biologic DMARDs in Japan. Further health economic analyses, using these data source would highly be desired.

S20-6

Affordability of RA Treatment, Patient's Perspectives

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Conflict of interest: Yes

It has been 10 years since the advent of biological treatment of RA. These drugs have had an enormous effect, and changed treatment to the degree that to call it a paradigm shift would not be an exaggeration. However, these drugs are expensive, and the expense increases year after year, and greatly affect overall medical costs. The costs, of course, are also borne by the patients. Not only in our own country, but in the western nations as well, the cost of these drugs can be a burden. Alternative dosing schedules and lower dosages are being implemented, as well as the use of bio-similar (BS) drugs in order to combat high costs. We conducted a patient survey to determine the monthly amount that patients felt was comfortably affordable to pay for treatment. (Methods) Our facility spearheaded a patient survey with the cooperation of 33 other facilities, with a total of 9,000 patients participating. It covered 16 aspects of treatment. This abstract addresses the section regarding treatment costs, in particular the question " What amount do you feel is comfortably affordable to pay monthly for treatment?" asked of both patients using biologics, and patients using DMARDS therapy. Results were tabulated separately by treatment type, and were also tabulated across 6 geographic areas spanning Japan. (Result) 88% of DMARDS treated patients and 69% of biologics treated patients replied that a cost of under 20,000 yen monthly was comfortably affordable. This is already attainted by DMARDS patients. There was no significant difference in replies regarding cost based on area. The survey demonstrated that in the case of biologics patients, medical costs are higher than they are comfortably able to pay. (Conclusion) The cost of RA treatment can adversely affect family finances. Further cost-saving approaches are needed to reduce individual patient burden.

S21-1

Differential diagnosis of polymyalgia rheumatica from point of view of clinical assessment - Especially difference from late-onset rheumatoid arthritis

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Conflict of interest: None

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease of older individuals and classic symptoms include pain and long-term morning stiffness of the neck, proximal arms and thighs with subacute phase; moreover, well-known association exists between PMR and giant cell arthritis. Although markers of inflammation are often raised, no specific laboratory test exists for the disorder. Therefore, the diagnosis is based on clinical assessment and it is necessary to distinguish between patients with PMR and late-onset rheumatoid arthritis (RA), which usually raise inflammatory markers as well. In 2012, a collaborative initiative of the EULAR and the ACR published provisional classification criteria of PMR. Sensitivity of this classification was 68%, which was lower than that of former classifications because it aimed early differentiation. Patients with RA basically have intra-articular synovitis and initial several swollen joints are small joint of the fingers and toes, which are usually not affected in patients with PMR. In terms of laboratory data, patients with PMR have negative rheumatoid factor and anti- cyclic cirullinated peptide antibody. Since main symptoms of PMR are bursitis and tenosynovitis, there is no increase of creatine kinase. In the X-ray, there is no evidence of bone destruction in patients with PMR whereas patients with RA gradually have peri-articular osteoporosis and bony erosion. Recently, Ultrasonography of the joints are quite useful and that is involved in the classification of PMR in 2012. Patients with PMR have tenosynovitis of long head of biceps tendon, subdeltoid bursitis. On the other hand, patients with RA usually have intra-articular synovitis. In summary, to differentiate PMR from late-onset RA, it is the key to assess comprehensively whether there is specific small joints arthritis (5^{th} MTP joints), peri-articular bursitis (PMR) or intra-articular synovitis (RA).

S21-2

The role of ultrasound in the diagnosis of polymyalgia rheumatica

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Conflict of interest: None

There are number of reports concerning the ultrasonographic findings in PMR. The possible problems are listed below. 1. As there is no golden standard in the diagnosis of PMR, the background of PMR patients are not standardized between studies. Therefore, the prevalence of positive US findings are variable. 2. There are also variations in the selection of control patients, leading to variations in the sensitivities and specificities. 3. The definition and evidence concerning inter- and intra- observer variations in the evaluation of bursitis, which is the most frequent findings in PMR, is limited. 4. The evidence concerning the usefulness of power Doppler evaluation in PMR is limited. 5. US evaluation is useful in the differentiation between PMR and non-inflammatory diseases but less so between PMR and elderly onset RA. 6. The relative importance of individual US findings (bursitis, tenosynovitis and joint synovitis) in PMR is unknown. 7. The evidence concerning the usefulness of the US evaluation of hip joint in addition to shoulders is limited. In order to standardize the patient populations, the new 2012 EULAR/ACR classification criteria for polymyalgia rheumatica might be of great value. The above mentioned problems might be solved with the conduction of clinical studies in multi-center trial. In clinical practice, the final diagnosis of PMR is made by considering the findings with high sensitivities and specificities. For example, although variations exist, the sensitivity of subdeltoid bursitis is relatively high in PMR, so the absence of bilateral subdeltoid bursitis rule out PMR with high probability. With point of care US, there are cases that PMR can be easily ruled out in minutes before waiting the results of blood exam. PMR should be diagnosed by expert clinician who has enough knowledge and experience along with clinical information included in the new classification criteria.

S21-3

Utility of FDG/PET in the differential diagnosis of polymyalgia rheumatica

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Conflict of interest: None

Clinical features of polymyalgia rheumatica (PMR) are scarce, which causes problems in the differential diagnosis. We identified the distinctive PMR lesion by using ^{18}FDG-PET/CT. PMR showed increased FDG uptake in the ischial tuberosities (ITs), greater trochanters (GTs), and lumbar spinous processes (LSPs). Positive results at two or more sites showed high sensitivity (85.7%) and specificity (88.2%) for diagnosing PMR. When PMR cases are classified based on the presence of large vasculitis, synovitis and bursitis are rare in PMR with vascular involvement. Differentiating elderly-onset seronegative spondyloarthritis (SpA) with PMR is difficult. We compared SpA with PMR in the PET findings. No significant difference in FDG uptake for the ITs, GTs, or LSPs was noted among SpA and PMR. Although FDG uptake in the ITs, GTs, and LSPs provides evidence of enthesitis in SpA, FDG accumulation at these sites in PMR may indicate bursitis. However, FDG uptake in sacroiliac joints was significantly higher in SpA than in PMR or RA. This PET/CT finding can distinguish SpA from RA and PMR. Moreover, we compared the FDG-PET/CT findings in patients with elderly-onset RA with those in patients with PMR. Specific uptake patterns were noted in the shoulders and hips in each group: circular and linear uptake patterns were noted around the humeral head in the EORA group, whereas focal and non-linear uptake patterns were noted in the PMR group. It is thought that the former shows synovitis, whereas the latter reflects the bursitis, with three-dimensional extension. Moreover, focal uptake before the hip joint, indicating iliopectineal bursitis, was limited to the PMR group. Conversely, as the bursitis in the ITs, LSPs, and iliopectineal part is difficult to identify on US and is specific for PMR, PET was suggested. We aim to determine the diagnosis by identifying the characteristic lesion sites with PET and clarify the pathology of PMR.

S21-4

Definition of disease activity, remission and relapse in polymyalgia rheumatica and glucocorticoid therapy

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Conflict of interest: None

Glucocorticoid (GC) therapy usually leads to rapid improvement in symptoms of polymyalgia rheumatica (PMR), and good response was included in a previous classic classification criteria. However, up to 29-45% of patients with PMR do not adequately respond to GCs within 3-4 weeks, and relapses are common. Long-term GC therapy is required to reduce the risk of relapse, and long-term GC exposure is associated with substantial morbidity. To assess effectiveness of GC treatment or relapse of the disease, disease activity of PMR should be evaluated. PMR-activity score (CRP (mg/dl)+VAS p (0-10)+VAS ph (0-10)+(morning stiffness (min)×0.1)+ the ability to elevate the upper limbs (3-0)) has been established in 2004, but the score has not been adopted in most of randomised controlled studies. One of problems of this composite score is that many older patients may continue to have pain and stiffness due to other rheumatic conditions. Time of morning stiffness may be difficult to determine for elderly patients. And so, remission and efficacy is pragmatically defined by the qualitative approach or proportion of patients in disease remission off corticosteroids, without relapse or recurrence. This symposium will review current evidence of GC treatment of PMR in terms of both effectiveness and safety. Data about GC and MTX therapy in retrospective cohort of PMR in Tokyo metropolitan geriatric hospital will be presented.

S21-5

New strategies for the treatment of PMR - Possibility of the biologic agents

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Conflict of interest: None

Most PMR patients are successfully treated with low-dose (10~15 mg/day) prednisolone (PSL) to achieve remission. However, some cases are refractory to PSL and have adverse events related to steroid, such as diabetes, osteoporotic fractures, etc. Female sex, high ESR (>40mm/h) and peripheral arthritis are considered to be associated with a higher relapse rate/or prolonged PSL therapy and MTX is conditionally recommended in such cases. Though TNFαinhibitors are not recommended from the point of considerable risk of potential harm and cost-effectiveness, there are many case reports that tocilizumab was effective for PMR. We tried steroid-free tocilizumab monotherapy for remission induction in13 PMR patients. Four cases abandoned the trial due to inefficacy in 2 and adverse events in 2 cases. The other 9 cases have been successfully treated to achieve clinical remission (no myalgia and normal serum CRP and ESR). Tocilizumab may be the alternative therapy instead of PSL in some PMR patients.

Educational Lecture

EL1

From ABC's of cytokine signaling to disease regulation

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Conflict of interest: Yes

Cytokines are physiologically active substance produced by multiple cells and act on neighboring cells through the receptor expressed on the cell surface. They possess diverse functions and have been analyzed with in vitro and in vivo experiments utilizing knockout animals. Their function in human has been demonstrated by the analysis of patients with mutation or deficiency of a specific gene. The utility and difference of findings in basic science has been also confirmed by comparing with those results. Broad usage of biologics have revealed the role of cytokines in human diseases without genetic mutation through their difference in efficacy and the rate of side effects over time. Although a single cytokine inhibition with a biologic is highly effective in rheumatoid arthritis, it has also been clear that non-negligible amount of patients cannot earn privilege. Recent development in biologics is targeting more than one cytokine. These clearly demonstrates that disease and cytokines are complexly intertwined and are not in pairs and can also vary depending on their disease stage. In recent years, small molecules targeting the intracellular protein activated by cytokines has demonstrated clinical efficacy. Therefore, there is increasing importance of understanding the biological function of cytokines and cytokine signaling. Within this lecture, I would like to overview the cytokine signaling and discuss on the relationship with disease along with the efficacy of inhibiting cytokine and cytokine signaling.

EL2

Current concept and management of sarcopenia

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Conflict of interest: None

Frailty is one of the features of geriatric syndrome, and the prevention from frailty and sarcopenia is a major problem in elderly population. Recent findings suggest that sarcopenia is caused by multiple processes that may involve decreased hormone levels, malnutrition, inflammatory status. Nutritional, pharmacological Intervention and exercise training may be promising candidates for the treatment of sarcopenia.

EL3

The Significance of Tojisha Kenkyu

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Conflict of interest: None

Tojisha kenkyu ("tojisha" means "the person centered" in Japanese, and "kenkyu" means "research") is an approach for tojisha with troubles, such as disabilities and illnesses, to discover the meaning and mechanisms of those troubles and their coping methods by treating their troubles as a subject of research and receiving the help of peers with similar experiences, without fully relying on doctors and supporters for interpretations and ways to cope with their troubles. Tojisha kenkyu originally began among individuals with mentally disorders, and later expanded to those with addiction, developmental disorders, chronic pain, and then dementia. Now, tojisha kenkyu is no longer limited to disabilities or illnesses and is even being done by people such as students, regular office workers, families and supporters. Tojisha kenkyu is significant for two reasons. It is academically significant since it enables the discovery of novel hypothetical knowledge on academic theories and coping methods that experts tend to overlook. Our group has created the framework in which testable hypotheses are extracted from tojisha kenkyu and verified with established experimental methods, especially regarding the topics of neurodevelopmental disorders and chronic pain. For example, against a commonly accepted view that individuals with autism spectrum experience persistent deficits in social communication, the hypothesis was suggested in tojisha kenkyu that the core problem is more the preceding sensory-motor characteristics. In addition, a hypothesis on chronic pain using a model of addiction has been proposed by a person with both addiction and chronic pain. In this lecture, several cases of such exploration will be introduced. Tojisha kenkyu is also significant for recovery, promoting the well-being of tojisha through participation in tojisha kenkyu itself. When defining recovery, there are often differences between the criteria proposed by specialists and tojisha. We propose "patient created outcomes", which are criteria attaching importance to the viewpoints of tojisha. In addition, we have just started a clinical trial in which we measure the effectiveness of tojisha kenkyu using such outcome criteria. This trial will be discussed briefly as well. Finally, consideration will be given to the intermediary role tojisha kenkyu should play between the self-advocacy movement and medicine.

EL4

Treatment of Lupus Nephritis: Up to Date

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Conflict of interest: Yes

Systemic lupus erythematosus (SLE) is an autoimmune disorder caused by the break of self-tolerance. Persistent acute or chronic inflammation leads to irreversible organ damages and dysfunction. Kidney is one of major targets of SLE. Lupus nephritis (LN) is primarily caused by depositions of immune complexes (IC) to glomeruli. According to ISN/RPS2003 classification, LN is categorized into 6 major classes; Class I to IV. While nucleosome-related antigens such as DNA or histones have been expensively studied as autoantigens comprising IC, recent studies identified glomerular epithelial cell- or complement-related autoantigens, which imply the multicomponent nature of LN autoantigens and are attracting increasing attention as biomarkers for LN. Sites of IC deposition determine histological responses of LN. Mesangial deposition is associated with Class I (minimal mesangial) or Class II (mesangial proliferative). Subendothelial deposition leads to endocapillary proliferation, which are further subdivided into Class III (focal) and Class IV (diffuse). Subepithelial deposition gives rise to Class V (membranous). Class VI is advanced sclerosis LN. Aggressive immuno-suppressive therapy is required for Class III, IV and V. We identified the presence of chronic lesions (A/C and C) and mixed type (Class III/IV+V) as histological findings indicative of poor renal prognosis. By analyzing 372 cases of LN registered to Japan Renal Biopsy Registry (J-RBR), we also found that mixed type comprises 20% of all cases, and whose proportion becomes higher among cases with repeat biopsies. Since the repeat biopsy is generally applied to patients with refractory or relapsing LN, this finding is consistent with our notion that mixed type is a Class with poorer prognosis. It would be critical how these patients are managed. In this lecture, I will overview the recent progress in treatment of LN as well as the progress in lupus pathogenesis and diagnosis.

EL5

Diagnosis and treatment of drug-induced lung disease

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Conflict of interest: None

Drug-induced lung disease (DILD) is defined as an adverse clinical event which supports a link between a drug and a respiratory adverse event. The link is suspected when a drug caused a particular clinical event, however its proof may be difficult to obtain. The diagnosis of DILD depends on this relationship. Current diagnostic criteria are, 1. There should be a history of drug exposure, 2. Clinical phenotype should conform to earlier observations with the drug, 3. Etiology of lung disease other than drugs should be ruled out, 4. Improvement should follow dis-

continuation of suspected drugs, 5. Symptoms should recur on rechallenge. In real clinical settings, cases to fulfill all five criteria are limited and many fail to prove the causal relationship, then clinicians have to make a reasonable inference. Defining clinical phenotype by evaluating clinical course, imaging, pulmonary function, blood testing, fiberoptic bronchoscopy, should be considered with a meticulous medication history. Differential diagnosis, therefore, depends on ruling out of non- DILD such as idiopathic interstitial pneumonias, infection, airway diseases and heart failure. Treatment of DILD is introduced when a clinician suspects that the etiology of lung disease may be due to drug (s) taken. In a case of clinical phenotype is mild, (A) Observe the clinical course by withdrawing the suspected drug. If a patient is thought to be moderate, (B) Administer corticosteroid; 0.5-1.0mg/kg of prednisolone (PSL), then taper PSL gradually (corticosteroid maintenance therapy). In case of severe disease, showing respiratory distress or PaO2 less than 60 mmHg, (C) methylprednisolone of 500-1,000mg pulse therapy should be performed and followed by the corticosteroid maintenance therapy. The result of treatment should be reconsidered for the diagnosis. A high index of clinical suspicion is required, and coupling of the diagnosis and treatment remains of value in DILD.

EL6

Treatment of rheumatic diseases during pregnancy and lactation

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Conflict of interest: Yes

Progress in treatment of rheumatic diseases and reproductive medicine has made it possible for more patients to have children. Active disease in patients with rheumatoid arthritis (RA) and systematic lupus erythematosus (SLE) tend to bring poor outcome of pregnancy. We have to strive to let outcome be good using medicine in safe. Many of RA patients in remission are capable to stop the medication after conception because RA tend to improve during pregnancy. SLE patients have to continue medication throughout of pregnancy. We have to pay attention to the teratogenicity in the 1st trimester and to the fetal toxicity in the 2nd and the 3rd trimester. SLE has tendency to have pregnancy complications as preeclampsia and intrauterine growth restriction especially with antiphospholipid antibodies syndrome. The rate of having anti-SS-A antibodies in patients with SLE is 40%. About 1% of fetus of mothers with anti-SS-A antibodies developed to congenital heart block. The method to predict or prevent CHB has not be established. We would like to introduce the findings produced by the research team for surveillance, the research program of the Japan Ministry of Health, Labor and Welfare, concerning the pregnancy outcome of mothers positive for anti-SS-A antibodies and antiphospholipid antibodies.

EL7

Visualization of skin immune responses

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Conflict of interest: None

Varieties of immune cells orchestrate cutaneous immune responses. To capture such dynamic phenomena, intravital imaging is an important technique and it may provide substantial information that is not available using the conventional histological analysis. Multiphoton microscopy enables the direct, three-dimensional, and minimally invasive imaging of biological samples with high spatio-temporal resolution, and it has now become the leading method for *in-vivo* imaging studies. Using fluorescent dyes and transgenic reporter animals, not only skin structures but also cell- and humor-mediated cutaneous immune responses have been visualized. In this forum, I will introduce recent findings in cutaneous immune responses in mice and skin structures in some skin diseases using two-photon microscope.

EL8

Basic immunology for rheumatologists

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Conflict of interest: Yes

Recent advance in the development of molecular-targeting drugs have changed the concept of treatment for rheumatic diseases. In addition, molecular targeted drugs have opened the door to studying and understanding the pathogenesis underlying these diseases. Therefore, it is becoming important to understand basic immunology to choose the proper therapy for a variety of patients. In this lecture, I overview the concept of basic immunology for rheumatologists.

EL9

Differential diagnosis of the arthritic diseases

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Conflict of interest: Yes

The classification criteria of rheumatoid arthritis (RA) were revised in 2010, which got closer to diagnostic criteria. The classification criteria work for the formation of the patient group to be analyzed, while the diagnostic criteria are to be considered for individual patient. The specificity of the revised RA classification criteria is entrusted by the requirement of differential diagnosis before stepping forward to the scoring system. The validity of the revised criteria in Japanese RA patients was confirmed by the subcommittee of the Japan College of Rheumatology, which listed several diseases to be differentially diagnosed: menopausal disorder, osteoarthritis, polymyalgia rheumatica, peripheral spondyloarthritis, systemic lupus erythematosus, parvovirus B19 infection, adult Still's disease, etc. The differential diagnosis procedures include an interview, physical examinations, blood tests, and imaging tests with the understanding of the strength and weakness of each. The interview may reveal the onset mode and the temporal change of the symptoms and it provides information of currently subsided symptoms and those hard to be examined. The examination of the joints is indispensable for the understanding of the current disease status and a future prediction. Around 70 joints must be examined, at least on the first visit. The joint swelling is different from bony protrusion and from subcutaneous edema with the mobility. We should examine for the presence of joint manifestations such as synovitis as well as tendon, muscle and skin disorders. The check for the inflammatory reactants and autoantibodies predominates in the blood tests, as well as the exclusion of possible infectious diseases. Recently, joint examination by ultrasound and MRI have been widely used. Ultrasound is particularly useful at the time of the first visit of patients by prompt identification of the presence of synovitis, tenosynovitis and the crystal deposition.

EL10

Application of iPS cell technologies to cartilage regeneration and disease modeling

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Conflict of interest: Yes

Primordial cartilage serves as skeletal templates during development that sustain the embryo bodies. It gives rise to two types of cartilage, growth cartilage and articular cartilage, after birth. Growth cartilage is where the bone grows in children, and its dysfunction due to genetic mutations cause dwarfism and skeletal malformation, conditions called skeletal dysplasia. Articular cartilage covers the ends of bones and provides shock absorption and lubrication to diarthrodial joints. Injury and degeneration of articular cartilage cause joint pain during motion, leading to osteoarthritis in adults. The conditions that compromise growth cartilage or articular cartilage are poorly understood, and curative drugs are not available. iPS cell technologies are beginning to be used to study these cartilage diseases. We have been developing a method in which human

iPS cells (hiPSCs) are differentiated toward chondrocytes, the cells that constitute cartilage. We are generating effective and safe hiPSC-derived chondrocytes as regenerative medicine technology to treat defects in articular cartilage and sustain healthy joint function. The goal is to use these chondrocytes in clinical tests. In a separate project, we have generated hiPSC-derived chondrocytes from patients with skeletal dysplasia. FGFR3 chondrodysplasia such as achondroplasia is caused by a gain-of-function mutation in the FGFR3 gene. We found that chondrocytes derived from hiPSCs generated from patients suffering from FGFR3 chondrodysplasia produce abnormal cartilage that reproduces the pathology of the diseases and thus offers an iPSC-based disease model.

EL11

Cutaneous manifestations of rheumatic diseases

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Conflict of interest: Yes

As the skin is one of the most commonly affected organs in rheumatic diseases, various cutaneous manifestations are observed. These skin symptoms indicate useful clinical information. First, as skin symptoms are frequently observed at the early stage, they provide a great clue to the diagnosis. Skin manifestations can be classified into disease-specific and non-specific. While disease-specific manifestations are of no doubt useful, non-specific findings are no less informative since they can be major symptoms in early stages or in mild forms. Secondly, skin manifestations are not only important in the diagnosis but also in the evaluation of disease activity. Some cutaneous symptoms of rheumatic diseases are correlated with disease activity, whereas others do not. Thus, it is critical to judge these symptoms precisely. It is also important to differentiate skin eruptions related to rheumatic diseases from those unrelated. It is especially important because patients with connective tissue diseases often develop drug eruptions and cutaneous infections. This lecture will primarily deal with systemic lupus erythematosus, systemic sclerosis, and dermatomyositis, and explore what we can read from skin rashes of patients with rheumatic diseases.

EL12

MTX treatment in collagen-vascular diseases

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Conflict of interest: Yes

The patients with collagen-vascular diseases such as rheumatoid arthritis (RA) have been treated with glucocorticoids. Since disease-modifying anti-rheumatic drugs (DMARDs) are necessary to change the natural history of disease course, methotrexate (MTX) has developed as DMARDs and now widely recognized as an anchor-drug for RA. In Japan, MTX was approved in 1999 for RA with the maximum dose of 8mg/week it was up to 16mg/week since 2011. In other collagen-vascular diseases including systemic lupus erythematosus, mixed connective tissue disease, and vasculitis syndrome, MTX are widely used to control synovitis and/or to reduce the dose of glucocorticoids. On the other hands, we still have problems with MTX. How should we maximige the efficacy and reduce the side effects? We need both the standard treatment algorithm and individualization. We can accept the rapid escalation and high dose strategy. In Japan, 6 to 8mg/week MTX is started with increment of 4mg/week over every 4 weeks, targeting the tolerable maximum dose at 12 weeks. The efficacy of MTX with such strategy is outstanding not only in clinical but also in structural point of view. However, less than 50% of the patents can't use 16mg/ week MTX, in part through the dose-dependent side effects such as stomatitis, epigastric discomforts, and elevation of liver enzymes. In addition, some patients can achieve clinical remission even with less than 16mg/week MTX. In order to personalize MTX treatment, one may measure the polyglutamated MTX (MTX-PG) in circulating RBC. I will introduce our approach to measure MTX-PG in a prospective cohort (MAGIK) in Japanese RA patients MTX and compare the MTX-PG concentration between Caucasian and Japanese. Finally I will touch the issues around MTX treatment in clinical practice in Japan.

EL13

Design of Clinical and Epidemiological Research

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Conflict of interest: None

Epidemiological research and clinical research using epidemiological methods have played a major part in "creating" evidence. Epidemiology is defined as "scientific research that clarifies the frequency and distribution of various health-related events, as well as the determinants that affect these (elucidation of cause and effect), that occur within a clearly specified population". Clinical trials evaluating treatment efficacy are methodologically included as interventional studies within epidemiological research. The starting point for evidence "creation" lies in clinical questions generated from the problem consciousness of the actual field. Clinical questions are those inquiries encountered in clinical practice by medical practitioners and providers, and the answers to such questions may improve patient outcomes. These questions change with new diagnostic methods, treatments, and medical knowledge. In order to prepare actual research, it is necessary to have a process that refines clinical questions and further clarifies them as research questions. One could define research questions as clarifying the greatest common denominator of clinical questions based on individual examples and aiming for generalization. Fukuhara has proposed an 8-item "FIRMNESS checklist" that aims to articulate research questions. What are meanings for clinicians to do clinical research? There are two points to be emphasized. One is the creation of clinical evidence which resolve unmet clinical needs, which is primary for clinical research literally. The other is a possibility that clinical research make participating clinicians to be better clinicians through research activity. Experiences of conducting clinical research may give clinicians better eyes to identify problems that patients are suffered, may make clinicians to record medical data better and may improve clinicians' communication with peers, other health professionals, patients and patient family. Namely, clinical research can create clinical evidence and make good clinicians as well. In the lecture, I would talk about how to design epidemiological and clinical research by introducing some examples. Furthermore, I would address to the significance that clinicians learn epidemiologic methods to promote clinical research which is derived from their keen awareness of the clinical problem.

EL14

How to use glucocorticoids: clinical pharmacology and important notice

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Conflict of interest: Yes

History of glucocorticoid clinical use was initiated by Hench to a patient with rheumatoid arthritis in 1948, resulting in a great success. Subsequently, glucocorticoids have played an important role in the treatment of rheumatic diseases, however, severe adverse events are usual, particularly at high doses. Lower risk/benefit ratio in the glucocorticoid therapy is a major target for all rheumatologists. Since glucocorticoids have a long history in medicine, many clinical evidences have been revealed by clinical trials. In contrast, empirical clinical uses of glucocorticoids are still common. Thus, I will summarize basic information of clinical pharmacology in this lecture first. I will then present important clinical notice at the glucocorticoid use that was based on evidence or just experience.

EL15

Treatment and prevention for the multiple drug resistant bacterial infection

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Conflict of interest: None

Antimicrobial agents are useful for the treatment for bacterial infection, but many kinds of bacteria are acquired resistance for the antimicrobial agents. Recently novel antimicrobial agents are limited and the development of these agents may be difficult. Methicillin resistant *Staphylococcus aureus*(MRSA) is the most popular multiple drug resistant strain. The treatment of MRSA infection is developing in recent years. MRSA is isolated from the patients in hospital, but many MRSA is isolated form the patients with community acquired infection. Sometimes, the outbreak of multiple drug resistant bacterial infections occurred in hospital and serious problem for the infection control for the hospital. Multiple drug resistant *Pseudomonas aeruginosa*(MDRP) and *Acinetobacter baumannii*(MDRA) are very important multiple drug resistant strain because very limited antimicrobial agents are effective for the infection of these strains. Vancomycin resistant Enterococcus (VRE) isolated form the patients reported very few case in Japan, but sometimes reported outbreak cases from the hospital. In this lecture, I suggest for the treatment of the multiple drug resistant bacterial infection used the novel antimicrobial agents and useful infection control protocol for these strains.

EL16

Microbiota in health and diseases

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Conflict of interest: None

The gastrointestinal tract is a site for colonization of bacteria, many of which are obligate anaerobic and therefore are hard to be cultured in vitro. Accordingly, the precise picture of intestinal bacteria remained long unknown. Recent development of next generation sequencer enabled us to analyze genomic sequence of intestinal bacteria as well as humans. There are over 1,000 species of bacteria in the intestine and they are called “microbiota”. In addition, microbiota is reported to possess over 400-fold genes (microbiome) compared to humans. These gene products include microbiota-specific enzymes that catalyze dietary compound to produce energy and nutrients for our body. Furthermore, development of effector B and T lymphocytes are recently shown to be induced by microbiota. Thus, intestinal microbiota contributes to the maintenance of our health. Accordingly, microbiota is involved in several disorders. Indeed, altered composition of microbiota, which is called dysbiosis, is observed several disorders. These include not only inflammatory bowel diseases but also immune disorders in non-gut tissues such as rheumatoid arthritis and multiple sclerosis. Dysbiosis is further observed in non-immune disorders such as metabolic diseases and neurodevelopmental diseases. Thus, intestinal microbiota is critically involved in our health and diseases.

EL17

Introduction to the genomics of rheumatic diseases

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Conflict of interest: Yes

Rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus have complex etiology, where multiple genetic and environmental components are involved. In most rheumatic diseases, specific alleles of HLA class I/II genes are strongly associated with the diseases, allowing them to be the most major determinants of disease susceptibility. This suggests that the presentation of self-peptides by specific HLA molecules is the central part of disease pathogenesis. In fact, *HLA-DRB1* *04:01 and *04:05 alleles are associated not only with the susceptibility to rheumatoid arthritis but also with the presence of anti-citrullinated protein antibodies in patients. In addition to HLA genes, genome-wide association studies (GWAS) have discovered many non-HLA loci for rheumatic diseases that showed relatively moderate risks compared to the HLA alleles. As some of these loci are shared among different diseases, combination of genetic factors may determine susceptibility to individual diseases. However, GWAS can only identify the disease-associated genomic regions, and the responsible genes and their disease causing mechanism are largely unknown in most of the loci. Previous Expression quantitative trait locus (eQTL) studies that examined association between genetic variants and gene expression levels have suggested that majority of rheumatic disease loci (~ 80%) are eQTLs, where disease causing variants affect expression of the responsible genes. This indicates that the cumulative effects of quantitative differences in risk genes leads to the onset of rheumatic diseases.

EL18

Synovial Features of Rheumatoid Arthritis -Learning new things from the past-

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Conflict of interest: None

Synovial tissues of rheumatoid arthritis (RA) include many kinds of cells such as lymphocytes, monocyte/macrophages, neutorophils, vascular cells, and fibroblastic-like synoviocytes (FLSs). Among them, FLSs exhibit varied morphological and functional features, appearing from oval, spindle and dendritic shaped figures, and existing in the superficial, upper and deeper of sublining, and deeper outer layers. Although FLSs seem to play a central role in RA inflammation, these complexities make it difficult to unravel the mechanisms of RA disease. Here, the characteristics of FLSs are shown by the methods of virtual microscopy, immunohistochemistry, electron microscopy, and in situ hybridization. Hitherto, FLSs have been divided into types A, B and AB based on morphological cell shape. Type A synoviocyte has been said to originate from macrophage and has round cytoplasm with many cytoplasmic processes. Type B synoviocyte originates from fibroblast and has spindle-shaped cytoplasm with abundant ER. Type AB synoviocyte has intermediate characteristics between these two. However, there has been a report from examination of rat joint that synoviocytes are derived from monocytes. FLSs generally express CD14, HLA-DR, and CD4dim antigens, and sometimes CD68. However, the expression of Ki67 marker associated with cell proliferation is not so remarkable, which suggests that FLSs do not proliferate in inflammatory synovial tissues but are derived from bone marrow via blood vessels. One of the most important unresolved issues in RA is the reason why RA inflammation persists so long. In this regard, we have shown that many CD14+ dendritic FLSs cells enclose the plasma cells and lymphocytes with their long cytoplasmic processes, a phenomenon called pseudoemperipolesis. Tomography by Transmission Electron Microscope (TEM) has shown the fusion of both cell membranes, called trogocytosis, which appears to be an important phenomenon for elucidating cell function of FLS.

EL19

Use of hydroxychloroquine in Japan

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Conflict of interest: None

Hydroxychloroquine (HCQ), originally developed as an antimalarial agent, is approved for the treatment of systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), and rheumatoid arthritis worldwide. HCQ has been used to treat SLE patients without organ damage such as lupus nephritis for many years. Recently, HCQ is recommended to use in all SLE patients because it can prevent organ damage and improve survival. HCQ was approved for the treatment of SLE and CLE in Japan in September 2015. The introduction of HCQ may decrease the use of steroids and promote a standard treatment of SLE in Japan. However, the risk associated with long-term use is not known in Japan. Clinicians should follow the updated Japanese guideline. 1) Dosing based on the ideal body weight (200-400mg/d) is important to avoid retinal toxicity. The dose should be reduced especially in patients with renal

impairment. 2) Hypersensitivity reaction may occur especially during the first 1-4 weeks. Hypersensitivity may mimic flare of CLE. In suspicion of hypersensitivity, HCQ should be stopped immediately. Steroids may be required. 3) Retinopathy is a rare but serious complication associated with long-use of HCQ (usually after 5 years). Eye screening is mandatory before starting HCQ to check underlying retinopathy or maculopathy. Eye screening must be followed at least annually. Eye screening should include all of the following: visual acuity, automated visual field, SD-OCT, funduscopic exam, slit lamp exam, color vision test, and ocular pressure. 4) Teratogenicity and fetal toxicity have not been reported in human. HCQ is recommended to continue during pregnancy because of the better pregnancy and fetal outcome.

EL20

ABC in the management of gout

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Conflict of interest: Yes

Gout is a crystal induced arthritis caused by over-saturated monosodium urate in the peripheral joint as the result of longstanding hyperuricemia. Hyperuricemia is a typical life-style related disease caused by disturbance of life-style in individuals with certain genetic background. Clinical positioning of gout is somewhat confusing, since hyperuricemia is a metabolic disease and gouty arthritis is a rheumatic disease. Owing to the acceptance of early intervention to hyperuricemia in Japan, Japanese patients with gout have generally milder diseases. On the other hand, management of difficult gout is a serious issue in the Western countries, because historically sufficient treatment has not been well applied. It is obvious that the appropriate management of hyperuricemia is crucial for the management of gout.Recently, etiology and pathophysiology of hyperuricemia have been well understood by the discovery of urate transporters and its genetic variants by GWAS studies, thus current strategy of management of hyperuricemia should be considered based on these findings.In the management of gout and hyperutricemia, we should consider the accurate diagnosis and management of gout and the appropriate management of hyperuricemia. Regarding the diagnosis, recent introduction of ultrasound imaging greatly improved the accuracy of the diagnosis. Regarding the treatment, evidences have been accumulated to show that sufficient long-term management of hyperuricemia is resulted in preventing gout flare and inhibiting the progression of renal damage. Thus, 'Treat to Target strategy' to keep serum urate level to less than 6.0 mg/dl has been proposed. Furthermore, we have now many therapeutic options of drugs by the addition of novel xanthine oxidase inhibitors or uricosuric agents.In this lecture, I would like review the current topics of gout and hyperuricemia, and explain useful information in the daily practice of gout and hyperuricemia to rheumatologists.

EL21

Clinical subsets and autoantibodies of polymyositis and dermatomyositis

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Conflict of interest: Yes

Autoantibodies to various cellular components are the hallmark of systemic autoimmune diseases. In polymyositis (PM) and dermatomyositis (DM), various myositis-specific autoantibodies (MSAs) are demonstrated to correlate to specific subsets and clinical manifestation. However, most these autoantibodies have been detected only by the complicated immunoprecipitation (IP) method. Recently, quantitative enzyme-linked immunosorbent assays (ELISAs) for some of these MSAs have been established and approved to use for diagnosis of PM/DM. Anti-aminoacyl-tRNA synthetases (ARS) are closely associated with a common clinical manifestation, termed "anti-synthetase syndrome" including interstitial lung disease (ILD). Anti-ARS antibodies are detected not only in PM/DM but also in apparently "idiopathic" interstitial pneumonia. This result suggests that anti-ARS detected in patients of ILD without myositis may predict possible future development of myositis. Anti-MDA5 (CADM-140) antibody is reported to be associated with clinically amyopathic DM (CADM) and rapidly progressive ILD especially in eastern Asian population. Anti-TIF-1γ(p155/140) antibody is selectively found in classic DM patients especially with cancer-associated adult DM, and anti-Mi-2 antibody is predominantly detected in patients with classic DM with favorable prognosis. Other MSAs such as anti-SRP, a marker of intractable necrotizing myopathy, are also associated with specific clinical pictures, although routine tests have not been established yet. The newly established ELISA systems for anti-ARS, anti-MDA5, anti-TIF-1γ and anti-Mi-2 antibodies are as efficient as the standard IP assay. These systems enable easier and wider use in the detection of MSAs in patients suspected to have PM/DM and classification of their subsets.

EL22

The classification and treatment of spondyloarthritis

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Conflict of interest: Yes

It is well known that spondyloarthritis (SpA), comprehensive disease concept including ankylosing spondylitis (AS) or psoriatic arthritis (PsA), exhibits various similar symptoms and response to the therapeutic medicine. SpA is roughly classified in axial SpA which is mainly involved sacroiliac joint or spine like AS, and in peripheral SpA which is involved peripheral joints like PsA or reactive arthritis. Since even PsA sometimes shows axial symptoms, we should not think that these two are totally different, but they are overlapped. This classification is important from the viewpoint of not only symptoms but also response to the medicine. The classification criteria and the treatment recommendation have been made in each. SpA presents various symptoms, such as arthritis of spine and limbs, enthesitis of Achilles' tendon, dactylitis, skin symptom like psoriasis, inflammatory bowel diseases such as Crohn disease or ulcerative colitis, uveitis, precedence infection like urethritis by the chlamydia. Since it is well known that association with HLA-B27 is high, it is very important to check the family history. The existence of the inflammatory back pain, which develops by 45 years old and continues more than three months, is a key to doubt axial SpA. Axial SpA shows good response to NSAIDs, the variety of symptom is sometimes relieved naturally without medication, and only small radiographic changes are seen for years. It is hard to distinguish axial SpA from mere lumbar pain or herniation of lumbar disc. It is important to confirm whether the inflammation is seen or not in sacroiliac joint or spine by MRI. When inadequate response to NSAIDs is seen in peripheral SpA, we consider the treatment with DMARDs next and biologic at third. However, in axial SpA, biologics come next. We can use TNF inhibitor, IL-17 inhibitor, and IL-12/23 inhibitor for SpA. Since PDE-4 inhibitor is under development, we will have more choices in future.

EL23

Lymphoproliferative disorders in patients with rheumatic diseases: important consideration for methotrexate-associated lymphoproliferative disorders

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is an immunological disease that causes proliferation of synovial tissue leading to joint destruction, and decreases quality of life of affected patients. Previous studies demonstrated higher incidence of malignant lymphoma (ML) in patients with RA compared to general population: standardized incidence ratio (SIR) of 2 to 3 in the meta-analysis and SIR of 4 to 6 in Japanese epidemiological studies. Patients with Sjogren syndrome and systemic lupus erythematosus also have higher risk for ML in common with RA. Methotrexate (MTX) is widely used as an anchor drug for RA in Japan as well as worldwide. Treatment with MTX improves signs and symptoms, inhibits progression of joint destruction, and increases quality of life in patients with RA. It also yields better vital prognosis and decreases risk for cardiovascular

events. MTX-associated lymphoproliferative disorders (MTX-LPD) has been reported since around 1990 and its clinical and pathological characteristics gradually has come into clear view. MTX-LPD includes a wide range of pathological diagnosis from hyperplasia to ML. In WHO classification of tumours of haematopoietic and lymphoid tissues (IARC Press, 2008), MTX-LPD appears on the list of 'Other iatrogenic immunodeficiency-associated lymphoproliferative disorders'. The higher incidence of ML in patients with RA irrespective of the use of MTX entails importance of proper diagnosis and treatment of MTX-LPD in patients with RA. Assessing incidence, clinical characteristics and risk factors of MTX-LPD, especially ML, and taking measures to this adverse drug reaction is definitely a pressing task to improve medium- to long-term prognosis of Japanese patients with RA.

EL24

Update of Fibromyalgia in Japan

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Conflict of interest: None

Much of Japanese rheumatologists has only notice of a disease name as fibromyalgia (FM), moreover they have a negative concept for FM and attitude of refusing the management of FM patients. From 2003, Japanese Ministry of Health, Labor and Welfare (MHLW) organized the study group for research on FM in Japan, thereafter, the study group is showing epidemiological various clinical and basic medical findings of FM in Japan. In this instructive lecture, the following findings obtained from the study group of MHLW would be described; clinical epidemiological findings of FM in Japan, pathophysiological studies containing by brain imaging study of PET-CT using ^{18}FDG (abnormalities in domain of default mode network system) or specific ligand (^{11}C-PK11195) of activating microglia (neuroinflammation), autoantibody (anti-VGKC antibody) analysis, neuro-physiological examination (loss of off-set phenomenon), socio-psychological basis of juvenile FM, medical economic indicators (QUALY, DALY et) and developing clinical guideline (revised by GRADE system).for the management of Japanese FM patients (including juvenile FM). It would be clarified that development of curative management based on the pathogenesis of FM, as well as good recovering of ADL/QOL, for the eradication of FM, further strategic studies for FM should be done by the Japanese study group of MHLW.

EL25

Primary immunodeficiency diseases that could exhibit symptoms and signs of rheumatic disorders or autoimmune disorders

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Conflict of interest: Yes

Primary immunodeficiency (PID) is a group of disorder in which part of immune system is missing or functions improperly. Patients with PID exhibit various symptoms and signs that arise from affected immune cells and systems. PID is usually genetic, categorized into nine groups; and has at least 250 disorders. More than 350 responsible genes have been identified so far. The major symptom of PID is susceptibility to infection. In fact "10 warning signs of PID" developed by Jeffery Modell Foundation show clinical features caused by infection as important signs. PID also includes "disorders of immune dysregulation"(eg. FoxP3 deficiency and AIRE deficiency) and "autoinflammatory diseases (AID)". Autoimmune lymphoproliferative disorder is a representative disease in the former category and sometimes resemble SLE. AID should be considered when one sees Juvenile idiopathic arthritis or sarcoidosis in infancy and childhood. In addition, common variable immunodeficiency (CVID) categorized in "predominantly antibody deficiency" exhibit autoimmune manifestation upon aging; and about 40% of the CVID patients develop autoimmunity. It is reasonable to guess that the autoimmunity is caused by defective immune regulation in CVID patients. In fact, some CVID patients show defect or dysfunction of regulatory T cells, regulatory B cells, or other regulatory cells. Recent advances in high throughput genetic analysis, accessible human gene databases, and development of mathematical tools for genetic data analysis led to identification of new responsible genes. Such disorders include ADA2 deficiency in polyarthritis nodosa, CTLA4 haploinsufficiency in CVID, and LRBA deficiency that shows defective CTLA4 induction. Many PID are now known to show autosomal dominant inheritance with low penetrance rate or are sporadic. These data indicate mutation or rare variant of a gene in PID could underlie at least a part of pathogenesis of rheumatic disorders.

EL26

State of the art surgical treatment for rheumatoid foot

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Conflict of interest: Yes

The foot is most frequently affected by rheumatoid arthritis. Even if activity of rheumatoid arthritis is well controlled by biologics, activity of daily living in some patients is severely limited by foot pain. Mild foot deformities or synovitis in few joints causes pain at a walk. The benefit has a big not only patient satisfaction but also medical care economy without increasing drugs if we can operate patients with minimum invasive surgery. Recent advancement of orthopaedic surgery in the foot and ankle field will be mentioned in this lecture. For the forefoot, we treat patients aiming at joint preservation as much as possible. Our study showed that morphological characteristic in rheumatoid hallux valgus are similar to general hallux valgus. Therefore, osteotomies should be indicated for rheumatoid hallux valgus, if articular cartilage did not much affected. For the midfoot and hindfoot, we can treat lesions using arthroscopic or endoscopic approach with benefit of progress of the arthroscope technology. Perfusion and traction work well for obtaining good arthroscopic views. Arthroscopic synovectomy is indicated for synovitis in not only the ankle but also Chopart joint, the hallux MTP joint and tenosynovitis around the ankle. On the other hand, terminal stage of foot deformities are difficult to be treated by drugs even if the paradigm shift of the treatment occurs. There are lesions to require resection arthroplasty and arthrodesis, and total ankle replacement still more. For the sever forefoot deformities, MTP arthrodesis or resection arthroplasty is performed. Partial tarsal fusions are selected for limited parts of tarsal joints. In addition, ankle fusion or total ankle arthroplasty is chosen for the ankle in terminal stage. A balanced treatment system of orthopedics treatment and systemic control by drugs is necessary for patient satisfaction.

Meet the Expert

MTE1

Infectious Diseases in Immunocompromised Host-Including Characteristics of Biologics-associated Infections-

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Conflict of interest: None

Appearance and spreading of antibiotic resistant organisms are everywhere in the world. In Japan, we have still problems of MRSA in the hospital and also recent epidemiological data demonstrated increase of community-associated MRSA (CA-MRSA) not only in healthy individuals but hospital-admitted patients. Not many, but we experienced several outbreaks of multiple drug resitant Pseudomonas aeruginosa and Acinetobacter baumannii infections. Recetntry, carbapenem-resistant Enterobacteriaceae (CRE) is becoming a topic because there are several reports of growing numbers of CRE outbreak in Western countries. The most important point and characteristics of antibiotic resistant organisms are an increase of community-associated antibiotic resistant organisms, such as CA-MRSA and CRE, which mean the successful acquisition of antibiotic resistance and virulence. Also the introduction of biologics and growing numbers of cases applied brought a huge impact on infectious diseases in those patients. Generally, biologics increase a risk and frequency of several infectious diseases, such as mycobacterial and fungal infections. Also modification of host defense systems by biologics is reported to sensitiazes those indivisuals to pneumoia, particularly to Legionella pneumonia. In this lecture, the topics of infectious diseases, such as antibiotic-resistance and emerging/re-emerging infectious diseases, will be reviewed. In addition, epidemiology, characteristics and pitfalls of infectious diseases frequently observed in biologics-associated infections will be discussed.

MTE2

Clinical approach and management of MTX-LPD in RA patients

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Conflict of interest: None

Recent studies have highlighted LPD, especially in patients with RA, and most LPDs are thought to be caused by MTX. The background of patients with RA, such as the duration of RA and MTX therapy and the total dose of MTX, appears to have no effect on the pathogenesis of LPD development. Various LPDs including B, T, and NK phenotypes occur, and often present atypical features. LPD regression after MTX withdrawal is seen in 40% of all MTX-LPD cases, and lymphocytes play an important role in this phenomenon. There are 3 distinct clinical patterns according to LPD regression pattern; regressive, relapsed, and persistent. Patients with regressive MTX-LPD have better overall survival than that of patients with the other 2 patterns, and DLBCL is a common phenotype. In contrast, relapsed LPD often flares up within a year after MTX withdrawal, and the ratio of Hodgkin lymphoma is higher compared to that in the other 2 patterns. Before development of LPD, patients with relapsed LPD often have high fever, lymphadenopathy, and elevated levels of LDH and sIL-2R in serum. In patients with persistent LPD, various LPD phenotypes are seen. Although persistent LPD often shows response to chemotherapy, delayed diagnosis leads to a long exposure to MTX, resulting in a poor prognosis. The age and the levels of LDH, CRP, and sIL-2R in serum are significantly important prognostic factors. Recent data supposes that EBV influences the pathogenesis of MTX-LPD, however, the mechanism underlying the pathogenesis of EBV is still uncertain. The contribution of anti-RA medication other than MTX toward LPD development is not clearly defined. Accumulating facts emphasize that tentative MTX cessation is important for patients with high fever, lymphadenopathy, and elevation of CRP/LDH levels; furthermore, careful follow-up is required for the elderly and for patients with poor performance status,

MTE3

Early diagnosis and treatment in systemic sclerosis

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Conflict of interest: Yes

Currently, there are no practical guidelines for patients with systemic sclerosis (SSc) because of lack of treatment modalities with high level of evidence and highly variable clinical presentation among patients. To treat SSc patients in routine clinical practice, it is essential to know natural history of the disease. Since acute exacerbation is rare during the course of SSc except renal crisis, future organ involvement and prognosis can be predictable in most cases based on detailed clinical evaluations at diagnosis. In addition, early detection and treatment is crucial for SSc patients since functional impairment is hardly reversible once normal tissue architecture has been replaced by fibrotic scarring tissue. In this regard, patients with Raynaud's phenomenon with nailfold capillary changes and/or SSc-related anti-nuclear antibodies should be regarded as SSc even in the absence of apparent skin thickness. This session is aimed to understand how to predict future outcomes in SSc patients by presenting typical case scenarios.

MTE4

A Practical Guide for Diagnosis and Treatment of Idiopathic Inflammatory Myopathies

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Conflict of interest: None

The idiopathic inflammatory myopathies, polymyositis (PM) and dermatomyositis (DM) are systemic connective tissue disorders characterized by chronic inflammation in skeletal muscle and involvement of multi-organs. The pathogenesis of these heterogeneous diseases is unknown, but appear to mediate an autoimmune disorder that culminates in the tissue damage. In recent years, autoantibodies directed against various cellular constituents have been found specifically in patients with PM/DM. Especially, it has been noted that these myositis- specific autoantibodies are closely associated with distinct clinical features and therefore significant tools for diagnosis, patient classification as well as predict of signs, symptoms of myositis, response to treatment, and prognosis. This session will review recent findings and progress on clinical and laboratory aspects of PM/DM, including clinical significance of myositis-specific autoantibodies and comprehensive therapeutic strategies for intractable pathological conditions. Finally, the clinical issues to be resolved as well as challenges in the patients with PM/DM will be discussed interactively, providing useful information and tips in the daily practice of rheumatic diseases for the participants in the session.

MTE5

Treatment of intractable ANCA associated vasculitis

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Conflict of interest: Yes

ANCA associated vasculitis (AAV) includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Recent developments of diagnostic methods and immunosuppressive treatment remarkably improved the clinical prognosis of AAV. However, Immunosuppressive treatment-resistant or frequent-relapse AAV indicates that AAV is still one of the intractable diseases. Steroid pulse and/or intravenous cyclophosphamide pulse therapy (IVCY) are the first line treatment for patients with serious AAV. Rituximab, anti-CD20 positive B cell monoclonal antibody, has been covered by insurance, for the management of refractory or severe relapsing GPA and MPA, since 2013 in Japan. Rituximab is increasingly used as a remission induction agent. Recently, several non-controlled studies

have suggested that rituximab may be useful as remission maintaining therapy in AAV. However, randomized trials showed that rituximab has similar severe side effects with cyclophosphamide. Intravenous Immunoglobulin therapy for EGPA and targeted biologic treatments, including several monoclonal antibodies and C5a receptor (CD88) blockade for AAV, have been reported. This lecture summarizes current information regarding the treatments for AAV. At the end of this meeting, participants will understand clinical characteristics and new treatments strategies for AAV.

MTE6

Clinical significance and interpretation of the autoantibody testing in systemic autoimmune diseases

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Conflict of interest: Yes

Connective tissue diseases (CTD) including rheumatoid arthritis (RA) are well known as systemic autoimmune disorders because high tiers of autoantibodies (auto Abs) are frequently observed in sera from CTD patients. Actually, lots of auto Abs, of which clinical significance is clearly identified, are examined in clinical practice. 1) Auto Abs associated with disease diagnosis Anti-CCP Abs in RA and anti-Sm and dsDNA Abs in systemic lupus erythematosus (SLE) are 'marker Abs'. These Abs are highly specific and included in the international classification criteria. 2) Auto Abs associated with specific manifestations Anti-aminoacyl tRNA synthetase (ARS) Abs including anti-Jo-1 are recognized in polymyositis/dermatomyositis (PM/DM). Patients with anti-ARS Abs, however, often show the similar clinical manifestations (anti-synthetase syndrome), which consist of fever, Raynaud's phenomenon, polyarthritis, and interstitial pneumonia (IP) in addition to myositis. Anti-U1RNP Ab is one of the critical risk factors for pulmonary arterial hypertension. 3) Auto Abs associated with severe clinical disorders Anti-melanoma differentiation-associated gene 5 (MDA5) Abs are closely associated with life-threatening IP especially in clinically amyopathic DM. Also, anti-transcription intermediary factor 1-γ(TIF1-γ) Abs are linked to the cancer-associated DM, so clinicians should check the malignancy before an immunosuppressive treatment. 4) Auto Abs associated with disease activity Titers of anti-DNA Abs and MPO/PR3-ANCA correlate with disease activity in SLE and ANCA-associated vasculitis, respectively. Such auto Abs may be repeatedly determined during the remission induction treatment. In the present seminar, we can discuss the best way to interpret the autoantibody testing according to the International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies (*ARD,* 2014).

MTE7

Practicing sonographic assessment of synovial inflammation

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Conflict of interest: None

Musculoskeletal ultrasound visualizes low-echoic synovial infiltration (i.e. synovial hypertrophy) and abnormal blood flow which accompanies synovial hypertrophy (i.e. synovial Doppler signal) and determines the presence/absence and the severity of synovitis, tenosynovitis, and bursitis. However, sonographic assessment has pitfalls as other clinical measures do and needs training and experience. The accurate assessment of synovitis is possible only when clear images are acquired and a certain knowledge and understanding of joint anatomy and ultrasound physics are necessary to acquire clear images. Pitfalls can be present in each process of machine/setting, image acquisition, or interpretation and may cause either false-negative/underestimation or false-positive/overestimation. In this session, these factors related to pitfalls will be presented with representative ultrasound images and how to avoid them will be discussed.

MTE8

Juvenile idiopathic arthritis (JIA) in the biologic era. How is it diagnosed and treated? Is it different from RA?

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Conflict of interest: None

JIA is a chronic disease characterized by joint inflammation of unknown cause which occurs before 16 years of age. It affects about 1 individuals in every 10,000 Japanese children; the incident is about 1/40 of RA. Therefore, JIA is not a rare disease and adult rheumatologists may encounter a child with JIA at the first referral. The diagnosis of JIA is difficult because there are no specific laboratory tests. RF and/or ACPA are negative in JIA except for RF positive polyarthritis. CRP or MMP-3 sometimes remains normal range due to small amount of synovial inflammation. Therefore, diagnosis should be made based on careful physical examination with excluding other arthritic diseases in children. Treatment strategy for JIA has been established by Pediatric Rheumatology Association in USA, EU, and Japan. Methotrexate (MTX) is a major treatment option for polyarticular JIA. Weekly MTX with dose of 10 mg/m^2/w is minimum to obtain the maximum efficacy; the dose is almost equal to adult RA due to rapid excretion from kidney in children. Polyarticular JIA patients resistant to MTX need to add biologic agents to prevent the progression of joint damage. At present, tocilizumab, etanercept, and adalimumab is approved for use, and the clinical study for abatacept is now undergoing. For systemic features of systemic JIA, glucocorticoid (GC), the most effective anti-inflammatory drug, is the major therapeutic option. This subtypes of JIA patients frequently develop to fatal condition such as macrophage activating syndrome (MAS) in active stage of disease, therefore, GC is used as the first line therapy. Tocilizumab is initiated in systemic JIA patients in case they are refractory to GC therapy or have serious side effects of GC. Prognosis of JIA has dramatically improved by newly developed biologic agents. Rheumatologists in the biologic era should aware that major cause of poor prognosis of JIA is not due to disease severity but due to the delay or inappropriate treatment.

MTE9

Rehabilitation for the patients with rheumatoid arthritis

Ryuichi Saura[1,2], Miyuki Murakawa[3], Kana Nagao[2], Koji Horaiya[5], Tetsuya Hinoshita[2], Ryuji Takayama[6], Yuka Iwai[2], Yuko Tamura[2], Syunsuke Ichikawa[7], Daisuke Itoh[2], Yuji Oda[2], Yasuko Ohnishi[2], Taro Tohchika[2], Hiroshi Ohno[2], Haruki Nakano[1,2], Masao Tomioka[1,2], Akane Doi[1,2], Michiaki Takagi[3,4]
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Conflict of interest: None

Aim of the rehabilitation is to let the peoples with any disabilities live as usual humans by diminishing or compensating the difficulties in daily life. Protraction of RA induces the disorders of joint function. As a result, activities of daily living (ADL) are deteriorated, which yields the limitation of social participation. Functional disorders have once developed, a plural number of it make disabilities worse. Therefore, along their disease activities and progressions, RA rehabilitation includes the various kinds of approaches such as patient education, exercise therapy, application of splints and utilization of long-term care insurance in order to prevent the progression of these problems. Recently, the high effectiveness of biological agents such as TNF blockers for RA is revealed and the goal of RA treatment is the achievement of functional and structural remission following clinical one. When the clinical remission has been successfully introduced by the biological agents, the problems confronting the execution of rehabilitation might be reduced. However, even if RA patients

have achieved their clinical remission by biological agents, joint destruction might progress rapidly by overuse of it when it had been damaged beyond the moderate stage. It seems that similar troubles such as tendon rupture during exercise may be observed in upper extremities. In conclusion, it must be emphasized that the execution of more prudent and appropriate rehabilitation are very important even in the time of biological agents mainly used for RA patients. To understand the rehabilitation for RA, follows are prepared. 1. To understand the impairments, disabilities and handicaps due to RA and the clinical usefulness of rehabilitation approach for the locomotor disorders. 2. To advice the way of home-based exercise and protection for joint damage in daily life to RA patients. 3. To make the simple splint or insole for relieving the pain due to RA.

MTE10

How to manage the refractory RA patients?

Atsushi Kawakami
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Conflict of interest: None

Prognosis of RA is improved after introduction of biologic DMARDs (bDMARDs) since the proportion of RA patients in clinical, functional and structural remission is proved to increase. However, some of the RA patients still remain to be refractory toward remission. In addition, physicians are eager to predict the mid to long clinical response at earlier opportunity. In general, RA patients at entry with high disease activity tend to be refractory. Even in the RA patients treated by bDMARDs, there is a relation of clinical response at 3 months with that at 1 year. The presence or titer of RF/ACPA, although some not verified by large-scale study or meta-analysis, is found to associate with the efficacy of some bDMARDs. These findings may help the decision-making of physicians. The clinical indices such as DAS28, SDAI, CDAI and HAQ are the principals, however, the imaging tools such as US and MRI may accurately reflect the refractory status in some cases. Furthermore, physicians experience the difficulty for treatment if T2T therapeutic strategy is not fully introduced to the RA patients. These cases include infection, pulmonary complications, renal disturbance, HBV carrier or those previously exposed to HBV. The guidelines or recommendations published by JCR/ACR/EULAR are quite useful to select the DMARDs in such cases. In particular, physicians take care of the elderly RA patients since they tend to have more complications. The safety profile of DMARDs is attached in such cases. Introduction of remission is difficult in advanced RA patients, therefore, the target may be changed to low disease activity. Special concerns are also necessary toward the management of RA, during pregnancy and those who wish pregnant. In this MTE, the above-mentioned items will be discussed.

MTE11

Treatment of difficult SLE

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Conflict of interest: Yes

SLE is so heterogeneous in the expression of symptoms and organ damage that it might be viewed as a syndrome instead of a disease. Underlying pathophysiology is immune complexes formation composed of mainly nuclear antigens and the corresponding autoantibodies. Immune complexes are delivered via blood stream to virtually all organs in the body and this accounts for the diversity of organ involvement. What is difficult SLE? There is no definition of it. In each organ involvement, the pathology spans from very slight to very severe, and severe involvement is always difficult treating. As a speaker of MTE in the JCR meeting, I select, arbitrarily, 1) lupus nephritis, 2) neuropsychiatric SLE, and 3) antiphospholipid antibody syndrome as difficult SLE. 1) Kidneys are small and they weigh ~0.3 kg, albeit, they receive ~25% of cardiac output. Therefore, they receive ~50 times more blood supply per weight compared to the other organs in the body, plenty of blood. Organs receiving more blood supply are more susceptible to inflammation caused by immune complexes delivered by blood stream. To mitigate lupus nephritis, immune complexes must be reduced in amount. To do so, immunosuppressant is usually employed along with glucocorticoid as a base drug. Cyclophosphamide has been the mainstay of immunosuppressant. Mycophenolate mofetil Ewas recently approved for the treatment of lupus nephritis in Japan, which gave us a stronger armamentarium and the method to prevent adverse effects incurred by cyclophosphamide. 2) NPSLE is very difficult in diagnosis in the first place because it spans real organic brain damage caused by SLE to mood change caused by treatment drugs. Infection may be the cause of neuropsychiatric symptoms. Treatment can not be accomplished without the help from psychiatrists. Lastly 3) antiphospholipid syndrome comes, which is the cause of biological false positive in serological test for syphilis. Catastrophic is the severest form and often fatal.

MTE12

Examination of joints in rheumatic diseases

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Conflict of interest: None

The roles of serological tests including anti-cyclic citrullinated peptide antibody and images including articular echography or magnetic resonance are getting larger in diagnosing rheumatic diseases. However, these tests and images cannot be performed at any time and in any place. The basic way of making diagnosis is to listen to patient's complain carefully and then examine patient thoroughly by using physician's eyes, ears, and hands. It is important to make diagnosis and judge disease activity for rheumatologist based on those clinical findings and supplemented by the results of blood tests and images. In diagnosis, it is important to evaluate whether pain, stiffness or swelling which patient complained come from joint or other tissues such as muscle, tendon or enthesis and coexisting skin lesions. Other joints in addition to 28 joints are need to be examined for redness, warmness, swelling, tenderness, and range of motion. Sometimes patient feels swelling of joint before physician can capture. In such condition, re-examination after a certain period interval may help to detect findings. Physician must pay attention to patients' response by seeing their face not to the examination cause pain and try to make good relationship with patient. It is also important to understand the condition that patient stands and aim of patient to visit physician. Clinical findings must be written in chart definitely and precisely. In this session, I would like to convey how to examine rheumatic joints to young rheumatologists.

MTE13

Rheumatic diseases of the elderly

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Conflict of interest: Yes

As for an important disease, rheumatoid arthritis (RA), the vasculitis syndrome, the polymyalgia rheumatica (PMR), the dermatomyositis, and the systemic sclerosis, etc. are enumerated in the differential diagnosis of senior citizen's rheumatic diseases. Rheumatologists may more frequently encounter elderly patients with rheumatic diseases due to longer life expectancy than before. There are elderly onset arthritis patients whose rheumatoid factor and anti-CCP antibody were both negative at baseline. Differential diagnosis between seronegative RA and PMR is not easy and is still challenging for many rheumatologists. Moreover, serious complication and bone destruction were developed over the period of the short time of a part of senior citizen. The diagnostic and treatment are promptly requested. There are very important diseases with PMR, RA and microscopic polyangitis as senior citizen's unknown fever and the an uncertain cause of the CRP high titer. How to diagnosis and treat such diseases? In this seminar, those topics will be discussed among the participants.

MTE14

Mechanisms and management of chronic musculoskeletal pain

Takahiro Ushida

Mulitidisciplinary Pain Ceter, Aichi Medical University

Conflict of interest: None

Musculoskeletal pain is defined as an unpleasant sensory and emotional experience. Thus pain is always subjective and experience it in one's brain. Concerning about popular chronic musculoskeletal pain, such as "chronic low back pain", medical providers usually pay careful attention to local organic issues (eg. Joint deformities, inflammations etc.) and conventional bio-medical approaches (use anti-inflammatory drugs, nerve block, joint/spine surgery, etc.) are chosen for the treatment. Beside, recent chronic pain researches revealed that chronic pain condition is a complex condition and it obtains organic factors as well as psycho-social factors. Also brain neuroscience technology clarified that activation of pain associate default mode network and pain memory in patients with chronic musculoskeletal pain conditions. Multidisciplinary approaches are necessary for analyze chronic pain conditions and team of specialists in anesthesiology, psychiatry and orthopedics as well as the relevant paramedical professionals are essential to provide diagnosis and therapeutic options. Therapeutic strategy is based on a cognitive-behavioral approach, and patients are taught about methods for restoring physical function and coping with pain, mostly with drugs and exercise therapy, so that any pain present does not impair function and the patient can reintegrate into society.

MTE15

Essentials of radiologic imaging of chest diseases in patients with RA

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Conflict of interest: None

Patients with RA are frequently complicated with a wide variety of chest diseases, such as pulmonary infection (e.g. bacteria, tuberculosis, non-tuberculous mycobacterium, Pneumocystis), interstitial lung diseases, bronchiectasis, and drug-induced lung diseases. Accurate diagnosis and proper management for those complications are challenging for not only rheumatologists but also pulmonologists.Respiratory symptoms are non-specific with regard to diagnosis, therefore importance of chest imaging, particularly chest X-ray films and CT scans, should be emphasized. It is recommended that rheumatologists have basic knowledge of analyzing chest imaging. In this program, I would like to share essentials of imaging of chest diseases and present actual chest X-ray films and CT scans commonly seen in patients with RA. Specifically, the audience will be able to learn about nuts and bolts of reading chest X-ray and CT scans. I am looking forward to having this interactive program with you.

MTE16

Examination method and treatment of the rheumatoid foot

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Conflict of interest: None

Although the introduction of powerful antirheumatic drugs has dramatically improved the treatment of rheumatoid arthritis (RA), many patients still experience progressive joint destruction. Painful forefoot deformities are prevalent in 80-90% of patients with RA, many of whom undergo surgery to treat them. Surgeries for the rheumatoid foot, including joint-preserving surgery, have been widely performed in Japan. However, in many cases, conservative therapy might have been effective if the physicians had previously noticed the foot deformities. One of the reasons for the failure to diagnose foot deformities is that scales evaluating 28 joints to determine the disease activity, such as the DAS28, do not include the foot and ankle. As a result, the disorders of the foot and ankle have been neglected. Indeed, I experienced a case in which foot surgery was finally performed, even though the patient's DAS28 indicated the maintenance of clinical remission over a long period. On the other hand, there are some patients who experience treatment delays due to the physicians' lack of knowledge of the various treatments for the rheumatoid foot, even though the physicians are aware of the progression of the foot deformities. To reduce such unfortunate cases, this presentation includes the following topics: (1) The critical points of clinical examination of the rheumatoid foot, (2) Conservative treatment that anybody is able to perform, (3) The timing of the consultation from the internist to the orthopedic surgeon, and (4) The latest developments in foot surgery for the rheumatoid foot.

MTE17

Perioperative management for patients with rheumatoid arthritis

Isao Matsushita
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Conflict of interest: Yes

A multidisciplinary approach is required to care for patients with rheumatoid arthritis (RA) in the perioperative period. In preparation for surgery, patients must have a respiratory risk assessment performed due to the high risk of lung disease in patients with RA. Rheumatologists have to assess the perioperative patient using chest radiography, spirometry, blood gas analysis and sometimes CT scan. Renal functions often decrease in long-standing RA patients. It is necessary for assessment renal function to use GFR and/or CCr. After total hip/knee arthroplasty, the use of small molecular weight heparin or Factor Xa inhibitors is recommended to prevent thromboembolism. However, anticoagulants are contraindication when the value of CCr of patient is below 30ml/min. RA can involve the cervical spine with important implications for perioperative management, particularly positioning for anesthesia. Rheumatologists must be aware of the risk of cervical instability which may be asymptomatic. If performed, radiology imaging should include at least flexion-extension views of the cervical spine. Methotrexate is widely considered the cornerstone of RA management. Cohort studies did not demonstrate any difference in perioperative infection between those who continued or discontinued methotrexate. JCR guideline for the management of rheumatoid arthritis 2014 demonstrates that discontinuation of MTX is not necessary in the perioperative period. On the other hand, in some reports comparing patients who used traditional DMARDs versus TNF-α inhibitors, there was an increased risk of surgical site infection (SSI) with TNF-α inhibitors. JCR guideline demonstrates that biological DMARDs slightly increase the risk of SSI, and recommends the discontinuation of biological DMARDs in the perioperative period. In this opportunity, I would like to talk about the knack and pitfalls of perioperative managements for patients with RA.

MTE18

The update for the pathophysiology and treatment of the osteoarthritis of the knee

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Conflict of interest: None

The recent epidemiological studies revealed that the one fourth of the reasons for requiring special assistance or nursing care in elderlies is currently the locomotive disorders. Osteoarthritis of the knee (knee OA), as well as the osteoporotic fragility fractures and the spinal canal stenosis due to spondylosis, is the one of three major locomotive disorders those are related to the requiring special assistance or nursing care in elderlies. The knee OA is an age-related progressive joint disease, which is characterized primarily by cartilage degradation. However, the subchondral bone, meniscus, synovium and ligament, in addition to the cartilage, have been known to be also involved in the pathophysiology of knee OA. OA is an increasingly important public health concern, as the prevalence of the disease is increasing with the aging of society, and is one of the representative age-related chronic motor organ diseases responsible for the locomotive syndrome. The ideal management of knee OA is illustrated as

a sequential, pyramidal approach. While it has been estimated that there are 25 million people with radiographic knee OA, it has been speculated that eight million have knee pain. Among the patients with painful knee OA, eighty-five thousand cases of total knee arthroplasty (TKA) are currently being performed each year in Japan. The concept of locomotive syndrome should therefore be promoted to allow for the earlier identification of patients with symptomatic knee OA to prevent the development of locomotive syndrome by providing adequate pain relief. Moreover, the development of pathophysiology of knee OA should be promoted to facilitate the earlier identification of asymptomatic knee OA and the development of novel treatment methods including in new drugs and interventions. In this session, based on the evidence found recently by the clinical researches, I'd like to focus broadly on from the pathophysiology to the treatment of knee OA.

MTE19

Management of Liver Injuries in Patients Receiving Immunosuppressive Therapies

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Conflict of interest: Yes

Drug-induced liver injuries (DILIs) may develop in patients receiving immunosuppressive therapy, whereas the therapies could not done in patients with liver damage. Glucocorticoids were the most frequent causative drugs for DILIs; serum ALT levels increase immediately after the intake, but may attenuate then later due to spontaneous attenuation of fatty liver. Also, methotrexate may provoke DILIs frequently in a dose-related manner, but such DILIs were well controlled via methotrexate dose-reduction and/or folic acid supplementation. It should be noted, however, that any drugs may cause liver damage. Patients with liver damage were diagnosed as having DILIs according to the criteria by JDDW2014 and histological findings on liver biopsy specimens. HBV carriers and patients with previously resolved HBV (prHBV) infection should receive immunosuppressive therapies in accordance with the guideline for HBV reactivation. In patients with prHBV infection, serum HBV-DNA are scheduled to be measured depending on serum anti-HBc levels as well as duration after the initiation of therapies. Entecavir should be administrated when serum HBV-DNA levels increased to 1.3 Log IU/mL or more. Tenofovir is not recommended since renal injuries and/or hypophosphatemia might develop. The prospective study to modify the guideline was initiated considering economic issues. Patients with HCV infection were recommended to receive DAA therapies, since liver function improves following HCV eradication. Ribavirin and/or DAASs as NS3/4A protease inhibitors, NS5A inhibitors and a nucleotide-type NS5B inhibitor are administrated in combination for 12 weeks depending of HCV genotypes, NS5A-RAVs, renal and cardiac diseases and underling drugs intake, and HCV eradication can be achieved in almost all patients. Such therapies were not allowed for decompensated patients. Thus, we conducted the clinical study to improve liver function in such patients by B-RTO procedures.

MTE20

Total joint arthroplasty for rheumatoid elbow and fingers

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Conflict of interest: None

The clinical course of rheumatoid arthritis (RA) has dramatically improved over the past decade with new treatment strategies and introduction of biologic DMARDs. However, significant number of patients still requires surgical reconstruction of elbow joints, as well as small joints in the hand because of functional impairment and change in patients' body image. In the current workshop, the surgical technique for AVANTA silicon implant arthroplasty for MCP joint will be presented. The mainstays of the soft tissue reconstruction are centralization of central slip (Wood), ulnar intrinsic release, and repair of radial collateral ligament. For swan-neck deformity without severe joint destruction at PIP joint, Modified Zancoli method is a useful option. Total elbow arthroplasty (TEA) is an established procedure and satisfactory long-term survival rate has been reported. Modern implant designs are linked and unlinked. In the current workshop, surgical procedure for TEA by alumina ceramic elbow (JACE) will be presented. The management and repair of the triceps tendon and medial collateral ligament preservation are important points in surgical approach. Resection of bony spur extending from sublime tubercle, and release of anterior capsule contribute the improvement of postoperative elbow extension. Further, rotational alignment in the setting of humeral and ulnar component is a key point to avoid the edge loading, and to obtain the longer survival rate of the implant.

MTE21

The therapeutic strategy for polyarticular damages in RA patients

Naoki Ishiguro, Toshihisa Kojima
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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by articular joint involvement, which leads to function impairment of human body. The recovery of function was gained with joint surgery such as joint replacement. The recent developed therapeutic methods may change the situation in recent onset RA patients. However, previous studies demonstrated the various pattern of disabilities leaded to the limitation of living life and QOL impairment in patients with established RA patients. Even now, in clinical practice, most of RA patients have long-standing disease and structural damage in their joints. Reconstructive joint surgery should be needed for further improvements of physical function for long-standing RA patients. Because the reconstructive surgery may have only the limited effects on the disabled condition with established RA. It is very important to understand how much range of motion (ROM) should be needed to gain better physical function in each case. The ordinary living is supported with the variety on joint function. So the Rheumatologist should evaluate the living status of RA patients, not only the function of each joint.

MTE22

Tips for differential diagnosis of rheumatoid arthritis in daily practice

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Conflict of interest: None

For rheumatoid arthritis (RA), availability of various oral DMARDs including MTX and biological products has increased treatment options, improving both short-term and long-term outcomes and QOL. Appropriately-tailored treatment of individuals with RA in daily practice, however, depends on an accurate differential diagnosis which includes other autoimmune diseases, but is still often based on experientially-derived clinical judgement. A recent systematic literature review reported that the 2010 ACR/EULAR RA classification criteria have a moderate specificity of 61%(1), suggesting that clinical application of these criteria are only valid after careful consideration of alternative diagnoses. In this session, we aim to characterize the distinguishing clinical features of competing autoimmune and musculoskeletal diseases, helping us to avoid both under-diagnosis and misdiagnosis of RA, an otherwise treatable disease, and emphasizing the need for early diagnosis and its differential diagnosis. References 1. Radner H, *et al*. *Ann Rheum Dis* 2014; 73: 114-23

Joint Symposium (Research Group Joint Symposium on Intractable Vasculitis Syndromes)

JS-1

Guideline for management of large vessel vasculitis

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Conflict of interest: None

Large vessel vasculitis consists of Takayasu arteritis (TAK) and giant cell arteritis (GCA) according to CHCC2012. Whereas TAK is much more frequently observed than GCA in Japan, GCA is more frequently observed in the western countries. Glucocorticoids (GC) remain the principal therapy for large vessel vasculitis. These drugs suppress the clinical signs and symptoms of inflammation when administered in moderate to high doses, but a sizable number of patients with these conditions relapse upon tapering of GC dose or discontinuation. Such patients require retreatment and high cumulative doses of GC, resulting in substantial toxicity and morbidity. Thus, immunosuppressive drugs such as methotrexate, azathioprine, cyclosporine A, cyclophosphamide and, mycophenolate mofetil have been studied with an attempt to control the disease activity and lower doses of GC, especially in the patients with TAK. However, the results of the above immunosuppressive agents for the refractory patients with TAK are not still satisfactory. The pilot study using tumor necrosis factor (TNF)-alpha-inhibitors such as infliximab, eternercept, and adalimab in refractory TAK patients reported beneficial effects. In addition, interleukin-6 (IL-6) also has a crucial role in the pathogenesis of large vessel vasculitis (LVV) including TAK and GCA, since the expression level of IL-6 has been reported to be greatly elevated in the patients with LVV and to correlate positively with disease activity. Several recent studies have reported that IL-6 receptor (IL-6R) blockade with the IL-6R monoclonal antibody tocilizumab might be effective for treatment of the patients with refractory TAK. I would like to discuss the current therapeutic strategy according to the guideline for management of large vessel vasculitis.

JS-2

Japanese guidelines for the management of adults with antineutrophil cytoplasmic antibody-associated vasculitis

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Conflict of interest: Yes

Objective: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of refractory diseases characterized by multiorgan involvement and presence of ANCA in sera of the patients. AAV encompasses microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis, and physicians with various specialty take care of patients with these diseases. To further improve clinical outcomes of the patients with AAV, we have developed totally-revised clinical guidelines for the disease. Methods: The new guidelines are composed of two parts. Research Committee of Intractable Vasculitis Syndrome are in charge of the first part and developing the clinical guidelines using Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the clinical questions where body of evidence is appraisable. Research Committee of Intractable Vasculitis Syndrome of the MHLW, Research Committee of Intractable Renal Disease of the MHLW, Research Committee of Diffuse Pulmonary Disorders of the MHLW are collaborating in the second part to develop a clinical manual for AAV overall. Results: We have addressed three clinical questions: 1) which treatment regimen is recommended for primary induction of remission?; 2) is plasma exchange recommended for AAV with severe or serious renal failure?; 3) which treatment regimen is recommended for maintenance therapy? Systematic literature review team appraised the evidence profile and the guideline development group developed recommendations. We will introduce recommendations of each CQ in this symposium. Conclusion: Development of clinical guidelines for AAV as a whole is pertinent and indispensable to standardize treatment of the disease and to promote good health of Japanese public because AAV shows multi-organ involvement. GRADE system assesses values of treatments from various perspectives, but it involves an immense amount of time, effort and budget.

JS-3

New treatment strategy for antineutrophil cytoplasmic antibody-associated vasculitis with rituximab

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Conflict of interest: Yes

Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is a refractory and recurrent autoimmune disease. Although glucocorticoid (GC)+cyclophosphamide (CY) is effective as a remission induction therapy, concerns exist because of refractory cases and complications such as opportunistic infections. Maintenance therapy with GC+azathioprine (AZA) has issues such as recurrence. Furthermore, long-term GC complications, partly depending on the dosage and long dosing period of GC, cannot be ignored in Japan. Recently, the efficacy of GC+rituximab (RTX) was reported in randomized controlled trials abroad. These studies showed that GC+RTX was not only as effective as GC+CY, with a high remission rate, but also more effective in reinduction therapy. Regarding maintenance therapy, GC+RTX showed significantly higher remission maintenance rate than did GC+AZA. In Japan, 7 AAV cases treated with GC+RTX were reported. According to these results, RTX is licensed for treating granulomatosis with polyangiitis and microscopic polyangiitis in Japan. However, information on RTX for treating Japanese AAV patient is insufficient due to lack of clinical trials targeting Japanese patients. Besides, no postmarketing surveillance is planned, suggesting that RTX would continue to be used without any suitable evidence in Japan. These facts suggest the needs of evidence for treating Japanese AAV patients, which led to this prospective cohort study conducted by the Research Committee on Intractable Vasculitides on a strategic study group, to establish evidences for treatment guidelines on intractable vasculitis. All AAV patients treated with RTX have been enrolled from each institution and will be followed-up for 2 years. Various outcomes including efficacy and safety parameters will be analyzed. Biomarkers as useful predictors will also be searched. These plans are approved by the ethical committee of the Kyorin University, the research headquarter. The study is about to be launched.

JS-4

Current opinion survey for the Japanese practical guideline for ANCA-associated vasculitis using online questionnaire

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Conflict of interest: Yes

Purpose. In Japan, clinical management for ANCA-associated vasculitis (AAV) is usually shared by some departments such as rheumatology, pulmonary medicine, and nephrology. To date, the guideline (GL) for management of vasculitis syndrome (JCS 2008), clinical practice GL for ANCA-associated vasculitis (2014), and the evidence-based GL for rapidly progressive glomerulonephritis (RPGN) (2014) were published and used in clinical practice. Aim of the present study is to examine the current opinion for AAV GLs using online questionnaire and to contribute to wide spread of the developing GL by the Research Committee on Intractable Vasculitides. ***Methods.*** 1) The online questionnaire system was used for collecting individual opinion of rheumatologists (The Japan College of Rheumatology, 925 councilors), pulmonologists (the Japanese Respiratory Society, 631), and nephrologists (The Japanese Society of Nephrology, 399), who are involved in the management for AAV in Japan. 2) The best used GL, current opinions for AAV management and a critical point for discrepancy were examined. ***Results.*** Threehundred and thirty eight doctors answered online questionnaire. The majority was rheumatologists (43.2%) and nephrologists (31.4%). Among 3 GLs, clinical practice GL for ANCAassociated vasculitis (2014) was best used (63.4%) not only by rheumatologists but also by pulmonologists and nephrologists. Clinicians, who had a chance of consultation with other clinical division regarding AAV management, often felt some discrepancies with the immunosuppressant use (79.3%), steroid use (64.4%), and remission induction protocol (59.0%). Finally, what we can do for getting more consensus of opinion is to establish the common AAV-GL and to make a chance of discussion about GL among AAV clinicians. ***Conclusion.*** It seems important for enough consensus of some opinion discrepancies to discuss the revised clinical practice GL for ANCA-associated vasculitis in the scientific meeting with other specialities.

EULAR Session

EUS-1

Early rheumatoid arthritis - from the window of opportunity to the generation of management recommendations

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Conflict of interest: None

The new millennium is characterized by dramatic changes in our diagnostic repertoire with regard to imaging and laboratory tests as well as new treatment modalities. Moreover, the treat to target concept has greatly helped in adjusting therapy, if the target of remission or low disease activity is not reached. Now, the challenges consist of approaches to early disease recognition and immediate treatment after diagnosis to avoid damages. The majority of early RA patients can be identified by clinical examination (joint counts) and by laboratory results (ACPA, RF, ESR, and CRP). Especially anti-citrullinated peptide/protein antibodies (ACPA) are important markers, as they are associated with more severe disease as measured by the persistence of joint tenderness, erosions and MRI abnormalities, as well as extraarticular disease. They are more accurate than rheumatoid arthritis (RF) in diagnosis (equally sensitive but more specific) and correlate with shared epitope in RF-pos. and with HLA DR3 in RF-neg. rheumatoid arthritis. Nevertheless, rheumatoid factors are still very important in early arthritis and are part of the laboratory tools. In unclear cases, especially Power Doppler ultrasound and in selected cases MRI are helpful. Patients with acute symptoms should be treated immediately (analgesic and antiphlogistic therapy, glucocorticoids) while other rheumatologic or infectious causes are excluded. Diagnostic challenges in early arthritis are: seronegative RA, late onset rheumatoid arthritis versus acute flares of hand OA, and other rheumatic diseases with onset of symptoms in the small and medium joints (e.g. SPA, connective tissue diseases). Chest x-ray and abdominal ultrasound should be considered prior to/at the beginning of DMARD treatment (coincidence of malignancies and infectious diseases are not rare in early arthritis). Osteologically based diagnostics in patients with unclear symptoms may be considered (laboratory: calcium, phosphate, vitamin D, parathyroid hormone, TSH, ostase, DXA in postmenopausal women) for differential diagnosis of arthralgia and joint pain. A tight T2T management in all patients with early RA and strict treatment adjustment are essential to achieve the best outcome. In addition, early mobilization, functional and moderate strength training as well as life style changes are part of an integrative treatment concept which enables participation in the work force and social life leading to well-being of most patients. This lecture will focus on novel approaches to stay within an optimal “window of opportunity” in early arthritis and will allude to the current EULAR activities to generate and update management recommendations for clinically suspected arthritis, early arthritis and rheumatoid arthritis.

EUS-2

Low-dose glucocorticoids in rheumatoid arthritis: EULAR vision

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Conflict of interest: None

Inadequate production of endogenous cortisol in relation to ongoing inflammation is recognized in chronic inflammatory conditions like rheumatoid arthritis (RA). Therefore, daily amounts of exogenous glucocorticoid (GCs) are adminstered with the intention to act as a “replacement” therapy1. Beneficial effects of low-dose GCs in RA treatment have achieved today a clear evidence, and from 2007 an EULAR task force has produced several guidelines and recommendations2,3. However, some hesitation still exists about the actual benefit-risk balance, and the harm seems mainly related to dose and duration of GC treatment, as well as to the patient-specific status/comorbidities. The lowest GC dosages that are considered both efficient and with the most acceptable risk of harm for long-term treatment of RA seem ≤ 5mg/day prednisone equiva-

lent4. Dosages between >5 and ≤ 10mg/d may further alter the benefit-risk balance of long-term GC therapy. In early RA, the addition of low-dose GCs (<7.5mg/day) to DMARDs leads to a reduction in radiographic progression that may continue over several years5. In addition, there is some evidence that appropriate timing of exogenous GC release/availability (night-time) may reduce more significantly proinflammatory cytokine synthesis and result at least in less morning stiffness6. Indeed, EULAR recommendations for the management of early RA include, as first step, the use of low-dose GCs in combination with conventional and/or biologic DMARDs7. However, most recent ACR guidelines for RA therapy also include low-dose GCs (<10mg/day) for short-term at any time of the disease and in presence of RA flares8. 1Straub RH. Arthritis Res Ther 2014;16.I1 2Hoes JN al. Ann Rheum Dis 2007;66:1560 3van der Goes MC al. Ann Rheum Dis 2010;69:1913 4Cutolo M al. Arthritis Res Ther 2014;16.S1 5Gorter SL al. Ann Rheum Dis 2010;69:1010 6 Buttgereit F al. Lancet 2008;371:205 7Smolen JS al. Ann Rheum Dis 2014;73:492 8Singh JA al. A&R 2016;68:1

EUS-3

New insights to the pathogenesis of rheumatoid arthritis

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Conflict of interest: None

Recent GWAS and epidemiology studies clearly identify that host environmental interactions critically determine initial loss of B-cell tolerance to citrullinated epitopes which may well be of stochastic origin followed by a clearly genetically dependant breach of T-cell tolerance which leads to systemic manifestations of immune dysfunction and development of synovitis. Thereafter established disease mechanisms dominate which include probably host innate and adaptive immune crosstalk and a substantial component of tissue response and remodelling. In this lecture I shall update a variety of mechanisms that mediate the chronicity events which are the characteristic pathognomonic feature of rheumatoid arthritis and highlight the strategic implications of such observations, both in the context of new target discovery biomarker development and underlying disease causative insight.

Gender Equality Committee Planning Program

GEP-1

The Results of the Questionnaires Survey Conducted by the JCR Committee on Gender Equality

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Conflict of interest: None

JCR Committee on Gender Equality was established in April 2014. The aims of the committee are promoting gender equality in the JCR society and supporting each female or male JCR member for improving their skills as a rheumatologist. Our committee performed questionnaires surveys twice to gather data about what we should do to create a society in which women's professional value is recognized and promoted. The JCR Secretariat emailed first questionnaires to all JCR members in February 2015, and second ones to JCR certified educational facilities in February 2016. The first ones focused on members' (a) present professional status and satisfaction with work, (b) work–life balance, (c) career paths as doctors, and (d) attitudes toward gender equality. Female doctors gain full-time employment less than male in the periods of 11-25 year after graduation from medical school. Both men and women feel that female doctors cannot develop career paths equal to male doctors. They agree the reasons contain childcare and nursing, few role models, and little supervisor's expectation. However, 20% of women (W) and 27% of men answerer (M) also think that one of the factors is women's lack of vocation and responsibility. Answers to the questionnaire of ideal percentage of female JCR directors and councilors are less than 10%: W 4.2%, M 3.7%; 10~20%: W 40.5%, M 47.2%; 21~30%: W 38.7%, M 32.6%; and more than 31%: W16.5%, M16.5 %. Most answerer choose the ideal female proportion that is greater than the present one; no director in February 2015, one director (5.3%) at present, and 8% of councilors. The second questionnaires in February 2016 to JCR certified educational facilities are implemented. The questionnaires are asking the supporting systems in the facilities for gender equalities, work–life balance and career paths for doctors. We also ask responsible persons for rheumatologist education about attitudes toward gender equality. Based on the results, we discuss how our committee should precede with regard to both women and men members. Increasing the proportion of female rheumatologists may also lead to an improved work–life balance among men.

International Concurrent Workshop Clinical

ICW-C1-1

HLA-DRB1 analysis utilizing consecutive data of rheumatoid factor (RF) identified a genetically unique subset among rheumatoid arthritis and distinct genetic background of RF levels from anti-cyclic citrullinated peptide antibodies

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Conflict of interest: None

Objectives: HLA-DRB1 alleles are associated with positivity and titer of anti-cyclic citrullinated peptide antibodies (CCP) in rheumatoid arthritis (RA). However, fluctuations of rheumatoid factor (RF) over the disease course have made it difficult to define fine subgroups of RA according to consistent RF positivity and analyze genetic background of the subgroups and the levels of RF. Here, we define RA subgroups and analyze the genetic components characterizing the subgroups and the levels of RF. Methods: A total of 2,986 patients with RA and 2,008 healthy controls were recruited for two-staged analyses in this study. We genotyped HLA-DRB1 alleles for the participants and collected consecutive data of RF in the case subjects. We classified the case subjects into 3 groups based on RF positivity, namely, (1) RF+ group (positive all time), (2) RF- group (negative all time), and (3) seroconversion group (positive or negative at least one time each across the study period). We compared HLA-DRB1 alleles between RA subsets and healthy controls and performed linear regression analysis to identify HLA-DRB1 alleles associated with maximal levels of RF among RA subjects showing positive RF at least once. Results: A total of 1,532, 1,027, and 427 subjects were classified into subsets (1), (2), and (3), respectively. Shared epitope (SE) was associated with all subgroups including RF- group in comparison with healthy controls ($p<0.0001$). We found that SE was rather enriched in seroconversion group in comparison with RF+ group ($p=0.00042$). SE was rather negatively correlated with maximal titer of RF ($p=0.011$). Multiple linear regression analysis revealed this association was independent from positivity and levels of CCP. HLA-DRB1*09:01, which reduces CCP titer, was not associated with RF levels ($p=0.771$). Conclusion: The seroconversion group has different genetic characteristics among RA. Genetic architecture of RF levels is quite different from that of CCP.

ICW-C1-2

CIGARETTE SMOKE TRIGGERED CIRCULATING AND INFILTRATING NEUTROPHIL EXTRACELLULAR TRAPS BY AUTOPHAGY DEPENDENT WAY IN RA PATIENTS

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Conflict of interest: Yes

Background: Cigarette smoking is proved to be an independent risk factor for the development and progression of rheumatoid arthritis (RA). Neutrophil extracellular traps (NETs) are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. **Objectives:** In the current study, we analyzed the formation and magnitude of NETs from circulationg and infiltrating neutrophils, which triggered by smoking in RA patient. **Methods:** Circulating neutrophils were separated from peripheral blood of healthy volunteers (n=7) and RA patients (n=15). Infiltrating neutrophils were separated from knee synovial tissue, which were obtained with auto biopsy gun under B ultrasound-guided from smoking and non-smoking RA patients. These neutrophils were incubated with 0, 5, 10% cigarette smoke extract (CSE). The formation of Nets were observed using immunofluorescence (IF), labbed by anti-MPO/anti-H3, then autophagy were inspected by anti-LC3/anti-beclin-1. The magnitude of Nets was detected by fluorescent quantitative assay with PICO green. **Results:** Smoking RA patients showed a significant augment of NETs in both neutrophils circulating in peripheral blood and infiltrating in synovial tissues, which is dramatically higher than no-smoking patients and healthy volunteers. Meanwhile, CSE treated neutrophils highly increased NETs in non-smoking RA, but showed much slightly effect in healthy volunteers. Furthermore, synovial tissues demonstrated the colocalization of neutrophils with NETs and autophagy. Additionally, autophagy was idencitified as the orchestrator of NETs formation, as shown by inhibition studies using wortmannin or bafilomycin A1. **Conclusions:** Our data show that cigarette smoke probably triggered NETs of both circulating and infiltrating neutrophils by autophagy dependent way in RA patients.

ICW-C1-3

14-3-3η is associated with immunological and structural status as well as disease activity in rheumatoid arthritis

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Conflict of interest: Yes

Objective: 14-3-3η is a chaperon protein which is approved as a diagnostic marker for RA in Canada, USA, and Europe, being associated with radiographic progression. In this study we investigated the association of serum levels of 14-3-3η with disease activity indices and their changes after treatments in RA. **Methods:** Serum 14-3-3η was quantified in 149 RA patients prior to the initiation of therapy (BL) and at Yr1. The patients were initiated either of ADA, MTX, TCZ, or TOFA (n=49, 23, 50, 27, respectively). 14-3-3η positivity was defined at the diagnostic cut-off of ≥0.19 ng/ml. Relationship between 14-3-3η positivity and DAS28, CDAI and SDAI categorization, as well as group differences in disease activity measures, autoantibodies (RF, ACPA), and Sharp-van der Heijde score were analyzed. **Results:** The mean age was 57 years and 86% female. The median disease duration was 51 months. 14-3-3η-positive patients had higher disease activity (median), DAS28ESR [5.62 vs. 4.77, $p=0.010$], CDAI [24.7 vs 16.0, $p=0.015$] and SDAI [26.8 vs 18.8, $p=0.024$] as well as higher immune abnormalities, RF [84.5 vs 15.5 U/ml, $p<0.0001$] and ACPA [100 vs 16.9 U/ml, $p=0.0002$] than negative ones. Titers of 14-3-3η significantly correlated with DAS28ESR [$r=0.29$], CDAI [$r=0.25$], SDAI [$r=0.24$] and JSN [$r=0.18$]. Serum levels of 14-3-3η significantly decreased from 0.70 ng/ml at BL to 0.37 ng/ml at Yr1 ($p<0.0001$). At BL and Yr1, 110 (74%) and 97 (65%) were 14-3-3η positive (≥0.19). Among the 110 BL-positive patients, median Yr1 DAS-28ESR was significantly lower in the patients whose 14-3-3η turned to negative (n=18) compared to the 92 patients who remained positive (n=92) [2.0 vs 2.7, $p=0.004$]. **Conclusions:** These results indicate that 14-3-3η is potentially the triple-marker for immunological and structural status as well as disease activity in RA. Moreover, higher 14-3-3η titers reflect a higher disease status and may be considered for a post-treatment changes in 14-3-3η toward negative.

ICW-C1-4

Predictive value of the multi-biomarker disease activity (MBDA) score for flare and sustained remission in the HONOR study

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Conflict of interest: Yes

Objective: To determine the predictive value of the multi-biomarker disease activity (MBDA) score for flare and sustained remission after dis-

continuation of adalimumab (ADA) in patients with rheumatoid arthritis (RA) from the HONOR study[1],[2]. **Methods:** This retrospective subanalysis was conducted on 42 RA patients from the HONOR study. Patients receiving ADA and methotrexate (MTX) who maintained DAS28-ESR remission (<2.6) for ≥24 weeks and who subsequently agreed to discontinue ADA were enrolled. Clinical disease activity, functional status, and joint damage were recorded at ADA discontinuation (baseline), and after 24 and 52 weeks. MBDA (Vectra® DA) scores (remission, ≤25; low, 26-29; moderate, 30-44; high, >44) were determined from serum samples collected at baseline. The ability of predicting flare (DAS28-ESR ≤3.2) or sustained clinical remission (SC-REM) (DAS28-ESR <2.6) by MBDA score and patient characteristics were determined. **Results:** At ADA discontinuation, all patients had DAS28-ESR <2.6 with 81% female, 69% RF+, 81% ACPA+ and 30 months mean disease duration. The median MBDA score was 24.5 [quartile; 14.3, 30.8] with 22 (52.4%) patients in remission, 6 (14.3%) low, 9 (21.4%) moderate and 5 (11.9%) high. At 52 weeks, flare and SC-REM were observed in 12/42 (28.6%) and 19/42 (45.2%) patients, respectively. Rate of flare and percentage of SC-REM by MBDA category (remission/low/moderate/high) were 13.6%/50.0%/33.3%/60.0% (p=0.033) and 63.6%/33.3%/33.3%/0% (p=0.0066), respectively (P-value by two-sided Cochran-Armitage trend test). Univariate regression analyses identified MBDA score, DAS28-ESR and disease duration as predictors of flare at 52 weeks (p≤0.05). **Conclusions:** These findings suggest that the MBDA score could predict flare and SC-REM in RA patients in stable clinical remission, undergoing ADA withdrawal while maintaining MTX treatment. [1] Hirata S, et al, ART 2013;15:R135 [2] Tanaka Y, et al, ARD 2015;74:389-395

ICW-C1-5

What blood inflammatory marker should be the most influential on patient discomfort among rheumatoid arthritis patients treated with Infliximab or Tocilizumab?

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Conflict of interest: None

Objective: In clinical setting, we often encounter patient discomfort even though serum C-Reactive Protein (CRP) value within normal ranges using Infliximab (IFX) or Tocilizumab (TCZ). This study was designed to clarify what blood inflammatory marker should be the most influential on patient discomfort among CRP normalized rheumatoid arthritis (RA) patients treated with IFX or TCZ. Methods: We recruited fifty-three female RA patients receiving IFX (n=29) or TCZ (n=24). Their serum CRP values were all within normal ranges (< 3 mg/L). We measured blood inflammatory markers as white blood cell counts (WBC), CRP, erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3 (MMP-3) and serum amyloid-A (SAA) in addition to disease activity indexes as visual analogue scale (VAS), swollen joint counts (SJC) and tender joint counts (TJC). Among each group, Statistical analyses with Peason's correlation and multiple stepwise forward regression analysis were conducted to clarify what variable is the most influential on patient discomfort measured using VAS. Result: Among TCZ, only TJC had statistically significant positive correlation with VAS (r=0.539, p<0.01), while blood inflammatory markers did not have correlation with VAS (CRP: r= 0.134, p=0.54; ESR: r=-0.161, p=0.46; MMP-3: r=0.316, p=0.14; SAA: r=0.064, p=0.78; WBC: r=0.349, p=0.10). Among IFX, in contrast, blood inflammatory markers as CRP, MMP-3, SAA and WBC had statistically significant positive correlation with VAS (CRP: r=0.451, p=0.01; MMP-3: r=0.457, p=0.01; SAA: r=0.543, p<0.01; WBC: r=0.523, p<0.01), though neither TJC nor ESR had correlation with VAS (TJC: r= 0.349, p=0.063; ESR: r=0.116, p=0.55). Multiple regression analysis clarified that SAA was the most influential on VAS among IFX. Conclusion: Among CRP normalized RA patients with IFX, SAA, WBC, MMP-3 and CRP were significantly correlated with VAS, though any blood inflammatory markers did not correlate with VAS among RA patients treated with TCZ.

ICW-C1-6

Presepsin (soluble CD14 subtype) and procalcitonin as biomarkers of systemic bacterial infection in patients with rheumatoid arthritis

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Conflict of interest: None

【Object】To assess the diagnostic values of presepsin (soluble CD14 subtype) and procalcitonin in patients with rheumatoid arthritis (RA) by identifying those with bacterial infection 【Method】During June 2014-September 2015, 126 patients with RA and 25 healthy controls were enrolled. RA patients were divided into infection group and non-infection group. Infection was diagnosed by clinical symptoms, microbiological or radiographic method, and good response to antibiotics. Concentrations of plasma presepsin, serum procalcitonin, C-reactive protein (CRP), and white blood cell counts (WBC) were measured and compared in each group. 【Results】RA patients included 26 patients in the infection group, 45 patients in CRP-positive non-infection group (CRP > 0.3 mg/dL), and 55 patients in CRP-negative non-infection group (CRP < 0.3 mg/dL). Levels of presepsin and procalcitonin in the infection group were highest and significantly higher than those in the CRP-positive non-infection group [Presepsin; 677.9 ± 158.3 pg/mL vs 192.0 ± 12.0 pg/mL ($P < 0.0001$), procalcitonin; 4.052 ± 1.637 ng/mL vs 0.120 ± 0.032 ng/mL ($P < 0.0001$)]. Both CRP and WBC count were highest in infection group, but no significant difference between the infection group and CRP-positive non-infection group was found for the concentrations of CRP ($P = 0.21$), or WBC counts ($P = 0.56$). According to receiver operating characteristic curve (ROC) analysis, presepsin and procalcitonin levels appeared to have a higher diagnostic accuracy for infection than CRP or WBC. For the infection group, the Sequential Organ Failure Assessment Score positively correlated with the concentration of presepsin ($R^2 = 0.307$; $P = 0.0033$), but not with that of procalcitonin ($R^2 = 0.0034$; $P = 0.776$). 【Conclusion】Presepsin and procalcitonin may be useful to identify infection in RA patients. Presepsin may better reflect infection severity than procalcitonin.

ICW-C2-1

Repair of bone erosions in rheumatoid arthritis patients treated with the first biological disease-modifying antirheumatic drugs

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Conflict of interest: None

Objective: This study investigated the frequency of repair of bone erosions in rheumatoid arthritis (RA) patients receiving the first biological disease-modifying antirheumatic drugs (bDMARD). Methods: We retrospectively reviewed clinical courses and radiographic changes of RA patients who received bDMARD as the first biologic agent since 2009 in Yokohama City University hospital. This study included all RA patients that fulfilled the 2010 ACR/EULAR or ACR 1987 classification criteria and were treated with bDMARD for longer than one year. Estimated yearly radiographic progression of the hands was calculated by van der Heijde-modified Sharp score (TSS). The patients who had repair of bone erosions in any joints were defined as the repaired group, while the others were defined as the non-repaired group. Results: A total of 67 RA patients (86.6% female, age 52.1±14.7) received bDMARD as initial biological therapy (infliximab n=18, etanercept n=10, adalimumab n=8, golimumab n=2, certolizumab n=2, tocilizumab n=22, abatacept n=5). TSS was unchanged in 43 (64.2%), increased in 18 (26.9%) and decreased in 6 (9.0%) of the patients. Progression of bone erosions in any joint was observed in 10 patients (14.9%), while repair of bone erosion was ob-

served in 4 (6.0%). There was no significant difference in the baseline characteristics including age, gender, DAS28, and ultrasound findings between repaired group and non-repaired group. The repaired group showed more favorable clinical responses to bDMARD therapy in comparison to the non-repaired group. All patients showed a good response according to EULAR criteria. The disease duration was significantly shorter in the repaired group in comparison to that in the non-repaired group (p=0.025). Conclusion: The present study reveals that repair of bone erosion is associated with early induction of bDMARD and well controlled disease activity.

ICW-C2-2

Finger joint cartilage assessment by ultrasound and X-ray in rheumatoid arthritis (RA)

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Conflict of interest: None

Objectives: Joint destruction in RA includes both bone and cartilage lesions. By X-ray examination, cartilage destruction is evaluated as a joint space narrowing (JSN). However, joint space narrowing is not a direct evaluation of cartilage. The aim of the study was to examine the finger joint cartilage by ultrasound (US) imaging and to compare it with JSN score in relation to clinical relevance. Methods: We enrolled 27 RA patients in low disease activity or clinical remission (DAS28-CRP < 2.7) in this study. The cartilage thickness (CT) of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of 2nd to 5th fingers was bilaterally visualized and measured from a dorsal view, with approximately 90 degrees flexion. In addition, JSN of finger were scored by van der Heijde- modified Sharp method. Results: CT in MCP joints ranged from 0.0 to 0.8 mm (median 0.4 mm), and CT in PIP ranged from 0.0 to 0.4mm (median 0.2mm), respectively. The sum of total CT from 8 fingers ranged from 2.7 to 6.8 mm (median 4.7 mm), and there was a significant difference in CT, but not in JSN score, between male and female patients (5.6 versus 4.6, respectively, p=0.005). Importantly, CT was well correlated with JSN (r=-0.696, p<0.001). Although CT was not correlated with age, disease duration, DAS28-CRP, functional disability score, positivity of rheumatoid factor and anti-CCP-antibody, CT was reduced in RA patients with elevated serum matrix metalloproteinase-3 (MMP-3) values compared with those with normal MMP-3 (3.9 versus 5.0, p=0.015). Conclusion: The US method of direct visualization and quantification of cartilage in MCP and PIP joints can be valid and useful in RA, and our results may support the importance of MMP-3 in the pathophysiology of cartilage destruction.

ICW-C2-3

The discrepancy between patient's evaluation and ultrasonography assessment on the most affected joint in rheumatoid arthritis

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Conflict of interest: None

[Object] Although patients often request scanning the most symptomatic joints in power Doppler ultrasonography (PDUS) assessment, there is no evidence for benefits associated with assessment of a selected joint on demand from patients. Here we investigated whether the patient's subjective evaluation for the most affected joint agrees with US assessment.[Methods] PDUS was performed in 8 joints, including bilateral MCP 2, 3, wrist and knee joints, as a routine in a cumulative total of 406 RA patients. Patients declared the most symptomatically affected joint. If the most symptomatic joint was except the routine joints, the joint was additionally scanned. PD signals and gray-scale (GS) images were scored semiquantitatively from 0 to 3 in each joint. If PD or GS score of the declared joint was the highest of the scores of scanned joints, the patient's evaluation was regarded as agreeing with US assessment.[Results] Group A consisted of 209 patients having the most symptomatic joint among the routine 8 joints, whereas 148 having the most symptomatic joint other than the routine 8 joints were included in Group B. Forty-nine were asymptomatic. In the symptomatic group (Groups A and B), the agreement rates of the patient's evaluation with PD and GS scores were 64.4% and 60.2%, respectively. The agreement rate with PD score in Group B was significantly lower than in Group A (51.4% vs 73.7%, $P = 1.9 \times 10^{-5}$). The agreement rate with GS score in Group B was also significantly lower than in Group A (45.3% vs 70.8%, $P = 1.3 \times 10^{-6}$). Among the cases having positive PD score in any joints ($n = 285$), the agreement rate in Group B ($n = 109$) was significantly lower than Group A ($n = 176$) (33.9% vs 68.8%, $P = 1.2 \times 10^{-8}$). [Conclusions] This study suggests that agreement between patient's subjective evaluation and US assessment on the most affected joints was poor, especially in case the most symptomatic joint was except the routine 8 joints.

ICW-C2-4

Ultrasound evaluation of the efficacy of biologic and targeted synthetic DMARDs toward rheumatoid arthritis patients: Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort in Japan

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Conflict of interest: None

Background; We have been prospectively investigating the course of active RA patients by ultrasonography (US) after b/tsDMARDs being introduced in Kyushu region, Japan from June, 2013. **Methods;** A total 174 RA patients were consecutively recruited from June 2013 to September 2015. Disease activity was consecutively evaluated by both US and clinical composite measures every 3 months after introduction of b/tsDMARDs therapies. Twenty-two joints including MCP, PIP and wrist joints of bilateral hands were assessed by grey-scale (GS) and power Dopper (PD) US images. **Results;** One hundred twenty-five (52 in TNF inhibitors, 41 in TCZ, 29 in ABT, 3 in tofacitinib) out of 174 patients, who completed the first 6 months observation, were evaluated. In overall, treatment continuation rate was 89.6%. Clinical composite measures and total US scores improved significantly at 6 months. Age was older in ABT group, bDMARDs switchers were more frequent in TCZ group, and disease duration was shorter in TNF inhibitors group than in the other groups. Among the baseline variables, multivariate logistic regression analysis identified that total PD score at baseline and bDMARDs-naïve were the predictors of PDUS responder at 6 months. **Conclusions;** In addition to the baseline US disease activity, previous use of bDMARDs may affect the outcome of ultrasound findings in early phase of b/tsDMARDs therapies. Physicians are recommended to pay attention to this information to consider the efficacy of b/tsDMARDs therapies.

ICW-C2-5

Inhibitory effect of abatacept on joint damage in patients with rheumatoid arthritis assessed by MRI

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Conflict of interest: Yes

[Objectives] Although only a few studies have showed MRI-efficacy of abatacept (ABT) in patients with rheumatoid arthritis (RA), there were

no prospective studies for Japanese RA patients. We performed an "MRI-efficacy of ABT in RA patients in Kyoto"(MIYAKO) study. The aim of this study is to evaluate MRI-efficacy of ABT in Japanese RA patients. **[Methods]** This is a prospective observational study performed at our hospital from January 2012 to April 2015. Thirty-five RA patients who had not been received more than 1 biological agent were included in this study. MRI of bilateral hands was performed at baseline and 12 months (M) of intravenous ABT treatment. MRI images were scored for synovitis (0-42), osteitis (0-138) and bone erosion (0-460) according to the Rheumatoid Arthritis MRI Scoring System (OMERACT-RAMRIS). The primary endpoint was change from baseline in MRI-measured synovitis score (SS), osteitis score (OS) and bone erosion score (ES). **[Results]** Thirty-one patients completed this study for 12M. The rate of SDAI remission at 12M was 31%. Mean SS and OS showed statistically significant reductions at 12M compared with the baseline (SS at baseline/12M: 17.1±7.0/11.4±6.2 (p<0.0001), OS: 5.1±8.2/1.9±2.5 (p=0.003)). On the other hand, mean ES showed no change throughout the study (28.2±38.6/28.7±39.2 (p=0.38)). At 12M, 94% of patients showed no progressions in SS and OS. Reductions of ES were observed in 13% of patients, whereas 19% of patients demonstrated progressions in ES. The mean OS at 12M of patients achieving SDAI remission was statistically lower compared with that of patients not achieving SDAI remission (0.36±0.61/2.2±2.5 (p=0.03)). **[Conclusion]** This study demonstrated ABT has a strong inhibitory effect on joint damage reducing synovitis and osteitis and not progressing bone erosion in Japanese RA populations.

ICW-C2-6

MRI bone oedema at enrollment predicts the development of rapid radiographic progression at 1 year toward patients with early-stage rheumatoid arthritis: Results from Nagasaki University Early Arthritis Cohort

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Conflict of interest: None

Objectives To clarify whether MRI bone oedema predicts the development of rapid radiographic progression (RRP) in Nagasaki University Early Arthritis Cohort patients with early-stage rheumatoid arthritis (RA). **Methods** Early-stage RA patients (n=76) were enrolled and underwent Gd-enhanced MRI of both wrists and finger joints. Synovitis, bone oedema and bone erosion were evaluated using the Rheumatoid Arthritis Magnetic Resonance Imaging score (RAMRIS). RRP was defined as an annual increment > 3 at 1 year by plain radiographs and the GSS score. A multivariate logistic regression analysis was performed to establish the risk factors for RRP, using patients' characteristics, serum variables, MRI findings, therapeutic responses and regime. **Results** The patients' median age was 54.5 yrs, and their median disease duration at enrollment was 3 months. RRP was found in 12 of the 76 patients at 1 year. A univariate analysis revealed that matrix metalloproteinase-3, RAMRIS bone oedema score and RAMRIS bone erosion score were associated with RRP. Multivariate logistic regression analyses demonstrated that the RAMRIS bone oedema score at enrollment (5-point increase, OR 2.18, 95%CI 1.32-3.59, p=0.002) is the only independent predictor of the development of RRP at 1 year. An ROC analysis identified the best cut-off value for RAMRIS bone oedema score as 5. **Conclusion** Our findings suggest that MRI bone oedema is closely associated with the development of RRP in early-stage RA patients. Physicians should carefully control the disease activity when MRI bone oedema is observed in early RA patients.

ICW-C3-1

Prevalence of comorbidities for patients with rheumatoid arthritis: a nationwide cross-sectional study

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Conflict of interest: None

Objectives: Physical disability becomes worse with increasing levels of comorbidity for patients with rheumatoid arthritis (RA). However, limited information was available on comorbidities for patients with RA in Asian population. The purpose of this study is to investigate the prevalence of comorbidities for patients with RA in Taiwan. **Methods:** From the Taiwan's National Health Insurance Research Database, we conducted a nationwide cross-sectional study consisted of 14090 patients with RA who aged ≥20 years and 140900 non-RA people were selected with matching by age, sex, and low income for comparison. We identified 30 histories of diseases within recent 2 years as potential comorbidities for RA. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of RA associated with comorbidities were calculated in the multiple logistic regressions. **Results:** Hypertension (34.0%) was the most prevalent disease for patients with RA and the followings were mental disorders (28.6%), peptic ulcer disease (18.7), chronic obstructive pulmonary disease (15.6%), and urinary tract infection (15.1%). After adjustment, the top 5 significant comorbidities for patients with RA were systemic lupus erythematosus (OR 12.0, 95% CI 10.4-13.8), gout (OR 2.93, 95% CI 2.77-3.10), psoriasis (OR 2.22, 95% CI 1.89-2.60), peripheral vascular disease (OR 1.57, 95% CI 1.36-1.81), and osteoporosis (OR 1.56, 95% CI 1.44-1.68). **Conclusions:** This study provided the assessment of comorbidities for patients with RA. Our results remind clinical physicians to manage the comorbidities for patients with RA.

ICW-C3-2

Health Care Utilization Associated with Adverse Events among RA Patients Treated by TNF-alpha in Taiwan

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Conflict of interest: None

Objective. To evaluate the costs of adverse event (AE) in patients with rheumatoid arthritis (RA) treated with biological disease-modifying anti-rheumatic drug (bDMARD) in Taiwan. *Methods*. Data of RA patients from National Health Insurance Research Database (NHIRD) were analyzed within 1 year after the first prescription of bDMARD, to compare the number of OPD/ER visits and duration of hospitalization between the patients with AEs (Case group) and without AEs (Comparison group). AEs included tuberculosis and severe infection. AE-related costs were also investigated. *Results*. A total of 2809 RA patients, who received the first bDMARD during May 15th 2008 to December 31th 2010, were analyzed. Characteristics of age and gender in the case (n = 77) and comparison (n = 2732) groups were comparable. More patients in the case group received Adalimumab (58.44%), while more patients in the comparison group received Etanercept (51.54%). The number of OPD/ER visits was significantly higher in the case group (Case vs. Comparison: 51.58 vs. 42.13, p<0.0001). The length of hospitalization stay was significantly longer in the case group (Case vs. Comparison: 11.72 days vs. 0.51 days, p<0.0001). In the case group, the cost on OPD/ER visits was USD. 114.24/visit; on hospitalization was USD. 375.80/day. In the 1-year index period, the total AE-related cost on OPD/ER was USD. 84,655.42 (USD. 1,099.42/patient); on hospitalization was USD. 41,714.24 (USD. 541.74/patient). *Conclusions*. Patients with AEs demonstrated the higher number of OPD/ER visits and longer length of hospitalization stay than patients without AEs. The total AE-related cost (OPD/ER visits plus hospitalization) per patient was USD. 1,641.16 in the 1-year index period.

ICW-C3-3

Methotrexate toxicity among Filipino patients with rheumatoid arthritis included in the Rheumatoid Arthritis Database and Registry(RADAR)

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Conflict of interest: None

Objectives:1. To know rate of MTX toxicity 2. To identify risk factors 3. To describe management of toxicity Methods: This retrospective case control study used RADAR of Philippine General Hospital. All cases on MTX therapy were included.Disease activity was measured via DAS 28-ESR. Baseline characteristics,duration of MTX use, dose, concomitant drugs, and toxicities were noted. Specific management of events were described. Independent t-test, Mann Whitney U (numerical data) and Chi-square, Fisher's exact test (continuous data) were used for analysis. Results: Among 194 patients included, 25.7% had toxicity.Adverse events included:13% hepatotoxicity, 6% GI,4% hematologic, 2% dermatologic, 2% pulmonary.Risk factors directly correlated with toxicity were age ($p=0.024$), disease duration ($p<0.001$), dose ($p=0.03$), and duration of use ($p\leq0.001$). Anemia and osteoarthritis were associated with MTX toxicity. Subgroup analysis showed GI toxicity with concomitant DMARD use ($p=0.0007$), hepatotoxicity with longer disease duration and exposure to MTX ($p=0.009$, 0.039). Physicians either reduced dose (52%), maintained MTX (26%), added other DMARDs or biologics, or discontinued MTX (22%). Folic acid was given to those with toxicity. Conclusion:MTX toxicity is common in this cohort and comparable with other data in discontinuation rate.

ICW-C3-4

Assessment of peripheral blood subsets related to spontaneous regression of Methotrexate associated lymphoproliferative disorder (MTX-LPD)

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Conflict of interest: None

【Objective】 MTX-LPD is a relatively rare but well known complication among rheumatoid arthritis (RA) patients. Although the regression of LPD after MTX withdrawal is regarded as a distinct character of MTX-LPD and also as an evidence of lymphomagenic potential of MTX, mechanism of regression is still unclear. Therefore, we investigated the factors involved in spontaneous regression of LPD following MTX withdrawal.【Methods】 Whole blood sample was collected from RA patients with MTX-LPD (n=10) (week 0; day of MTX cessation, week 4 and 12) and clinically matched RA patients (control, n=10), and flowcytometric analysis was performed. Patients with MTX-LPD were divided into regressive LPD group (Regressive group, n=7) and persistent LPD group (Persistent group, n=3) depending on the status of LPD at week 12.【Results】 At the time of MTX cessation, number of lymphocytes was significantly decreased in Regressive group, while proportion of effector memory CD8+ T cells (EM CD8+) and Epstein Barr Virus antigen specific CD8+ T cells (EBV specific CD8+), Th1 cells were significantly decreased in both groups compared to control group. After MTX cessation, significant increase of lymphocytes and proportion of EM CD8+ and EBV specific CD8+, Th1 cells, were observed in Regressive group, but not in Persistent group. Whereas granulocytic myeloid derived suppressor cell (Gr MDSC) was significantly increased in LPD group at week 0, and significantly decreased after MTX cessation only in Regressive group, but not in Persistent group. Proportion of Gr MDSC negatively and significantly correlated with the proportion of EM CD8+T and NK cells.【Conclusions】 Proportion of Th1 cells, EM CD 8+, EBV specific CD8+ and Gr MDSC is altered following MTX cessation and is involved in regression of MTX-LPD.

ICW-C3-5

Pulmonary barrier function rather than systemic immune state is crucial for the development and exacerbation of non-tuberculous mycobacterial (NTM) infection in patients with rheumatic diseases

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Conflict of interest: None

Objective: To identify the risk factors of the development and exacerbation of NTM infection in patients with rheumatic diseases. Methods: Among 7013 patients with rheumatic diseases visiting Ohashi Medical Center and Tokyo Medical Center, 20 patients were enrolled in this study by meeting the diagnostic criteria of NTM infection by The Japanese Society for Tuberculosis and The Japanese Respiratory Society, and being followed-up for more than 1 year. The medical records of enrolled patients were retrospectively reviewed. Results: Eleven patients with rheumatoid arthritis, 4 patients with vasculitis, 3 patients with Sjögren's syndrome and 1 patient with dermatomyositis and systemic lupus erythematosus for each. Mycobacterium avium complex (MAC) was detected in 13 patients, M. chelonae in 2 patients and M. abscessus and M.kansasii in 1 patient, and undetermined in 3 patients. Notably, bronchiectasis was the predominant pulmonary complication which was observed in 13 patients, followed by interstitial lung diseases in 6 patients. Although a total of 7 patients ever experienced the exacerbation of NTM, immunological state including peripheral blood leukocyte (6500±2658 /μl versus 6892±2630 /μl; $p=0.721$) and lymphocyte counts (1422±445 /μl versus 1105±345 /μl; $p=0.104$) and the serum IgG level (1597±485 mg/dl versus 1183±310 mg/dl; $p=0.096$) were comparable between ever and never exacerbated patients, respectively. Conclusion: NTM infection in patients with rheumatic diseases is likely to develop on the dysfunction of pulmonary barrier rather than the systemic immune state.

ICW-C3-6

A risk analysis of Pneumocystis pneumonia in patient with rheumatoid arthritis by the National Database of Rheumatic Diseases by iR-net in Japan

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Conflict of interest: None

【Objectives】To clarify the risk factors for developing Pneumocystis pneumonia (PCP) in patients with rheumatoid arthritis (RA) by using a large registry of RA. 【Method】We identified 64 cases of PCP among 57,768 patients with RA registered in National Database of Rheumatic Disease by iR-net in Japan (NinJa) from 2010 to 2015. Clinical variables of the cases were compared to the patients who did not develop PCP. 【Result】Results from the univariate analysis indicated that development of PCP was significantly associated with older age and male sex. In a multivariable logistic regression model, development of PCP was significantly correlated with male sex (OR 2.16, CI: 1.18-3.83), as well as Steinbrocker classification classII(OR 3.41, CI 1.53-8.70) and III(OR 4.25, CI 1.55-12.42). 【Conclusion】Male sex is the high risk of PCP in Patients with RA, which correlate with the results of previous studies.

ICW-C3-7

Possible preventive effect of salazosulfapyridine against development of *Pneumocystis* pneumonia in methotrexate-receiving patients with rheumatoid arthritis

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Conflict of interest: None

Objective: *Pneumocystis* pneumonia (PCP) is a serious complication of rheumatoid arthritis (RA) patients in Japan. However, the preventive administration of trimethoprim/sulfamethoxazole (TMP/SMX) has been limited due to the risk of intolerable adverse events. Therefore, we examined the possible preventive effect of salazosulfapyridine (SASP) against PCP development in methotrexate (MTX)-receiving RA patients. Methods: We conducted a retrospective case-control study of 210 RA patients treated with MTX between January 2005 and October 2013, 61 of whom were also placed on continuous SASP. The observation started at the commencement of MTX in our department, and it ended at the development of PCP or the last observation date with MTX. PCP was diagnosed by a compatible clinical course and chest images, and the presence of *Pneumocystis jirovecii* as determined by polymerase chain reaction (PCR) or elevated serum β-D-glucan level. Results: Despite similar patient characteristics, PCP developed in 10 of the 149 patients who did not receive SASP and none of those who did (p = 0.038 by Fisher's exact test). And the comparison between 10 PCP (+) and 200 PCP (-) patients confirmed the similarity in RA treatments except for SASP and the use of prednisolone, although none of PCP (+) patients received prednisolone above 5 mg/day. Conclusion: Our findings suggest a novel and convenient primary prevention of PCP in RA patients.

ICW-C4-2

Distinct clinical features distinguishing IgG4-related disease and multicentric Castlesman's disease

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Conflict of interest: None

Objectives: Features of IgG4-related disease (IgG4-RD) and multicentric Castlesman's disease (MCD) are somewhat similar with lymphadenopathy, multiple organ involvement and serum IgG4 elevation. The aim of this study was to clarify differences in clinical characteristics and laboratory findings between the two diseases. Methods: Forty-eight patients with IgG4-RD and 32 patients with MCD in our institute were included. Patient characteristics and laboratory data at the time of diagnosis were retrospectively collected, and compared. Results: Patients with IgG4-RD were older compared to MCD (57.4 vs 46.6 years, p<0.0001) and there was no difference in gender distribution, while lymph nodes were affected less frequently in IgG4-RD (50 vs 100%, p<0.0001), lacrimal glands, salivary glands and pancreas were affected only in IgG4-RD. The levels of serum IgA and IgM were significantly lower in patients with IgG4-RD compared to MCD (IgA: 173 vs 705 mg/dl, p<0.0001, IgM: 84 vs 280 mg/dl, p<0.0001), however, there was no difference in serum IgE. Although serum IgG4 was equivalent (618 vs 410 mg/dl, p=0.356), IgG4/IgG ratio was significantly higher in IgG4-RD compared to MCD (0.31 vs 0.10, p<0.0001). On the other hand, elevated C-reactive protein (CRP), anemia, thrombocytosis, hypoalbuminemia and hypocholesterolemia were distinguishing to MCD. Conclusion: The involvement of lacrimal gland, salivary gland and pancreas was unique for IgG4-RD, and intense inflammation was the distinct characteristics for MCD. Our findings have provided information for differential diagnosis of IgG4-RD and MCD, and also suggested the involvement of different pathological pathways resulting in somewhat similar clinical features.

ICW-C4-3

Cardiac Magnetic Resonance Imaging Reveals Myocardial Fibrosis and Inflammation in Dermatomyositis/Polymyositis Without Cardiac Manifestation; a pilot study

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Conflict of interest: None

Objective; Our aim was to evaluate cardiac involvement in patients with PM/DM without cardiac manifestations, assessing by CMR. **Methods;** Consecutive female PM/DM patients (pts) and controls without cardiac symptoms were enrolled. Late gadolinium enhancement (LGE) was obtained for the assessment of myocardial fibrosis. Using black blood T2-WI, myocardial inflammation could be assessed. We compared the pts and controls in terms of prevalence of CMR abnormalities, and explored possible associations between CMR abnormalities and PM/DM disease characteristics. **Result;** We compared sixteen females (mean age, 51.9±11.0 years; seven DM, nine PM) with age, and gender matched sixteen healthy control (mean age, 52.6±5.3 years). There were no difference of prevalence in LGE and T2-W1. LGE was detected in 8 of 16 pts (50%). Three of 16 pts were detected not only T2-W1, but also LGE positive. T2-W1 was located in same place with LGE. There were no difference of prevalence in LGE and T2-W1 between PM (56% and 11%) and DM (43% and 29%). Compared with controls, there were no difference of ejection fraction (EF) (p=0.23). The main finding observed in 7 of 16 pts showed concentric remodeling that were 75% of LGE positive, and mass/EDV were significant higher PM/DM pts than controls (p=0.006). PM/DM pts tended to have higher NT-proBNP than controls. LGE positive was significantly correlated with concentric remodeling among PM/DM pts (P=0.04). Anti-Jo1 antibody positive tended to be related with LGE positive. Adjustment for disease duration, anti-Jo1 antibody, LGE positive did not modified association with concentric remodeling. **Conclusion;** DM/PM pts without cardiac symptoms have a high prevalence of cardiac abnormalities. DM/PM pts with LGE associated with abnormal morphology, even with normal EF. Moreover, anti-Jo1 antibody might related with prevalence of LGE. **Conflict of Interest;** none declared.

ICW-C4-4

The relevance of inflammatory cytokines to ILD (Interstitial lung disease) with acute respiratory failure in CTD (Connective tissue disease)

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Conflict of interest: None

Objectives; Although acute exacerbation of ILD in CTD patients is critical, effective therapeutic strategy has not been established. We here assessed the relevance of serum markers to acute exacerbation of ILD in rheumatoid arthritis (RA), ANCA-associated vasculitis (AAV) and dermatomyositis (DMy). **Methods;** We retrospectively examined the association of various serum markers with CT scores (fibrosis score=F-score, GGO (ground grass opacity) score=G-score) in 14 RA, 12 AAV, 12 DMy with ILD and acute respiratory failure who were admitted to our hospital within a decade. **Results;** Baseline characteristics [RA/AAV/DMy] were: gender (M:F) [10:4/5:7/2:10], age (years) [70.2/71.4/65.1], disease duration (months) [89.5/30.2/17.7], LDH (mg/dl) [331.6/446.2/785.1], KL-6 (U/ml) [331.6/446.1/1574.9], F-score [1.9/1.4/1.5], G-score [2.6/2.1/2.2](max score 3), survival rate at 90 days (%) [42.9/33.3/8.3]. Unlike RA and DMy patients, serum KL-6 levels were significantly correlated with F-score and G-score (r^2=0.71, p<0.01 and r^2=0.91, p<0.01, respectively) in AAV patients. Serum MDA-5 and anti-ARS antibodies (PL-7) had no correlation with CT score in DMy patients. Among serum levels of cytokines (IFN-γ, TNF-α, IL-1β, IL-6, IL-12), IL-6 and IFN-γ were significantly increased and IL-6 was significantly correlated with F-scores (r^2=0.94, p=0.03) in DMy patients. Furthermore, IL-6 and IFN-γ characteristically formed statistical clustering with F-score and G-score, respectively. **Conclusion;** Our results suggest that pathological processes of acute exacerbation of ILD are different among RA, AAV and DMy: in AAV KL-6 is useful for interstitial or fibrotic changes, in DMy IFN-γ and IL-6 are useful markers for interstitial inflammation and fibrotic changes, respectively. IFN-γ and IL-6 are, therefore, involved in pathological processes of acute respiratory failure of ILD and might be considered as therapeutic targets for fatal DMy cases.

ICW-C4-5

The analysis of risk factors for infection in patients with inflammatory myopathies complicated with interstitial lung disease

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Conflict of interest: None

Background/Purpose: Inflammatory myopathy (IM) patients often undergo intensive immunosuppressive therapies (IS) for controlling interstitial lung disease (ILD). To prevent the patients from complicating fatal infection, it is important to perceive and care high risk patients for infection. **Methods:** We retrospectively analyzed episodes of serious infection among 106 IM patients with ILD who received initial treatment at 2 Yokohama City University hospitals from 1993 to 2015. Episodes which needed additional treatment for controlling infection within 6 months after starting IS were counted as 'serious infection'. We conducted univariate and multivariate analysis to extract risk factors for infection from the clinical, laboratory and HRCT findings at baseline and therapeutic regimens including accumulation amount of predonisolone (PSL). **Results:** Baseline clinical data of 106 patients (female 73%, age 55±14 y.o., PM 19, DM 49, ADM 38) were as follows: CK 224 (41-10712) IU/l, CRP 0.5 (0-26.5) mg/dl, lymphocyte 1030±555/ml, albumin 3.4±0.6 g/dl. Initiate therapies they received were mPSL pulse 73%, intravenous cyclophosphamide (IVCY) 41%, calcineurin inhibitor 69%, combined IS 35%, and prophylactic ST 50%. Forty patients (38%) had 54 episodes of serious infection after 40±26 days from initiation of IS and 5 died because of infection. Respiratory site was the most common infected lesion; bacterial pneumonia 19, lung suppuration 2, pneumocystis pneumonia 9, CMV infection 15, and the others 9. The infected group showed lower albumin and higher CRP level and more often received mPSL pulse, calcineurin inhibitor, or combined IS compared to the other group, whereas multivariate logistic regression analysis revealed that hypoalbuminemia (<3.5 g/dl) was an independent risk factor for infection. **Conclusion:** We should do appropriate monitoring, prophylaxis and early treatment intervention for infection to manage IM patients with ILD, especially who show hypoalbuminemia.

ICW-C4-6

Primary prophylaxis for pneumocystis pneumonia(PCP) by Sulfamethoxazole/Trimethoprim (ST) under immunosuppressive therapy in patients with systemic autoimmune diseases

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Conflict of interest: None

Objective: To clarify the retention rate, reason for withdrawal, factors associated with withdrawal of primary prophylaxis of PCP with ST and incidence of PCP under immunosuppressive therapy in patients with systemic autoimmune diseases. **Methods:** During Sept. 2012 and Sept. 2015, ST was administered as primary prophylaxis for PCP in 428 patients (pts) with systemic autoimmune disease under immunosuppressive therapies according to the predefined criteria; ≥2 out of 3 factors ((1) age≥65, (2) use of glucocorticoids, (3) coexisting pulmonary disease) in RA, or ether (1)PSL≥1mg/kg as monotherapy or (2)PSL≥0.5mg/kg with immunosuppressants) in non-RA. Retention rates were assessed by Kaplan-Meier method, and factors associated to withdrawal of ST by Cox proportional hazard model. **Results:** Mean duration of administration of ST was 437 days. Among 428 pts, 69 (16%) discontinued ST, due to adverse events in 49 (71%) (15 renal failure, 11 liver failure, 11 hematopoietic disorder, 7 rash, and 6 others and reduction of immunosuppressive agents in 20 (29%). In non-RA, age>65, elevated ALT>30U/l, elevated Cr (≥1.0 mg/dl in male, ≥0.8 in female) and suppressed platelet count<150,000/μl were identified as factors associated with the reduced retention rate. Of the 69 pts who failed to continue ST, 36 were switched to Pentamidine inhalation, 3 ware switched to Atovaquone, and 36 took no alternative agents. No pts who could continue ST developed PCP, whereas 4 (11%), including 3 with Pentamidine and 1 without any alternative agents, developed PCP. **Conclusions:** In this 3-years follow-up, the retention rate of ST was 84%. In non-RA, age, liver and renal dysfunction, reduced platelet counts were associated with withdrawal of ST. Patients who could not continue ST developed PCP at high rate. Taken together, improved retention rate of ST and suppressed risk of PCP could be approached by tailor-made medicine according to baseline characteristics in systemic autoimmune diseases.

ICW-C4-7

Comparison of the efficacy and safety of low dose trimethoprim/sulfamethoxazole (SMX/TMP) therapy with high dose SMX/TMP therapy in connective tissue disease with Pneumocysitis pneumonia (PCP); A retrospective multicenter study

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Conflict of interest: None

[Objectives] To compare the efficacy and safety with either low dose SMX/TMP therapy or high dose SMX/TMP therapy in connective tissue disease with PCP. [Methods] We retrospectively analyzed 64 connective tissue patients with PCP and allocated to low dose SMX/TMP therapy group and high dose SMX/TMP therapy group. We defined low dose therapy group if patients received within 6 tablet of SMX/TMP and also defined high dose therapy group if patients received above 7 tablet of SMX/TMP. [Results] Twenty five patients were allocated low dose therapy group and thirty nine patients were allocated high dose therapy group. The Clinical characteristics were same except for tablet and drug dose in both groups. Median treatment interval of initiation dose was 12.3 days in low dose therapy group and 9.7 days in high dose therapy group. Lack of therapeutic efficacy was 8% in low dose therapy group, 2.5% in high dose therapy group (P=0.55). Successful treatment rate which indicates that patients could receive consecutive initial dose of SMX/TMP therapy without discontinuation of the treatment failure or adverse effects was 44% in low dose therapy group, 26% in high dose therapy group (P=0.40). The most common treatment-limiting adverse effect was nausea, 8% in low dose therapy group, 25% in high dose therapy group (P=0.10). Treatment-limiting adverse effect rate was higher in high dose therapy group (48% vs.71%), however, which was no significant difference (P=0.06). Kaplan-Meyer method revealed that cumulative persistence rate was no significantly differences between the groups (P=0.07). Cumulative treatment-limiting adverse effect rate in low dose therapy group was lower than high dose therapy group (P=0.04). The overall mortality rate was 8% in low dose therapy group and 2.5% in high dose therapy group (P=0.55). [Conclusions] Low dose SMX/TMP therapy was as effective as high dose therapy and lower side effects than high dose therapy in connective tissue disease patients with PCP.

ICW-C5-1

The evaluation of usefulness of treatment and fracture healing for bisphosphonate-associated atypical femoral fractures

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Conflict of interest: None

(Objective) To evaluate the usefulness of treatments and fracture healing for bisphosphonate (BP)-associated atypical femoral fractures. (Subjects and Methods) Nine patients (10 limbs) of AFFs were treated from Jan. 2009 to Jun. 2014. The average age was 62 years old (36 to 86) and all were female. Fracture site was subtrochanteric in 5 cases (6 limbs) and diaphysis in 4 cases (4 limbs). Primary diseases were systemic lupus erythematosus (SLE) in 3, rheumatoid arthritis (RA) in 2, primary osteoporosis in 2, polymyalgia rheumatica (PMR) in 1, and sarcoidosis in

1. Oral methylprednisolone were administered in 7 cases, 7.3 mg/day on average. Administered BPs were alendronate in 7 cases for 4.8 years on average, risedronate in 2 for 1.7 years. The other one was switched to minodronate for 4 years after alendronate for 1.3 years. Operative procedure, time point of cease of BPs, and aftertreatment such as LIPUS (Low Intensity Pulsed Ultra Sound) and daily teriparatide (dTPTD) were examined. When fracture line is not detected on plain X-ray (both anterior-posterior view and lateral view), it was defined as fracture healing (union). The union rate and duration to union were also examined. Follow up duration was 1.8 years on average (6 months to 4.25 years). (Results) Intramedullary nail was performed in all cases. Of these, 2 cases were required for revision surgery due to implant failure but they finally achieved union. Although BP was continued until 9 months after surgery in the first case, it was ceased preoperatively in all other 8 cases. LIPUS was administered in 8 cases. dTPTD was administered in 6 cases. Fracture healing was observed in 4 case (5 limbs) (union rate was 50%) and the average duration to union was 1.75 years (6 months to 2.75 years). Of these cases, dTPTD was administered in only 1 case. (Conclusion) Compared to previous report, union rate of AFFs was not high and it took longer time to union even they were treated with LIPUS and dTPTD.

ICW-C5-2

The histomorphometric findings of fracture sites in patients with bisphosphonate-related atypical femoral fractures:Local accumulation of osteocyte necrosis and microdamage in the cortex cause atypical fractures

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Conflict of interest: None

[Objective] Microdamage accumulation was induced by long term use of BPs in dog (Mashiba T et al, 2001). However, how high microdamage accumulation is associated with the occurence of AFF in human is not clarified. The aim of this study was to explore the mechanism of AFFs by evaluating the degree of microcracks and osteocyte necrosis in the cortex. [Subjects and Methods] Nine AFF patients who fulfilled with ASBMR clinical features (Shane E, et al. 2014) were registered. All were female, age was 78 years old (66 to 93) on average. Primary diseases were primary osteoporosis in 6, rheumatoid arthritis in 2, and sarcoidosis in 1. The fracture sites were subtrochanteric in 7, and diaphysis in 2. Used BPs were alendronate (ALN) in 5 cases, risedronate in 2, minodronate (MIN) in 1, and in the other one case, ALN was used following MIN. The average duration for BPs exposure was 6.9 years (0.5 to 12). At the surgery (osteosynthesis), the specimens of fracture sites were collected and bulk staining were performed to detect microcracks. The crack number (Cr.N) and mean crack length (Cr.Le) were measured. In addition, they were subjected to measure osteocyte density and empty lacuna density after Villaneuva bone staining. [Results] Microcrack was detected in the fracture site of each specimen, suggesting the accumulation of microdamage. On the othr hand, microcrack was never detected in callus formation area. The average Cr. N was 49.3 (range; 7.5 to 145). The average Cr. Le was 112.2 (range; 87-152) μm. Of 9 cases, 5 specimens were evaluated osteocyte density and empty lacuna density. Of these, empty lacuna density showed higher than osteocyte density in 3 cases (60%), suggesting the decrease in bone metabolism. [Conclusion] In the cortex of fracture sites, microcrack is highly related empty lacuna density. The appearance of empty lacunae (osteocyte necrosis) can impair the healing of microdamage and results in the occurence of BP-related AFFs.

ICW-C5-3

The incidence of bisphosphonate-related beaking (atypical incomplete fracture of femur) and the change of its form among patients with autoimmune diseases taking glucocorticoid; from a longitudinal study for three years

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Conflict of interest: None

[Objectives] Beaking has been reported to precede atypical femoral fractures (AFFs). The aim of this study was to identify the incidence of bisphosphonate (BP)-related beaking (atypical femoral incomplete fracture of femur) among patients with autoimmune diseases under glucocorticoid treatment. [Methods] One hundred and twenty five patients with autoimmune diseases taking BP and glucocorticoid were included and 111 patients underwent annual X-ray and serum bone metabolism markers for three years. Localized periosteal thickening of the lateral cortex in femoral X-rays was defined as beaking. [Results] Beaking was detected in 15 femora in 10 patients at the recruitment. In three year observation period, the frequency of beaking was increased to 23 femora in 15 patients (three femora in two patients in the first year, three femora in a new patient and a patient who had been detected beaking of the other femora at the recruitment in the second year, and two femora in two patients in the third year). A complete AFF at the location of beaking occurred in a patient. The mean age of patients with beaking was 55.2 years old (42-73), all of them were females and taking alendronate, the mean duration of BP usage was 6.37 years (3.9 -8.4), and the mean prednisolone dose was 9.4 mg/day (5-15). Ten out of 15 was patients with systemic lupus erythematosus. Among all patients with beaking, prodromal pain was presented in four femora of four patients. Bone alkaline phosphatase, undercarboxylated osteocalcin, serum NTx, and urine deoxypyridinoline levels were not elevated, but urine NTx was elevated in some patients with beaking. Twelve patients with beaking discontinued taking BP after detection of beaking. Beaking of seven femora in six patients became dull within three years with BP withdrawal. [Conclusion] The development of BP-related beaking was observed in eight femora in five patients within three year observation period. BP withdrawal could affect beaking to be dull.

ICW-C5-4

Medial Meniscus Extrusion and Spontaneous Osteonecrosis of the Knee

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Conflict of interest: None

Objectives: Although the pathogenesis of spontaneous osteonecrosis of the knee (SONK) remains unclear, medial meniscus tear has been proposed as a potential etiology behind development of SONK. No information is available on correlation between meniscal extrusion and SONK. Our purpose was to determine association of the extent of meniscal extrusion with the severity of SONK. **Methods**: We examined 12 knees in 12 patients with a diagnosis of SONK in the medial femoral condyle. All patients were examined by X-ray and MRI that confirmed the diagnosis of SONK. There were four men and eight women, with a mean age of 70 years (55 to 82). The stage of progression of SONK was determined according to the radiological classification system. After measurement of anteroposterior, mediolateral, and superoinferior dimensions of the lesion by MRI, its ellipsoid volume was calculated from the three dimensions. The extent of medial meniscus extrusion and its degeneration and tear were also evaluated by MRI. **Results**: The mean volume of the lesions in 12 patients with SONK was 2837 mm^3(324 to 7464). Degeneration and tear of the medial meniscus were found in 12 and 11 patients, respectively. The mean extrusion of the medial meniscus was 6.7 mm (3.0 to 10.2). Of the 12 knees with SONK, 2 knees showed the radiographic stage 2 lesions, 7 knees the stage 3, and 3 knees the stage 4. When the ellipsoid volume of SONK lesion was compared among stages, the volume tended to increase with the stage progression (P=0.062 by ANOVA). Medial meniscal extrusion was likely to increase with the stage progression, although no statistically significant difference was found (P=0.234 by ANOVA). The simple linear regression of the ellipsoid volume of SONK lesion on medial meniscal extrusion showed a significant correlation (R=0.761, P=0.004). **Conclusion**: The extent of medial meniscal extru-

sion was significantly associated with the size of the lesion of SONK, which could determine the prognosis of the disease.

ICW-C5-6

Risk factors for femoral head avascular necrosis in pregnant women with antiphospholipid syndrome

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Conflict of interest: None

[Objective] Pregnancy, excessive corticosteroids, and autoimmune disorders can predispose to avascular necrosis (AVN). By investigating pregnant women with antiphospholipid syndrome (APS), our study intended to find the risk factors for femoral head AVN development. **[Methods]** This single-center retrospective study included patients diagnosed with either definite or non-criteria APS, giving birth during 2010 to 2012, and aged over 30 years at delivery. The medical records until January 2015 were reviewed. Their clinical presentations, disease duration, AVN occurrence, medications, pregnancy histories, and laboratory data were analyzed statistically. **[Results]** There were 43 patients included, and apparent femoral head AVN developed in 10 (23.3%). One of them happened at 32 weeks gestation, and the others occurred, on average, 14.9 months after delivery. The analysis of pre-pregnancy baseline features revealed significantly higher daily doses of steroids in the AVN group. During pregnancy, low gestational age at birth, administration of azathioprine, steroid pulse and mini-pulse therapies, and high coefficients of variation (CVs) of plasma D-dimer levels of the first two trimesters were significantly associated with AVN occurring. The age, APS categories, associated diseases, levels of antiphospholipid antibodies, and cumulative doses of steroids during pregnancy did not significantly differ between the AVN and non-AVN groups. By binary logistic regression analysis, it was a higher CV of D-dimer levels in the first trimester found to increase the risk of AVN (p=0.03). **[Conclusions]** Highly fluctuating D-dimer levels in early pregnancy may indicate APS flares requiring aggressive treatment with steroids and azathioprine. Besides, active APS can lead to preterm labor. In this study, factors related to APS activity could predict the development of AVN of the femoral head. Further research on AVN prevention for such patients should focus on the management of APS activity.

ICW-C6-1

The importance of Syk and Btk in B cell in patients with Systemic Lupus Erythematosus

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Conflict of interest: None

Objectives; B cells play a pivotal role in the pathogenesis of autoimmune diseases. Although Syk and Btk function as key molecules in BCR signaling, the pathological role in SLE remains unclear. **Methods;** We assessed the effect of αBCR, CD40L, CpG (ligand of TLR9 (Toll-like receptor 9)) or IL-21 on B cell functions in vitro. PBMCs were isolated from healthy subjects (HDs) and SLE patients, and p-Syk and p-Btk in B cells were analyzed by FACS and their association with clinical characteristics was assessed. **Results;** We found that B cell activation were slightly induced by αBCR, CD40L, while combination with αBCR, CD40L and CpG caused robust proliferation, cytokine production, AICDA, BCL6, XBP1 gene expression and IgG production, especially in memory B cells. A Syk inhibitor (BAY613606) abrogated these B cell functions. Following stimulation through all 3 receptors, B cell subsets induced marked expression of TLR9, TRAF6 and p-NFκB, which were again abrogated by a Syk inhibitor. αBCR, CD40L and IL-21 also induced B cell activation, which was abrogated by a Btk inhibitor (ONO-A). Although p-STAT1 and p-STAT3 were induced by IL-21 with αBCR, CD40L, p-STAT1 in the nucleus, but not cytoplasm, was exclusively impaired by a Btk inhibitor. In addition, phosphorylation of STAT1, but not STAT3, in the nucleus was preferentially decreased in Btk-knockdown BJAB cells after IL-21 stimulation as well as in primary B cells. Furthermore, pronounced expression of p-Syk and p-Btk was noted in B cells from SLE patients compared with HDs and levels of p-Syk correlated with the disease activity score such as SLEDAI and BILAG. **Conclusion;** Our results suggest that Syk and Btk not only play a conventional role in the regulation of BCR-signaling, but also mediate signal-crosstalk among BCR, CD40L, TLR and IL-21 in human B cells. Phosphorylation of Syk and Btk were pronounced in B cells of SLE, indicating the relevance to pathological processes as well as a potential as treatment-target.

ICW-C6-2

Negative correlation between miR-326 and Ets-1 of regulatory T cells in new-onset patients with systemic lupus erythematosus

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Conflict of interest: None

Objectives: To analyze the relationship between miR-326 and Ets-1 mRNA levels in regulatory T cells and clinical manifestations in patients with systemic lupus erythematosus and explore the role of miR-326 and Ets-1 in the pathogenesis and activity of SLE. **Methods:** The newly diagnosed SLE patients who had not take glucocorticoid or immunosuppressants. Inactive SLE patients had been taking prednisone 10 mg/day with stable dose for more than 1 year, but not taking immunosuppres sants. Regulatory T cells were purified by MACS from 20ml peripheral blood, in which the quantity of miR-326 and Ets-1 mRNA were assessed by real-time PCR. **Results:** The level of miR-326 was significantly higher in regulatory T cells in SLE patients [1.95 (0.611, 6.164)] than that in healthy controls [0.921 (0.345, 1.879)](p=0.023). The difference between new-onset SLE patients [6.083 (0.649, 15.074)] and healthy controls was significant (p=0.012). Significant difference of the miR-326 expression was found between new-onset SLE patients with serous cavity effusion and that without it (P<0.05). Significant positive correlation was found between the expression of miR-326 mRNA in regulatory T cells with CRP and anti-C1q antibody in new-onset SLE patients. The level of Ets-1 mRNA was decreased in SLE patients [0.355 (0.182, 0.484)] compared to healthy controls (p=0.012). The difference was also found in new-onset SLE patients [0.198 (0.118, 0.296)] while compared to healthy controls. Also, the level in new-onset SLE patients was lower than that in inactive SLE patients [0.459 (0.382, 0.495)](p=0.001). Negative correlation was found between miR-326 and Ets-1 mRNA expression in Treg cells from new onset SLE patients (r=-0.670 p=0.01). There was no correlation of miR-326 or Ets-1 mRNA expression with SLEDAI. **Conclusion:** The upregulated of miR-326 expression in regulatory T cells from SLE patients may inhibit the expression of Ets-1 to participate in the pathological process of SLE.

ICW-C6-3

Evaluation of Soluble α-Klotho in Neuropsychiatric Systemic Lupus Erythematosus

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Conflict of interest: None

[Objectives] Neuropsychiatric systemic lupus erythematosus

(NPSLE) is a serious complication in SLE. No reliable diagnostic markers for NPSLE have been identified, because of the variability of NPSLE manifestations. Alpha -Klotho is a single-pass transmembrane protein expressed in multiple tissues, especially brain and kidneys. A reduction of Klotho protein is known to be associated with endothelial dysfunction and neuronal damage. **[Methods]** We sought to determine whether soluble alpha-Klotho (s-Klotho) in cerebrospinal fluid (CSF) could be a candidate marker for the diagnosis of NPSLE. We retrospectively analyzed the laboratory data, symptoms and radiological image findings of patients with NPSLE (N=34). Patients with SLE patients (N=17), viral meningitis (VM) (N=19), multiple sclerosis (MS) (N=15) and neuromyelitis optica (NMO) (N=16) were included as controls. The s-Klotho level in the CSF of each subject was measured by enzyme-linked immunosorbent assay. We conducted univariate and multivariable competing-risks regression analyses to determine the predictive factors for diagnosing NPSLE. We also evaluated a cutoff value of s-Klotho for the diagnosis of NPSLE by determining the receiver operating characteristic (ROC) curve.**[Results]** We found that the CSF s-Klotho levels of the NPSLE patients were significantly lower than those of the SLE. The multivariable analyses revealed that lower CSF s-Klotho level (odds ratio [OR], 0.98; 95% confidential interval [CI], 0.96-0.99), lower anti-Smith antibodies (U/mL) (OR, 0.93; 95%CI, 0.82-0.99) and higher C3 (mg/dL) (OR, 1.08; 95%CI, 1.02-1.18) were significant factors for predicting NPSLE. The sensitivity and specificity of the CSF s-Klotho level for the diagnosis of NPSLE were 82.4% and 94.0%, respectively at the cut-off value of 230.2 pg/mL.**[Conclusion]** Our data suggested that the determination of CSF s-Klotho levels contribute to the diagnosis of NPSLE and help elucidate the mechanisms underlying this disease.

ICW-C6-4

Combination of anti-beta2-glycoproteinn I domain I and phosphatidylserine-dependent antiprothrombin antibodies may be a candidate of effective screening tests for diagnosis of antiphospholipid syndrome

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Conflict of interest: None

[Object] Routine detection of antiphospholipid antibodies (aPL) for diagnosis of antiphospholipid syndrome (APS) is exhaustive and burdens the laboratory department. Recently, several studies showed 2 non-criteria aPL: anti-beta2-glycoprotein I domain I IgG antibodies (aDI) and phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT), had the strong correlation with thrombotic events in APS. We hypothesized they could serve as an efficient screening procedure for APS diagnosis. [**Methods]** This study involved a cohort of patients with autoimmune diseases who visited our rheumatology clinic from 2005 to 2013. ADI and aPS/PT tests were performed together with criteria aPL tests in all patients. Diagnostic value was assessed using the Sapporo classification criteria Sydney revision for APS. APL score (aPL-S), a quantitative diagnostic marker of APS, was calculated. [**Results]** The study comprised of 157 patients. ADI and aPS/PT (IgG and IgM) had high positive predictive values (PPV) for APS diagnosis (1.00, 0.924 and 0.923, respectively) among all aPL. All 21 patients positive for both aDI and aPS/PT (IgG and/or IgM) as well as all 10 patients positive for aDI and negative for aPS/PT met the APS criteria. The aPL-S was high (46 [34-56] and 22 [8-26], respectively) in those patients corresponding with high prevalence of APS diagnosis. Of the 14 patients positive for aPS/PT and negative for aDI, 11 (79%) met APS criteria, and the aPL-S was 23 [15-37]. Of the patients negative for both aD1 and aPS/PT, only 8%(9/112) were diagnosed as APS, and their aPL-S was 0. AD1 and aPS/PT could cover 82% of the patients with APS in our autoimmune disease cohort with a false-positive rate of 6.7%. [**Conclusions]** Detection of 2 non-criteria aPL with high PPV enabled the diagnosis of APS in our autoimmune disease cohort with a very low false-positive rate and correlated with aPL-S. The combination of aDI and aPS/PT would make a very efficient screening procedure for APS diagnosis.

ICW-C6-5

Clinical and immunological consequences of Total Glucosides of Paeony treatment in Sjögren's syndrome: a randomized controlled trial

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Conflict of interest: None

Objective: To investigate the clinical and immunological consequences of total glucosides of paeony (TGP) treatment in patients with Sjögren's syndrome (SS). **Methods:** Forty-five patients with primary SS participated in a randomized, double-blinded, placebo-controlled clinical trial. Patients were assigned randomly to TGP or placebo group in a ratio of 2:1 and followed up for 24 weeks. Clinical assessment was performed by EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), stimulated and unstimulated salivary flow rate, Schirmer test and erythrocyte sedimentation rate (ESR). The proportions of B cells in peripheral blood were detected by flow cytometry. The levels of serum IL-6, TNF-α, IFN-γ and BAFF were measured before and after treatment. This trial was registered on www.chictr.org, with the register number of ChiCTR-TRC-12002325. **Results:** As compared to placebo control, the mean (SD) for ESSPRI in the patients who got 3 to 6 score at baseline was significantly reduced in TGP group at 18- and 24-week changed from 4.81 (0.60) to 4.15 (1.27) (P=0.012) and 4.20 (1.46) (P=0.027). Stimulated salivary flow rate increased at week 24 from 1.80 (0.39) to 2.01 (0.51) (P=0.031) and unstimulated salivary flow rate increased from 1.30 (0.92) to 1.55 (0.90) (P=0.011) in TGP group, but the placebo group showed no significant difference. ESR was decreased significantly in comparison to the placebo group at 12- and 24-week from 40.9 (18.0) to 29.4 (12.2) (P=0.003) and 30.4 (17.3) (P=0.024) in TGP group. The percentage of naive B cells decreased at week 24 in TGP group from 77.34 (12.20)% to 64.59 (15.60)%(P=0.005), while memory B cells increased from 21.79 (11.97)% to 34.21 (15.48)%(P=0.006). The concentrations of TNF-α and IFN-γ decreased in TGP group at week 24 from 32.51 (26.67) to 24.22 (13.56) (P=0.017) and 10.71 (8.94) to 6.55 (4.88) (P=0.022), respectively. **Conclusion:** TGP appears to improve the glandular secreting function and ameliorate the inflammatory process.

ICW-C6-6

Characteristic phenotype of peripheral blood lymphocytes in patients with IgG4-related disease

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Conflict of interest: None

[Objectives] The aim of this study was to investigate the characteristic phenotype of immune cell subsets in IgG4-RD. **[Methods]** Peripheral blood mononuclear cells were obtained from 16 patients with IgG4-RD, 4 with primary Sjogren syndrome (pSS) and 23 healthy donors (HD). The phenotype of circulating lymphocyte were defined based on comprehensive flow cytometric analysis for human immune system termed 'the Human Immunology Project' by NIH/FOCIS. The proportion of immune cell subsets was assessed for correlations with serum IgG, IgG4 and the existence of extra glandular manifestations. **[Results]** Baseline characteristics of patients with IgG4-RD were; age 60 years old, serum IgG 2735 mg/dl, IgG4 694 mg/dl. There was no difference in the proportion of classical subset of helper T cells (Th1, Th17, and Treg) between IgG4-RD, pSS and HD. On the other hand, the proportions of effector T cells, follicular helper T cells (Tfh) and plasmablast were significant higher in IgG4-RD compared to pSS and HD. Moreover, the proportion of Tfh in peripheral blood was reflected that of Tfh in biopsy site. Among immune cell subsets, Tfh and plasmablast were positively correlated. Of note, the percentage of plasmablast was correlated with serum IgG levels. Furthermore, the proportions of plasmablast and Tfh were higher in patients with extra glandular manifestations compared to patients without extra glan-

dular manifestations. After treatment with glucocorticoids, the proportions of plasmablasts and Tfh decreased with improvement of clinical manifestations. **[Conclusion]** These results revealed that the higher proportion of Tfh cells and plasmablast is characteristically observed in IgG4-RD. The frequency of Tfh was correlated with that of plasmablasts, and the Tfh/plasmablast axis contributed to organ manifestation. Our findings would clarify the pathogenesis of IgG4-RD through the interaction between Tfh and plasmablasts and suggest a potential as the therapeutic target of this disease.

ICW-C7-1

Deadly chik: a report of two atypical and fatal cases of chikungunya fever complicated by severe vasculitis and renal failure

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Conflict of interest: None

Chikungunya is generally considered self-limiting and has been reported as non-fatal in the past. However, after the March 2005 outbreak in La Reéunion Island, there have been several reports of unusually severe complications and deaths. To date, there have been no published reports of severe atypical and fatal cases of Chikungunya fever in the Philippines. We thereby present two cases that initially presented with the usual fever, arthropathy and rash of CHIK, but during the course of their hospital stay, their rash worsened into violaceous, vesiculobullous, and vasculitic lesions over the extremities accompanied by edema and oliguria. Rheumatologic workup and bacterial cultures were negative. Treatment was mainly supportive on admission (NSAIDs, antipyretics). Hydrocortisone was started for arthritis refractory to NSAIDs. Pulse therapy with methylprednisolone was started in the first case once with the appearance of vasculitic lesions, eventually given IVIG infusion as a last resort. They both worsened with the development of acute renal failure and cardiopulmonary collapse necessitating continuous renal replacement therapy, vasopressor and ventilatory support. Despite intensive care, they both succumbed to sudden wide QRS bradyarrhythmias and subsequently died. At post- mortem, RT-PCR was positive for CHIKV Asean genotype 1 for both patients. Although it is generally self-limiting, this report illustrates that CHIK can be a rare cause of vasculitis and acute renal failure. Early identification of features of severe disease with timely aggressive therapy may be prudent especially in the elderly population. Mortality with CHIK may be underreported but it should be noted that the risk of complications increases with age. Since there is no specific treatment for CHIK, prevention through vector control and public health education is key.

ICW-C7-2

Development of an outcome measure including imaging for Large Vessel Vasculitis

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Conflict of interest: None

Objective Outcome assessment in LVV remains challenging and this impairs patient management and the conduct of clinical studies. Previous proposals for outcome tools have not included image, this study aimed to develop an imaging damage score in large-vessel vasculitis (LVV) by determining the optimized weight of imaging findings and to assess the difference between Takayasu arteritis (TAK) and giant cell arteritis (GCA) and the correlation between the new imaging measure and other indices. **Methods** Ninety-six patients (41 TAK, 55 GCA) were identified. Combined damage assessment scores was employed and imaging lesion including stenosis, occlusion and aneurysm were evaluated in 25 arterial regions with enhanced CT or MRA. Multiple regression analysis was performed and the weight of lesions defined as a damage index. **Results** We defined a damage index by multiple regression analysis and propose the name: "Combined Arteritis Damage Score (CARDS)'; CARDS= number of mild stenosis × 0.6 + number of moderate to severe stenosis × 1.2+ number of occlusions × 1.6 + number of aneurysms × 0.8 in 25 arterial regions. As a result, median CARDS was higher in TAK than GCA (4.1 and 0.6, $p < 0.001$). **Conclusion** We have developed a damage assessment tool based on imaging in LVV of potential value to clinical studies and patient management. And these results clarified that there are differences in severity, although similarities in the pathology and distribution of vascular lesions have led to claims that TAK and GCA are one disease.

ICW-C7-3

Imbalanced expression of dysfunctional regulatory T cells and T-helper cells in polyarteritis nodosa

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Conflict of interest: None

Objective. Immunological etiology of polyarteritis nodosa (PAN), necrotizing arteritis affecting medium- and small-sized blood vessels, remains elusive. In this study, we investigated the characteristics of circulating T-helper (Th) cells and regulatory T cells (Tregs) in PAN. **Methods.** Peripheral blood samples were obtained from 14 patients with PAN. Nine patients having granulomatosis with polyangiitis (GPA) and 11 healthy individuals (HC) were enrolled as controls. Representative phenotypes of $CD4^+$ T cells, including Th1, Th2, Th17 cells and Tregs, were analyzed by flow cytometry. Suppression assay of Tregs was simultaneously performed by evaluating the proliferation of conventional $CD4^+$ T cells co-cultured with Tregs. **Results.** The number of Th cells was found to be significantly higher in patients with PAN than in HC. In comparison with GPA, the expression of Th1 cells was higher but that of Th17 cells was lower. Additionally, significant induction of Tregs was observed in PAN; however, defects in suppressive ability and CTLA-4 expression were observed. On the other hand, IFN-γ and IL-17 expression in $CD4^+FoxP3^+$ cells from PAN were higher than those from HC. A significant decrease in the frequency of Th1 cells was demonstrated after immunosuppressive therapy in PAN; however, there were no improvements in other phenotypes or in Treg function. **Conclusion.** T-helper cell expansion and Treg dysfunction are thought to be associated with the pathogenesis of PAN. Th1 cells show a response to immunosuppressive therapy; however the persistent immune abnormalities may interfere with complete recovery in patients with PAN.

ICW-C7-4

Cardiac, Pulmonary, Neurologic and Cutaneous manifestations of Eosinophil Granulomatosis with Polyangiitis and their outcomes: a Single Center Series review

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Conflict of interest: None

Background. Churg Strauss syndrome is a rare vasculitic disease involving small blood vessels, characterized by peripheral eosinophilia, asthma, neuropathy, & pulmonary infiltrates. **Case series.** We describe 8 cases of Eosinophilic Granulomatosis with Polyangiitis, aka Churg-Strauss Syndrome, diagnosed at our institution. The mean age at diagnosis was 55 +/- 15 years, and all of them had eosinophilia (ranging between 13-71%), cutaneous manifestations (erythematous rashes or digital ischemia) and neuropathy All were previously diagnosed with asthma at a mean of 6.62 years prior to EGPA diagnosis, while five patients had

ENT or pulmonary infiltrates. Four patients had arrhythmia or heart failure. Five were positive for ANCA. All of them received corticosteroids, while seven received cyclophosphamide therapy, half of which were given Rituximab and the other maintained on Azathioprine. All patients subsequently exhibited improvement of their symptoms within 6 months of therapy. **Conclusion**. EGPA has various clinical manifestations that require early recognition as well as carry morbid complications as a result of the disease activity itself or failure to initiate early treatment.

ICW-C7-5

Risk factors for the relapse in patients with ANCA-associated vasculitis received remission induction treatment with cyclophosphamide

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Conflict of interest: None

[Objectives] Although the efficacy of rituximab as remission induction and maintenance therapy for ANCA-associated vasculitis (AAV) patients has been recently reported, intravenous cyclophosphamide pulse therapy (IV-CY) is still widely used for remission induction in patients with AAV. We performed a retrospective study to detect risk factors for the relapse after the remission induced by IV-CY. [Methods] We analyzed AAV patients treated with IV-CY between January 2009 and December 2013. [Results] IV-CY was administered in 41 AAV patients, and 37 cases (90.2%) achieved the remission. The mean age of 36 patients with one-year observation period was 70.3 ± 10 years, and the mean eGFR was 41.4 ± 29 ml/min/1.73m^2. Six patients (16.7%) experienced relapse of AAV, and patients with relapse were significantly older (80.2 vs. 68.4 years, p=0.0068). Lower total CY dose group (total dose ≤2g) presented significantly higher relapse rate (31.3 vs. 5.0%, p=0.0315). Multivariate analysis with age (≥75 vs. <75 years), total CY dose, renal function (eGFR ≥30 vs. <30 ml/min/1.73m^2) and initial glucocorticoids (GC) dose (PSL >0.8 vs. ≤0.8 mg/day/kg) detected the old age (≥75 years) as an independent risk factor for AAV relapse (OR: 9.6), and revealed that lower total CY dose tends to be a risk factor for relapse (OR 10.1, p=0.0657). Infection which required hospitalization occurred in 14 cases (38.9%). Initial GC dose was higher in infection group than non-infection group (0.96 vs. 0.87mg/day/kg, p=0.0505), whereas there was no difference in age or total CY dose. [Conclusions] Remission induction therapy with adequate amount of CY and low-dose GC might bring better outcomes in patients with AAV.

ICW-C7-6

Corticosteroid-free trial of tocilizumab monotherapy for microscopic polyangiitis

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Conflict of interest: None

Objectives. To assess the efficacy of tocilizumab (TCZ) monotherapy for the remission induction of microscopic polyangiitis (MPA) in a prospective single-arm, single-center, cohort, pilot study (UMIN000011242). **Methods.** Eligible patients were aged between 20 and 80 years and were newly diagnosed with MPA according to Watts' classification algorithm. Seven patients received 8 mg/kg of intravenous TCZ fortnightly for the first two months (five courses), and monthly for the next 10 months (10 courses). One year after TCZ monotherapy, the patients were followed-up without any treatment. The protocol did not permit the use corticosteroids or any other immunosuppressants. Complete remission (CR) was defined as the Birmingham Vasculitis Activity Score of 0 for at least four weeks. **Results.** CR was achieved in two out of six patients (33.3%) at six months and three patients (50.0%) at 12 months. Two patients were withdrawn because of ineffectiveness at six weeks and flare at six months, respectively. One patient was withdrawn for his own will after CR at three months. Four patients (66.6%) could be kept drug-free after one year of TCZ without relapse for 5-13 months at the last visit. **Conclusion**. TCZ monotherapy may be an alternative treatment strategy in some patients with MPA.

ICW-C8-1

Diagnostic Utility of Anti-citrullinated Protein antibody (anti-CCP) Compared with Rheumatoid Factor (RF) in Rheumatoid Arthritis (RA) in a Philippine Tertiary Care Setting

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Conflict of interest: None

Background In RA, most specialists rely on combination of clinical acumen and laboratory studies to make a diagnosis. The RF assay has been used for over 50 years as part of the ACR classification criteria despite its shortcomings. Thus the development of the anti-CCP as a diagnostic test for RA, which in initial studies showed it to be adequately sensitive and specific in healthy patients and even in the presence of other rheumatic diseases or infectious diseases. To date, there have been no published studies on the sensitivity and specificity of anti-CCP in the Philippines, which is the aim of this study. **Methods** A cross-sectional analytical study, wherein laboratory records of patients with both RF and anti-CCP from Jan 2012 to Dec 2013 were retrieved, then matched with patient records. Inclusion criteria were presence of clinical synovitis in at least one joint and if seen by a rheumatologist. A preformed data collection form comprising of demographic and clinical details was recorded. Subjects were then scored using the 2010 ACR/EULAR RA classification criteria, which served as the gold standard. **Results** Out of 334 records retrieved, 208 subjects were included. The ACR/EULAR RA classification criteria showed 41 cases with RA. The mean age of the group was 47+14 years, majority being female at 83.3%. The sensitivity and specificity of anti-CCP were both higher than RF assay for the diagnosis of RA, which were 87.8% and 100% versus 68.3% and 98.8% respectively. The sensitivity and specificity were also determined for when a combination of anti-CCP and RF tests were used which showed the following values: 60.98%, 100% respectively; exhibiting that anti-CCP alone still fared better. **Conclusion** Anti-CCP is useful for the diagnosis of RA due to its higher sensitivity and specificity compared with RF or even in combination with RF assay. Therefore in a Philippine tertiary care setting, it can be used alone as both a screening and confirmatory serological marker.

ICW-C8-2

The factors associated with remission induction for patients with rheumatoid arthritis

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Conflict of interest: None

【Objective】 Recently, remission has been accepted as the primary goal of the treatment of rheumatoid arthritis (RA). The aim of this study was to assess the factors associated with remission in Japanese patients with RA.【Methods】 A total of 305 patients with RA were enrolled in this study. All the patients met 1987 ACR and/or 2010 ACR/EULAR classification criteria, and visited our center between May 2014 and March 2015. Their medical records were reviewed for tender, swollen, painful and stiff joint counts, physician's global assessment (MDGA), patient's global assessment (PtGA), patient's pain visual analog scale (Pain VAS), health assessment questionnaire-disability index (HAQ-DI), treatments, and laboratory data.【Results】 Methotrexate, oral glucocorticoids and biological disease-modifying antirheumatic drugs (bDMARDs) were re-

ceived by 63.6%, 17.0% and 29.8% of patient, and the remission rates by SDAI were 49.5%. The patients achieving SDAI remission were younger, less positive for rheumatoid factor and less treated with biological DMARDs. SDAI remission was significantly less achieved in elderly (age ≥65, n=201) patients than non-elderly (age <65, n=104) patients (44.8% versus 58.7%, P=0.022). MDGA was not significantly different, but PtGA was significantly worse in elderly patients than non-elderly patients (23.5 versus 15.4).【Conclusion】The composite measure of RA disease activity and remission criteria should be prudently applied in daily clinical practice for elderly patients.

ICW-C8-3

Factors associated with work and activity impairment in Japanese RA patients

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Conflict of interest: None

Objectives: Rheumatoid arthritis (RA) causes profound impacts on pain, functional capacity, quality of life and work capacity. Among them, a decline in work capacity is critical for patients' lives, family income and social costs. In this study, we aimed to identify factors associated with work and activity impairment in Japanese patients with RA. *Methods*: All RA patients aged ≥18 years in our institute were included in this study. Demographic and clinical characteristics, and work and activity impairment measured using Work Productivity and Activity Impairment Questionnaire (WPAI) were cross-sectionally collected from their medical records. In employed patients, logistic and linear regression analyses were performed to identify associated factors for absenteeism, presenteeism, and activity impairment. *Results*: A total of 1,274 RA patients were included. Their mean age was 62.2 and 85.7% were female. The mean DAS28 was 2.63 and the EQ5D was 0.77. Among 451 employed patients, absenteeism, presenteeism, and overall activity impairment were 5.2%, 52.7% and 59.6%, respectively. Presenteeism and activity impairment were significantly increased with DAS28 ($p<0.01$), whereas absenteeism was not ($p=0.05$). In multivariable regression analyses adjusted for significant variables in crude analysis, age ($\beta=-0.17$, $p<0.01$, and $\beta=-0.11$, $p=0.046$ for presenteeism and activity impairment, respectively), pain VAS ($\beta=0.20$, $p<0.01$; $\beta=0.31$, $p<0.01$), HAQ ($\beta=6.60$, $p<0.01$; $\beta=9.56$, $p<0.01$), and EQ5D ($\beta=-47.39$, $p<0.01$; $\beta=-42.06$, $p<0.01$) were factors associated with presenteeism and activity impairment, whereas absenteeism was only associated with EQ5D (OR=0.01, $p<0.01$). DAS28 was associated with overall activity impairment ($\beta=1.08$, $p=0.02$). *Conclusion*: In RA patients, worse disease activity and EQ5D was relevant with impaired work productivity. In addition, pain and functional disability were the most influential to presenteeism and overall activity impairment.

ICW-C8-4

Patient's pain score with visual analogue scale as a index for prediction of CDR in rheumatoid arthritis treatment

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Conflict of interest: None

[Objectives] It has been suggested that patient's pain score measured with visual analogue scale (PS-VAS) closely correlates with disease activity and Health Assessment Questionnaire Disease Index (HAQ-DI) in rheumatoid arthritis (RA) patient [(1)]. If that is the case, comprehensive disease remission (CDR) should be predictable in evaluating PS-VAS. From the background, probability of CDR in measuring PS-VAS had been investigated. [Methods] 362 RA patients who had been treated for more than 3 years had been analyzed in this study. All the patients have been measured their PS-VAS, clinical disease activity index (CDAI), HAQ-DI. X-ray pictures of hand and foot have been taken every another year. Their average Sharp/van der Heijde score have been calculated and average value of yearly progression of SHS (dSHS) was calculated once a year. Patients were divided according to average PS-VAS with 10mm division of scale. CDR is evaluated with average value of CDAI, dSHS, and HAQ-DI within their remission level. Sensitivity and specificity of each level of PS-VAS for CDR was calculated. [Results] Sensitivities for CDR of PS-VAS were 70.0%, 41.8%, 30.9%, 25.2%, 21.6%, 20.9%, 20.2%, 19.5%, 19.4%, and19.3%, while specificities have demonstrated 82.2%, 89.1%, 94.1%, 96.0%, 93.1%, 97.0%, 100.0%, 100.0%, 100.0%, and 100.0%, from 10mm to 100mm with 10mm division in scale, respectively. [Conclusions] It is strongly suggested that monitoring patient's PS-VAS is extremely important that could predict CDR in RA treatment. Patient's PS-VAS within 10mm in average would be reliable for expecting to attain CDR in probability of 70%, and if it is more than 30mm, risk to fail in CDR will be reliable with more than 90% probavility. (Reference) (1) Yoshii I. The importance of pain VAS measurement in Treat to Target treatment for rheumatoid arthritis in adding to composite index. Ann Rheum Dis2015;74 (Suppl2): 982.

ICW-C8-5

Are the patient-reported pain and stiffness at each joint level clinically relevant in the evaluation of patients with rheumatoid arthritis?

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Conflict of interest: None

Objective: Patient-reported outcome has been considered as an important aspect in the evaluation of patients with rheumatoid arthritis (RA). The objective of this study was to elucidate the clinical significance of self-reported joint pain and stiffness of each joint by examining the association of those subjective findings with ultrasound (US) joint synovitis and tenosynovitis. Methods: A total of 40 patients with RA were enrolled in this study between October 2014 and June 2015. All the patients reported the presence of pain and/or stiffness in each joint of hands including bilateral interphalangeal (IP) joints of the thumb, proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints and wrist joints. They also received joint examination by rheumatologists for the presence of tenderness and swelling, and US joint examination for the presence of joint synovitis and tenosynovitis. The medical records were reviewed for the patient characteristics and laboratory data. Results: The median age was 66.5 years and the median disease duration was 3.7 years. The median DAS28-ESR was 2.7. Although joint pain and stiffness were similarly observed among IP/PIP, MCP and wrist joints (pain in 9-11% of joints and stiffness in 5-6% of joints), US joint synovitis was detected in 6% of IP/PIP joints, 16% of MCP joints and 38% of wrist joints, and US tenosynovitis in 2% of IP/PIP joints, 8% of MCP joints and 18% of wrist joints, respectively. The concordance defined by κ value indicated moderate correlation with US synovitis ($\kappa=0.43$), while subjective joint pain and joint stiffness, respectively, poorly correlated with US synovitis ($\kappa=0.19$ and 0.13, respectively) and US tenosynovitis ($\kappa=0.03$ and -0.04, respectively). Conclusion: Patient-reported joint symptoms, especially joint stiffness, were not sensitive enough, and they did not correlate well with US joint findings.

ICW-C8-6

Does the time-average DAS28 correlate with bone destruction better than a one-point DAS28 in rheumatoid arthritis?

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Conflict of interest: None

Objectives: Disease Activity Score 28 (DAS28) is one of correlates of bone destruction in rheumatoid arthritis (RA) as well as RA-related

autoantibodies and disease duration. Although one-point DAS28 is used as a covariate in many studies addressing correlates of joint destruction, time-average DAS28 would fit better than one-point DAS28 and increase the power of the studies. Methods: We recruited a total of 204 RA patients in the 2012 KURAMA cohort whose data of Total Sharp Score (TSS), consecutive DAS28 and other correlates of TSS were available. We calculated time-average DAS28 and modeled TSS using time-average DAS28 and the other covariates. We randomly picked up DAS28 in each patient and constructed 100 sets of DAS28 to model TSS. We empirically evaluated fitting of the model using time-average DAS28 among the 100 models using one-time DAS28. Results: In conditioned for the autoantibodies and disease duration, the time-average DAS28 showed significant improvement of model fitting than one-time DAS28 (R^2: 0.456 vs 0.445±0.0046, p=0.04). We obtained the same result when we log-transformed TSS. Conclusions: Time-average DAS28 fits TSS better than one-time DAS28. Usage of time-average DAS28 as a covariate would increase the power of studies to identify novel correlates of TSS.

ICW-C9-1

Sero-positivity for rheumatoid factor is an independent predictor for achievement of good EULAR response at 24 weeks in ACPA high-positive RA patients treated with abatacept: Results from Japanese multicenter registry

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Conflict of interest: None

[Objectives] Recently, some reports have been published regarding the positive association between sero-positivity for ACPA and clinical efficacy of abatacept in rheumatoid arthritis (RA) patients. The aim of this study is to demonstrate the effect of double-seropositivity for ACPA and rheumatoid factor (RF) on the efficacy of abatacept. [Methods] Participants were consecutive 508 RA patients treated with abatacept who were registered in the Tsurumai Biologics Communication Registry. A total of 199 biologics-naïve patients with baseline data of both ACPA (anti-CCP antibody) and RF were included in this study. We studied the percent decreasing of DAS28-CRP score from baseline at 4, 12, and 24 weeks. [Results] In the patients with ACPA low-positive (4.5 < anti-CCP Ab <13.5 U/ml), there was no significant difference in percent decreasing of DAS28-CRP score between the RF negative (RF < 20 U/ml) group and the RF positive (RF > 20 U/ml) group at all time points. In the ACPA high positive (anti-CCP Ab > 13.5 U/ml) patients, the percent decreasing of DAS28-CRP scores in the RF positive group were significantly greater than those in the RF negative group at all time points (e.g. -32.3 vs -12.6% at 24 weeks, $p < 0.01$). Multivariate logistic regression analysis (adjusted with gender, age, disease duration, MTX and oral steroid usage, and DAS28-CRP score at baseline) revealed that the RF positivity was not a significant predictor for the achievement of moderate EULAR response at 24 weeks, but was an independent strong predictor for the achievement of good EULAR response at 24 weeks (adjusted odds ratio: 5.42, $p = 0.035$). [Conclusion] We clearly demonstrated that the positive association of the sero-positivity for RF with the good clinical response for abatacept in the ACPA high-positive RA patients. This new evidence regarding the effect of double-seropositivity is the valuable real-world data for the prediction of clinical efficacy of abatacept in daily clinical practice.

ICW-C9-2

Early improvement of musculoskeletal ultrasound findings can predict future clinical response to certolizumab pegol in patients with rheumatoid arthritis

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Conflict of interest: None

Object: Certolizumab pegol (CZP) brings rapid improvement of the signs and symptoms of RA. Musculoskeletal ultrasound (US) has been proved to be useful at assessing synovitis precisely in patients with RA, however, whether early US assessment of synovitis can predict future clinical response is unclear. In the present study we ascertain whether US is useful for predicting future clinical response to CZP in RA patients. **Methods:** Twenty patients with RA were treated with subcutaneous CZP 400 mg at weeks 0, 2, 4 followed by 400 mg every 4 weeks or 200 mg every 2 weeks. The mean age of patients was 55.2 years old and the mean disease duration was 5.9 years. The mean disease activity at baseline (week 0) was 4.91 and 23.2 for 28-joint disease activity score (DAS28) and simplified disease activity index (SDAI), respectively. At baseline and weeks 2, 4 and 12, US examination was performed at bilateral MCP, PIP, IP, and wrist joints. Gray-scale (GS) and pulse Doppler (PD) signal was recorded in each joint using semi-quantitative score (0 to 3). The sum of these scores obtained from each joint was used as GSUS and PDUS score. PDUS50 response is defined as marked reduction of PDUS score to less than 50% of baseline. **Results:** Both GSUS and PDUS score were improved significantly as early as 2 weeks after treatment (p=0.031 and 0.011) and gradually reduced during study period. At week 12, six patients (30%) showed DAS28 remission (responders) and other 14 patients did not (non-responders). Four out of those 6 responders (67%) showed PDUS50 response at week 2, whereas only one out of 14 non-responders (7%) showed PDUS50 response at that time. Furthermore, the proportion of responders in the patients who showed PDUS50 response at week 2 was significantly higher than that of those who did not show PDUS50 response at week 2 (80% and 13%, p=0.014). **Conclusion:** Early improvement of US findings can predict future clinical response to CZP in RA patients.

ICW-C9-3

Attaining comprehensive disease remission (CDR) in the first treatment year is most important for predict of sustaining CDR in a long term in rheumatoid arthritis treatment

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Conflict of interest: None

[Objectives] Comprehensive disease remission (CDR), what means remission in all of disease activity (DA), joint structural maintenance (SM), and ability of daily activities (ADL), is the ultimate target in rheumatoid arthritis (RA) treatment. We have investigated predictable factors for CDR in our cohort. [Methods] 439 RA patients who had been treated more than 4 year were recruited. We adapted clinical disease activity index (CDAI) for DA, yearly progress of Sharp/van der Heijde score (dSHS) for SM, and modified health assessment questionnaire (mHAQ) for ADL. Remissions are defined as less than 2.8 in CDAI, less than 0.5 per year in dSHS, and less than 0.5 in mHAQ. Patients average CDAI, dSHS, and mHAQ were calculated for every year. Result was classified. When all of three indices accomplished their remission level, it is evaluated as remission (R), two as near miss (NM), one as failure (F), and nothing as burn (B). Probabilities of same evaluation in next year were analyzed for each year. Sensitivity and specificity for CDR, of Boolean remission, and combination of Boolean remission and pain score that demonstrated within 10 mm with visual analogue scale (PS-VAS) were evaluated in yearly period. [Results] Probabilities of R, NM, F, and B in next year were 89.4%, 69.2%, 77.3%, and 80.0% for 1st year, respectively, while 78.4%, 81.0%, 83.1%, and 71.4% for 2nd year, 85.6%, 77.3%, 89.6%, and 83.3% for 3rd year, and 80.8%, 73.5%, 84.5%, and 83.3% for 4th year. Sensitivity for CDR demonstrated 55.4%, 55.8%, 46.5%, and 48.3% for Boolean, while being raised up to 67.6%, 61.2%, 54.1%, and 53.9% with the combination of PS-VAS from 1st to 4th year respectively. Specificity demonstrated more than 80% in every year period for both indices. [Conclusion] These results suggest that attaining CDR in the first treatment year is important for maintaining CDR. Boolean remission and PS-VAS can predict CDR in future with higher probability than Boolean remission alone.

ICW-C9-4

Reducing and spacing after achieving sustained remission in rheumatoid patients in real world from local biologics registry

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Conflict of interest: None

Background: Data on reducing and spacing of biologics (BIO) medication after sustained remission are limited. Objectives: To retrospectively analyze the re-flare of disease in RA patients in sustained remission, either continuing, reducing or spacing BIO. Methods: Local prefectural (ZAO) registry which is open-labelled biologics cohort study in our area has registered 191 RA patients. RA Patients were enrolled into this study if they maintained in DAS remission (DAS28-ESR < 2.6) more than one year after starting BIO and were observed more than one year after their remission. Results: Twenty-two RA patients (18 female) using BIO was fulfilled in the criteria of this study. Mean age was 52.3 year-old, mean RA affiliation 10.9 years before BIO and mean duration of remission 4.2 years. Of 22 RA Patients fulfilling DAS remission, 10 RA patients has reduced or spaced BIO after maintain DAS remission more than one year. In the latest observation, all of continuing, reducing or spacing group maintained DAS remission. Conclusions: Reducing or spacing of BIO may have potential to maintain the remission for RA.

ICW-C9-5

Prospective Study About 6-week Extended Dosing Interval With Tocilizumab Therapy In Rheumatoid Arthritis Patients In Remission Maintenance

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Conflict of interest: None

Object To evaluate the efficacy and tolerability of 6-week extended dosing interval with tocilizumab (TCZ) in RA patients in remission. **Methods** Eligible patients were those who met the 2010 ACR/EULAR classification criteria. Consecutive patients at our institute who had received over 6 times of TCZ injection in remission maintained over 3 months with their informed consent between December 2013 and April 2015. The cut-off value of remission was DAS28-ESR <2.6. **Results** Twenty-one patients were enrolled. At baseline, mean age was 54.7 ± 12.5 year-old, and the percentage of female was 85.0%. Mean disease duration was 12.1 ± 10.3 years. 30.0% and 10.0% of patients used concomitant methotrexate and glucocorticoids, respectively. 65.0% of patients previously used biologics. Mean duration from starting TCZ until beginning the extension of dosing interval was 40.9 ± 25.6 months. Mean DAS28-ESR was 0.93 ± 0.56 at baseline. Nineteen (90.5%) patients have completed TCZ with 6-week extended dosing interval until Week 24. Among them, 16 patients maintained in remission, though DAS28-ESR mildly increased to 1.97 ± 1.05 at Week 24. The patients with shorter disease duration, lower increases in CRP, ESR and DAS28-ESR at Week 6 maintained lower disease activities (Spearman's rho=0.43, p=0.059, rho=0.52, p=0.019, rho=0.61, p=0.004, rho=0.72, p<0.001, respectively). One patient dropped from the study because of the RA flare and returned to 4-week interval at Week 18. Six adverse events were noted in 6 patients. TCZ was discontinued due to the recurrence of lymphoproliferative disorder in one patient at Week 5. The other 5 events (2 mild upper respiratory infections, the fracture of humerus by falling accident, stasis dermatitis and ureterolithiasis) did not lead to cessation of TCZ. **Conclusions** This trial suggested that 6-week extended dosing interval with TCZ therapy is effective and tolerable in RA patients as remission maintenance in daily clinical practice.

ICW-C9-6

Discontinuation of tofacitinib after achieving low disease activity (LDA) in patients with established rheumatoid arthritis (RA) : a prospective, multicenter, observational study

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Conflict of interest: None

[Objectives] The aim of this study was to determine whether tofacitinib could be discontinued in patients with RA after achieving LDA by tofacitinib. **[Methods]** RA patients in LDA after tofacitinib treatments in the clinical trial were enrolled in this study. The discontinuation or continuation of tofacitinib was determined, based on the informed consent. The primary endpoint was the proportion of patients who remained tofacitinib-free at week 52. Clinical outcomes were compared between those who continued and those who discontinued tofacitinib by LOCF method. **[Results]** Of 64 patients, 54 discontinue and 10 continued tofacitinib treatment. After 52 weeks, 20 of the 54 patients (37%) remained tofacitinib free. Comparing with the continuation group, the disease activity of discontinuation group was higher than that of continuation group (SDAI 9.6 vs 4.8, p=0.001). The proportion of patients who maintained LDA was also lower (68% vs 100%). However, univariate analysis revealed that there were significant differences of the titer of RF (40 vs 113 U/ml) between the patients who achieved discontinuation and the patients who did not. In patients with low RF, the proportion of patients who maintained LDA increased to 81% and the disease activity decreased (SDAI 6.9), with no difference comparing with continuation group (p=0.17). On the other hand, in the patients who could not achieve discontinuation, escalation of MTX and/or re-initiating tofacitinib resulted in the reduction of disease activity. Rates of safety events were generally similar between discontinuation group and continuation group; however, one patients (10%) had herpes zoster in continuation group. **[Conclusion]** It was possible to discontinue tofacitinib without flaring in patients with established RA. Lower RF may predict maintenance of LDA after discontinuation of tofacitinib.

ICW-C10-1

The availability of Nailfold Videocapillaroscopy (NVC) in patients with dermatomyositis and polymyositis and dermatomyositis (PM/DM)

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Conflict of interest: None

[Object] NVC has been applied for the diagnosis of systemic sclerosis. However, the availability of NVC findings in patients with PM/DM is unknown. The aim of this study was to identify the possibility of their diagnostic and prognostic value in patients with PM/DM. **[Methods]** 33 patients with PM/DM (7 PM/26 DM) were enrolled between April 2014 and October 2015. NVC findings, autoantibody profiles by immuno-precipitation methods, pathological findings of the skin and clinical features (rash, Raynaud phenomenon, CRP, CK, ferritin, CT score) were assessed.

[Results] Of 33 patients, 16 (48%) showed NVC alterations. The proportion of the patients with NVC alterations was higher in DM (58%; 15/26) compared to PM (14%; 1/7). There were no significant difference in the clinical features between patients who had NVC alterations and those who did not. However, the proportion of the patients with NVC alteration was higher in clinically amyopathic dermatomyositis (CADM) (85%; 11/13) compared with classic DM (p=0.001). The proportion of the patients with NVC alterations was also higher in patients with anti-MDA5 antibody (p=0.057), whereas the proportion was lower in patients with anti-ARS antibody (P=0.007). Next, we focused on the correlation between NVC and pathology of the skin. Interestingly, perivascular inflammatory infiltrate in the upper dermis were characteristically observed in patients who had the NVC alterations. On the other hand, of 8 patients who could follow up after the treatment intervention, 7 (86%) showed the improvement of NVC alterations along with improvement of CT score. **[Conclusions]** The clinical and serological relevance of the NVC alterations to CADM, indicating that the NVC is an useful tool to predict a prognosis in patients with PM/DM. Furthermore, the NVC alterations were associated with perivascular inflammatory infiltrate, but they were improved after the treatment, suggesting that the NVC is also useful to clarify pathological mechanisms of PM/DM.

ICW-C10-2

Inflammatory myositis associated with malignancy: A retrospective multicenter study of 213 Japanese patients with Dermatomyositis and Polymyositis

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Conflict of interest: None

[objectives] To analyze clinical characteristics, therapeutic response, and survival rate of myositis associated with malignancy. [methods]Out of 213 patients with myositis in our database, malignancy was found in 36 patients.We compared them with 177 myositis patients without malignancy. We defined myositis associated with malignancy if the tumor was diagnosed within 5 years before or after the onset of myositis. [Results] The most common cancer was breast cancer (9 patients) and fiftysix percent of the tumors were diagnosed within1 year before or after the onset of myositis. Myositis patients with malignancy were significantly older and higher prevalence of dysphagia than patients without malignancy (P<0.001). In malignancy associated myositis,thirty four patients received prednisolone and twelve patients received immunosuppressive drugs.Two patients did not receive prednisolone and recovered aftersurgery and chemotherapy. Five patients were resistant of immunosuppressive therapy, but improved after the surgery or chemotherapy. Cumulative survival rate of myositis with malignancy were significantly lower than myositis withoutmalignancy (P<0.001). However, there were no patients who died of interstitial pneumonia in myositis with malignancy. [Conclusion]In malignancy associated myositis, patients were older and higher prevalence of dysphagia than myositis without malignancy.A part of them were resistant of immunosuppressive therapy,but improved after the cancer treatment. Survival rate of myositis with malignancy was significantly lower than myositis without malignancy,but they did not die of interstitial pneumonia.

ICW-C10-3

Clinical course and treatment of two refractory cases of anti-HMGCR antibody-associated necrotizing autoimmune myopathy

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Conflict of interest: None

【Background】Myopathy with 3-hydroxy-3-methylglutaryl-coenzyme a reductase (HMGCR) antibody have been suggested to be statin-induced, but about 40% of the patients are not associated with statin including our two cases. Though it's sometimes difficult to distinguish to other idiopathic inflammatory myositis (IIM) by clinical features, muscle fiber necrosis without inflammatory infiltrates is characteristic. Part of patients can achieve the complete or partial remission by conventional immunosuppressive therapy, but most cases relapse frequently during the taper of drugs and fail to response to aggressive immunosuppression. Our two cases were suffered from frequently relapse in spite of using multiple immunosuppressive agents, but only respond to intravenous immunoglobulin (IVIG).【Case1】A 26-year-old women was diagnosed IIM with proximal muscle weakness and elevated serum creatine kinase (CK) levels. Malignancy and neuromuscular degenerative disease was ruled out and muscle biopsy demonstrated predominantly necrotizing myopathy. During 15 years follow-up, she relapsed frequently with gradual progression of muscle weakness under the taper of steroid and showed resistance against multiple immuno-suppressants such as methotrexate (MTX), tacrolimus (TAC), cyclosporine A, mizoribine, cyclophosphamide, azathioprine and rituximab. HMGCR antibody was detected and periodic administration of IVIG was required to prevent the disease progression.【Case2】A-71-year-old man was also suffering from proximal muscle weakness with elevated CK levels. Malignancy and infectious disease was ruled out and necrotizing myopathy with HMGCR antibody was proven. He was also required monthly IVIG because of resistance to the induction therapy with steroid, MTX and TAC.【Conclusion】Our cases suggested that IVIG is most effective for refractory necrotizing myopathy with HMGCR antibody. The detection of HMGCR antibody was useful for the prediction of clinical course and response of treatment.

ICW-C10-4

Assessment of peripheral joints by musculoskeletal ultrasonography in polymyalgia rheumatica patients predicts future DMARDs use

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Conflict of interest: None

[Objectives] To identify factors associated with prednisolone-resistance in polymyalgia rheumatica (PMR). [Methods] We retrospectively analyzed 115 patients who were diagnosed with PMR based on the Bird's criteria and followed up in our department between April 2006 and October 2015. Clinical characteristics such as presence of peripheral joint tenderness, initial prednisolone (PSL) dose, rate of tapering PSL, concomitant DMARDs use, musculoskeletal ultrasonography (MSUS) findings, power Doppler (PD) signals in peripheral joints in peripheral joints were investigated. [Results] Patients' characteristics were as follows; 49 male, 66 female, mean age of onset 73.5 ± 8.0 y.o., CRP 7.3±4.3 mg/dl, ESR 85.5±31.6 mm/hr, RF or ACPA 6.1%. Peripheral joint pain was found in 62.6% of the patients. During the follow up periods (3.5 ± 3.5 yr), 44 cases (38.3%) had achieved remission, 48 cases (41.7%) required increase dose of PSL, and 17 cases (14.8%) initiated of DMARDs. Forty cases were investigated by MSUS. Thirty-two cases had positive PD signals in peripheral joints, including wrist (57.5%), metacarpophalangeal (MCP) joint (15.3%), and knee (52.6%). Fifty percent of cases with PD signals in wrist and/or MCP joints required DMARDs in addition to PSL, whereas the 6.3% in the PD absent cases (p=0.01, OR 15.0, 95%CI 20.5-109.9). [Conclusion] MSUS in PMR revealed high frequency of peripheral PD signals, which may be associated with prednisolone-resistance. In line with EULAR/ACR 2015 Recommendations for the Management of Polymyalgia Rheumatica, current study confirmed that peripheral arthritis is one of the risk factors for relapse/prolonged therapy.

ICW-C10-5

Tocilizumab (TCZ) but not methotrexate (MTX) is steroid-sparing in polymyalgia rheumatica (PMR): a single-center retrospective study

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Conflict of interest: None

【**OBJECTIVE**】We have previously reported the effectiveness of TCZ against PMR in a prospective cohort, but there was no control group. Here we aimed to investigate whether TCZ has a steroid-sparing effect in the treatment of PMR as compared with MTX. 【**METHODS**】We retrospectively studied all patients with PMR that had been treated at our institution for at least 6 months between November 2005 and October 2015. The patients were divided into 3 groups based on the treatment at the last follow-up (f/u): prednisolone (PSL) monotherapy (PSL group), MTX combination (MTX group) and TCZ combination (TCZ group) therapies. We evaluated the PSL dose in each therapy group at the last f/u. There was no patient that used both MTX and TCZ. 【**RESULTS**】Of 130 patients, 105 were in PSL group, 18 in MTX group, and 7 in TCZ group. The proportion of women in PSL, MTX, and TCZ groups was 76%, 100%, and 72%, respectively; the mean age, and PSL dose at diagnosis were 74, 75, and 79 years, respectively, 14, 17, and 13 mg/day, respectively; the mean disease duration at the last f/u in PSL, MTX, and TCZ groups was 75, 68, and 44 years, respectively. There was no significant difference between each pair of the groups. The mean duration of combination treatment was comparable between MTX and TCZ groups (29 vs 23 months). The mean dose of MTX at the last f/u in MTX group was 7.3 mg/week. The mean dose of PSL and the PSL discontinuation rate at the last f/u in PSL, MTX, and TCZ groups were 3.7, 5.3, and 0.4 mg/day, respectively, and 17, 11, and 86%, respectively; thus, TCZ group was significantly superior to the other groups regarding steroid-sparing effects. The mean reduction rate of PSL at 6 months after initiating combination therapy was significantly higher in TCZ group than in MTX group. No patients discontinued TCZ because of adverse events. 【**CONCLUSION**】TCZ but not MTX may serve as an effective therapeutic option for patients who require rapid reduction or discontinuation of PSL.

ICW-C10-6

The glucocorticoid-sparing effect of tocilizumab (TCZ) is superior to that of methotrexate (MTX) in polymyalgia rheumatica (PMR): a single-center retrospective study

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Conflict of interest: None

OBJECTIVE: Although there have been several reports regarding the effectiveness of TCZ against PMR, to our knowledge, there has been no comparative study of TCZ with MTX, which has been conventionally used as a GC-sparing agent. We sought to investigate the GC-sparing effect of TCZ in PMR compared with that of MTX.METHODS: Our study included all patients with PMR that were treated at our institution for at least 6 months between November 2005 and October 2015. We stratified them to 3 groups where Prednisolone (PSL) monotherapy, MTX add-on and TCZ add-on therapies were used at the last observation. We analyzed the PSL-sparing effect in those therapies at the last observation. We excluded 3 patients who used both MTX and TCZ from analysis.RESULTS: Of 89 patients, PSL monotherapy was used in 67, MTX add-on in 14, and TCZ add-on in 8. The proportion of women was 76.4 %; the mean age, CRP level, and PSL dose at diagnosis were 71.6 years, 6.2mg/dl and 14.2mg/day, respectively; the mean disease duration at the last observation was 6.6 years. There was no significant difference between each pair of the groups. There were no differences in their background. The mean add-on treatment duration were comparable between MTX and TCZ groups (36, 20 months; p=0.06). The mean PSL dose and the PSL discontinuation rate at the last observation in PSL group, MTX group and TCZ group were 2.5, 2.5, 0.2 mg/day, respectively, and 46, 29, 75%, respectively; TCZ group was superior to the other groups. The mean PSL reduction rate at 6 months after initiating add-on treatment was significantly different between MTX group and TCZ group (38.9, 63.5%; p=0.03). No patients discontinued TCZ because of adverse events.CONCLUSION: TCZ could significantly reduce and discontinue PSL early even though TCZ group had shorter add-on period than MTX group. TCZ can be considered as an effective treatment option for patients who require quick reduction or discontinuation of PSL.

ICW-C11-1

Clinical, and immunological characteristics in 290 patients with systemic lupus erythematosus in South Korea

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Conflict of interest: None

Object: There are studies regarding to clinical characteristics in patients with Systemic lupus erythematosus (SLE) in several countries, mostly from Middle Eastern Asia and Western countries, but not from South Korea located in Northeast Asia. Our study aimed to investigate the demographic, clinical, and immunological features in patients with SLE in South Korea. **Methods:** We reviewed the medical records of 290 SLE patients diagnosed at a university-affiliated rheumatology center in Pusan, South Korea from January 1998 to January 2015. All patients fulfilled 1997 revised American College of Rheumatology classification criteria for SLE and were ethnically Korean. **Results:** Twenty-six patients (9%) were male, 90 patients (31%) had biopsy proven lupus nephritis (LN), 30 patients (10.3%) were diagnosed prior to age 18 (pediatric SLE) and the mean age at diagnosis was 31 ± 12.3 years. The most common clinical manifestations were arthritis (57.9%), followed by alopecia (47.2%), malar rash (44.1%), and fever (43.1%). Anemia was found in 81%, hemolytic anemia in 10.0%, leucopenia in 70.7%, thrombocytopenia in 44.5%, and pancytopenia in 21.7%. Antinuclear antibodies were detected in 98.2%, anti-Sm in 37.5%, anti-cardiolipin IgG in 25.7%, anti-cardiolipin IgM in 10.5%, lupus anticoagulant in 24.5%, anti-dsDNA IgG in 59.8%, anti-Ro in 65.7%, and anti-La in 31.3%. The cumulative frequency of pericarditis, anemia, hemolytic anemia, thrombocytopenia, and pancytopenia were more prevalent in patients with LN, as compared with those without LN. **Conclusions:** Our study provides new epidemiological data regarding the clinical and immunological characteristics in patients with SLE in Northeast Asia.

ICW-C11-2

Clinical features of elderly onset systemic lupus erythematosus

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Conflict of interest: None

<Objective> To clarify clinical features of elderly onset systemic lupus erythematosus (SLE). <Methods> We investigated consecutive patients with newly onset SLE, who admitted to our department between January 2012 and October 2015. We regarded patients who developed SLE at≧60 years old as elderly onset, while the patients at <60 years old as young or middle aged onset. 1) clinical symptoms, 2) laboratory data, 3) organ involvements, and 4) induction therapy were compared between elderly onset and young or middle aged onset groups, retrospectively. <Results> 14 elderly onset patients (66.0±5.5 years old, 8 males/6 females) and 28 young or middle aged onset patients (35.3±12.5 years old, 2 males/26 females) were identified. Male patients were significantly more dominant in elderly onset group than in young or middle aged onset group ($p<0.05$). 1) Malar rash (1/14 cases) and oral ulcer (1/14 cases) were significantly less common in elderly onset group than in young or middle aged onset group (16/28, 15/28 cases, respectively) ($p<0.05$). 2) Blood cell counts (WBC, hemoglobin, and platelet), serum creatinine, levels of complement, and titers of anti-DNA antibody at baseline were comparable between groups. On the other hand, the positivity for anti-Sm antibody was significantly lower in elderly onset group (0/14 cases) than in young or middle aged onset group (9/28 cases) ($p<0.05$). 3) Frequency of nephritis, serositis (pleuritis and pericarditis), and interstitial pneumonia were similar among two groups. 4) Use and dose of corticosteroid as well as concomitant use of immunosuppressants for induction therapy were comparable between groups. <Conclusion> Male dominancy and

uncommon malar rash, oral ulcer, and anti-Sm antibody were characteristic features of elderly onset SLE compared with young or middle aged onset SLE. However, other laboratory findings, organ involvements, and induction therapy of elderly onset SLE were similar to those of young or middle aged onset SLE.

ICW-C11-3

Possible association between positive serum anti-Sm antibodies and delayed-onset lupus nephritis

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Conflict of interest: None

[Objectives] Associations between serum anti-Sm antibodies (Ab) and specific organ involvement in systemic lupus erythematosus (SLE), including lupus nephritis (LN), have been reported. This study investigated the prevalence of serum anti-Sm Ab in SLE patients with reference to two categories of LN based on our previous report (Takahashi et al., Mod Rheumatol, 2009): delayed [develops after SLE onset (D-LN)] and early [manifests at the time of SLE onset (E-LN)] LN. [Methods] We retrospectively examined the 146 patients in our hospital diagnosed with SLE between January 1996 and October 2010. Patients with an observation period from the onset exceeding 5 years were enrolled and then classified into E-LN, D-LN, and SLE without LN during the observation period (non-LN SLE) disease groups. Positive serum anti-Sm Ab was defined by at least once positive result before or at LN manifestation in the disease course. We also investigated the time at which serum anti-Sm Ab was first found to be positive in the disease course of each anti-Sm-positive patient. [Results] The study enrolled 129 SLE patients: 39 E-LN, 23 D-LN, and 67 non-LN SLE patients. The frequency of positive serum anti-Sm Ab was higher in the LN group than the non-LN group (27/62 (43.5%) *vs*. 16/67 (23.9%), $p = 0.025$), especially in the D-LN group (15/23, 65.2%), compared with non-LN patients ($p = 0.001$). Anti-Sm Ab first turned positive in the course of SLE in 5 of 43 anti-Sm-positive patients. [Conclusion] Positive serum anti-Sm antibodies may be associated with delayed-onset lupus nephritis, which may reflect a more active, intractable SLE and a poorer prognosis than E-LN. Serum anti-Sm Ab sometimes appears in the course of SLE. Anti-Sm-positive SLE patients without LN should be followed closely for subsequent LN development.

ICW-C11-4

Presepsin (sCD14 subtype) Concentration Is Elevated and Reflects Disease Activity in Systemic Lupus Erythematous Patients

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Conflict of interest: None

【Object】Presepsin (soluble CD14 subtype) has recently been identified as a novel biomarker for predicting sepsis. Because presepsin is produced as a consequence of cellular phagocytosis, it may reflect monocyte activation. Recent evidence indicates monocytes play an extremely important role in systemic lupus erythematosus (SLE). We tested the hypothesis that presepsin concentrations are elevated and associated with disease activity in patients with SLE without infection. 【Methods】Fifty patients with SLE and 22 healthy controls were enrolled in this study. Concentrations of plasma presepsin, serum C3, C4, and total hemolytic complement (CH50) levels were measured. Plasma presepsin concentration was measured using a chemiluminescent enzyme immunoassay. The levels were compared between the groups. The SLE disease activity index (SLEDAI) was calculated in the SLE group. Eight out of 50 SLE patients who underwent intensified immunosuppressive therapy were tested twice at 2 weeks after treatment to evaluate the correlation between the concentration of presepsin and the disease activity. 【Results】Patients with SLE had significantly higher concentrations of presepsin [220.7 (95% confidence interval (CI) 178.4- 263.0) pg/mL] than the healthy controls [118.4 (95% CI 97- 139) pg/mL; $P < 0.0001$]. There were significant correlations between presepsin and compliment C3 ($R^2 = 0.189$; $P = 0.002$) and CH50 ($R^2 = 0.168$; $P = 0.035$) but not between presepsin and C4 ($R^2 = 0.077$; $P = 0.054$). In patients with SLE, the concentration of presepsin was significantly correlated with disease activity as assessed by SLEDAI scores ($R^2 = 0.718$; $P < 0.0001$). The concentration of presepsin was significantly decreased after treatment ($P = 0.016$). 【Conclusion】Measurements of plasma presepsin can be useful in assessing the disease activity of SLE and may be used to monitor the efficacy of treatment.

ICW-C11-5

Low Levels of Vitamin D and Vitamin A Serum Predicted the Disease Activity in Systemic Lupus Erythematosus Patients

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Conflict of interest: None

Objective: The aim of this research was to determine the role of vitamin D and vitamin A as predictive markers for disease activity in SLE. **Methods:** Female SLE patients (n=55) and matched healthy subjects (n=55) were recruited from Rheumatology and Immunology Clinic, Saiful Anwar Hospital, Malang, Indonesia. Disease activity was assessed using SLEDAI score. Patients were categorized as mild activity (score ≥5) and moderate-severe activity (score ≥6). Serum vitamin D and vitamin A levels were measured with ELISA. **Results**: Compared to healthy control, SLE patients had lower vitamin D (p=0.000) and vitamin A (p=0.024) levels significantly. SLEDAI score negatively correlated with vitamin D (p=0.000, r= -0.704) and vitamin A (p=0.004, r= -0.515) levels. Higher SLEDAI score was found in patients with low vitamin D (<30 ng/dl) and vitamin A (<20 ng/dl) levels compared to patients with normal vitamin levels (p=0.000). Receiver operating characteristic (ROC) curve revealed that vitamin D (cut-off value 23.4 ng/dl) was sensitive (92.3%) but less specific (58.8%) to predict patient with moderate-severe disease activity (AUC=0.744). Whereas, vitamin A (cut-off value 31.7 ng/dl) had similar sensitivity (92.3%) but higher specificity (76.5%) with AUC=0.919. **Conclusion:** Low vitamin D and vitamin A levels are associated with high disease activity in SLE and have high sensitivity but less specificity to predict SLE patients with moderate to severe disease activity. Therefore, vitamin D and vitamin A levels can be taken into consideration to be predictive markers for disease activity in SLE.

ICW-C11-6

Chronic daily headache survey in Korean patients with systemic lupus erythematosus

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Conflict of interest: None

Background: Headache is common in patients with systemic lupus erythematosus (SLE). Chronic daily headache (CDH) is a category of headache disorders that occur more than 15 days per month and associated with profound decline in quality of life. Objectives: The aim of this study is to investigate the clinical chracteristics of CDH in patients with SLE and their association with the disease severity and the quality of life. Methods: A total of 40 consecutive patients with SLE underwent the survey. We investigated headache characteristics, visual analogue scale (VAS) for pain, and six-question headache impact test (HIT-6) to evaluate the impact of headache on quality of life. The patients underwent required blood tests for assessment of the disease activity by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Results: Six patients (15%) met the criteria for CDH. The total score of HIT-6 is significantly higher in SLE patients with CDH than in them suffered from headache without CDH ($P = 0.027$). Especially, SLE patients with CDH had more “wish could lie down” than them suffered from headache without CDH ($P = 0.017$). The multivariate regression analysis indicated that the

headache days per month was predictor for the headache-related disability. Conclusions: As far as we know, this is the first study evaluating correlation of CDH and the quality of life in Korean patients with SLE. CDH may deteriorate to the quality of life in patient with SLE.

ICW-C12-1

Psoriatic Nail Involvement and Its Relationship with Distal Interphalangeal Joint Disease

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Conflict of interest: None

Background Psoriatic nail disease and distal interphalangeal (DIP) arthritis both are common manifestations of psoriatic arthritis (PsA). Several clinical characteristics are allegedly associated with DIP joint damage, particularly psoriasis nail. However, there is little evidence to substantiate this phenomenon. **Objective** To investigate the relationship between DIP involvement, psoriasis nail and other parameters. **Methods** A cross-sectional observation study involving 45 patients from local Rheumatology clinic. 450 psoriatic fingernails scored, and the radiograph of all these fingers were reviewed to define PsA DIP arthritic changes. **Results** 64.4% of PsA patients had nail psoriasis and 35.6% had DIP arthritis. Univariate analysis identified that swollen joint-count, digits with chronic dactylitis, HLA-B27 status and psoriasis nail, were associated with DIP arthritis. Regression model supported that nail disease was the most significant associated factor of DIP arthritis, with an odds ratio of 9.7; p=0.05. Nail psoriasis was identified in 40.2% of digits. Pitting (29.6%), onycholysis (15.1%), crumbling (8.2%), nail-bed hyperkeratosis (2.0%) were noted with the mean modified Nail Psoriasis Severity Index of 0.95 +/- 1.68. Among all digits, 57 had DIP arthritis while 393 did not. Within DIP joint with PsA radiological change, 59.6% had nail disease. Chi-square test with Bonferroni correction further supported an association between nail psoriasis and DIP involvement with p-value of 0.001. Two specific nail subtypes - crumbling and onycholysis, were found to be significantly associated with DIP disease.**Conclusion** A significant proportion of PsA patients had nail involvement and DIP arthritis. This study suggests an association between these two manifestations. Early identification of psoriasis nail among PsA patients is warranted to prevent future joint damage.

ICW-C12-2

Standardized training can improve the validity of assessing synovitis and tenosynovitis by musculoskeletal ultrasound: a pilot study in Chinese doctors

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Conflict of interest: None

Objective: To evaluate the validity of assessing synovitis and tenosynovitis by using musculoskeletal ultrasound scoring system after standardized training in Chinese doctors. **Methods:** All participants received a 30 minutes' training concerning the ultrasound scoring systems of synovitis and tenosynovitis. The presence of grey scale and power Doppler of synovitis and tenosynovitis was assessed by a four scale semi-quantitative scoring systems developed by Scheel et al, Szkudlarek et al and OMERACT, respectively. Four rounds consisted of ten still images on various grades of B mode and power Doppler of synovitis and tenosynovits were applied for evaluation in different orders before and after training. Paired t-test was used to assess the differences before and after training. **Results:** Thirteen rheumatologists and two radiologists completed the entire procedure. The validity was improved after training when assessing the severity of gray scale of synotivis and power Doppler of synovitis and tenosynotis, which showed significant differences. However, no significant difference was found when assessing the gray scale of tenosynovitis. **Conclusions:** Standardized training is helpful to improve the validity of ultrasound scoring systems of synovitis and tenosynovitis in Chinese rheumatologists and radiologists. The validity of assessing gray scale of tenosynovits needed improvement yet.

ICW-C12-3

Evaluation of hand psoriatic arthritis with dual-energy CT iodine mapping: comparison with contrast enhanced MRI

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Conflict of interest: None

Objectives To assess the feasibility of contrast enhanced dual-energy CT (CEDECT) with iodine mapping in the evaluation of hand psoriatic arthritis (PsA). **Methods** This is a prospective study. 13 consecutive psoriasis patients with finger joint symptoms were included. All patients fulfilled CASPER criteria. The Patients were scheduled for both CEDECT and contrast enhanced MRI (CEMRI). Examination interval between CT and MRI was within 30 days and there was no therapy intervention. CEDECT of the hand was performed with 80kV/140kV, and iodine maps were created. We modified the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Scoring System (PsAMRIS) for evaluation of both CEDECT and CEMRI images. This semi-quantitative scoring system was adapted for evaluation. Images were evaluated by 2 radiologists independently under blinded to clinical data and other images. An inter-observer agreement (with using weighted κ) was calculated in each image. With using consensus score, sensitivity and specificity of CEDECT about inflammatory lesions (synovitis, tenosynovitis, and periarticular inflammation) were calculated with CEMRI as gold standard. About structural changes (bone erosion and bone proliferation), we used CEDECT as gold standard and calculate sensitivity and specificity of CEMRI. **Results** Inter-observer agreement of CEDECT and CEMRI were both good (weighted κ=0.79 in CEDECT, weighted κ=0.78 in CEMRI). As to inflammatory lesions, CEDECT inter-observer agreement was also good (weighted κ=0.78). Sensitivity and specificity of CEDECT about inflammatory lesions were both 0.87. About structural changes, CEMRI had poor sensitivity (0.29) and high specificity (0.99). **Conclusion** CEDECT iodine mapping is useful in the evaluation of hand PsA. It can be used as an alternative examination for patients who are not able to perform MRI.

ICW-C12-4

Quality of Life in Patients with Gout in South Western Sydney

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Conflict of interest: None

Objectives: To determine health related quality of life (HRQOL) in gout patients of South Western Sydney, and the utility of the Gout Impact Scale (GIS). To compare GIS in patients with acute versus non-acute gout and high frequency of gout attacks versus low frequency of gout attacks. To compare Short Form 36 version 2 (SF36v2) in our gout cohort with normals and other chronic diseases. **Methods:** Postal cross-sectional survey study of adult patients diagnosed with gout recruited from 3 public hospitals and a private clinic. SPSS software facilitated analysis. **Results:** 128/183 patients recruited with a 69.9% response rate. The overall impact of gout on their life was 5.8/10, higher in acute gout vs non-acute gout, mean 6.7 vs 5.1, p<0.02. Of patients with gout attack in the last 3 months, the severity of pain was 6.7/10. Patients with more frequent attacks of gout had higher overall severity of gout, mean 7.4 vs 5.1, p<0.001. Patients with acute gout had higher mean scores for gout concern overall (GCO), gout medication side effects (GMSE), unmet gout treatment need (UGTN), well being during attack (WBDA) and gout concern during attack (GCDA), compared to non-acute gout, p<0.02. Pa-

tients with more frequent attacks had higher mean scores for GCO, GMSE, UGTN, WBDA and GCDA, compared to those with less frequent attacks, p<0.01. Gout patients scored significantly lower in all 8 domains of SF36v2 compared to Australian normative data and diabetics. **Conclusions:** Results of the Gout Impact Scale made sense with greater impact of gout in all 5 scales in patients with acute gout or more frequent attacks, suggesting it is a robust instrument in the diverse gout population. The impact of gout was not confined to just physical domains, but had a significant negative impact on psychological health.

ICW-C12-5

Musculoskeletal ultrasound features of gouty arthritis during different episodes

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Conflict of interest: None

Objective To investigate the ultrasound features of gouty joints during the acute and previous attacks. **Methods** Clinical data and ultrasound features of joints during the acute and previous attacks of gouty patients who was experiencing an acute attack were collected. The differences of ultrasound features between two episodes, as well as the relationship with clinical characteristics were analyzed. **Results** Sixty-four patients were enrolled with 21 (32.8%) patients at their first attack. The first metatarsophalangeal (MTP1) joints were most frequently involved, meanwhile, 9.4% patients had two or more joints attacked during one episode. The most prevalent feature was synovitis at the acute phase, followed by double contour (DC) sign (28.1%), bone erosion (18.8%) and tophi (15.6%), while 35.9% patients had two or more pathologies. Whereas, the DC sign was found most in previously attacked joints (33.3%), followed by tophi (26.7%), bone erosion (23.3%) and synovitis (13.3%).No positive pathologies were found in asymptomatic joints. Synovits was more common in joints during their acute attacks (80.0% vs13.3%, P=0.000), however, DC sign and tophi were more common in previously attacked joints (9.5% vs 33.3% and 0.0% vs 26.7%, P<0.05, respectively). Both the DC sign and tophi were positively correlated with the disease duration. **Conclusions** Synovitis was the most prevalent feature in gouty joints during acute episodes; even bone erosion was found at their first attack. The DC sign, tophi and bone erosion were more common in previously attacked joints. The prevalence of both DC sign and tophi was growing with disease durations. Subclinical synovitis was detected with a mild percentage in joints which were not at an acute episode.

ICW-C12-6

Adherence with urate-lowering therapies among male patients with gout in a routine clinical setting

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Conflict of interest: None

Objectives The aims of this study were to assess adherence ((compliance and persistence) and factors that might contribute to non-adherence to urate-lowering therapies (ULT) in male patients with gout during a 12 month period in a routine clinical setting. Methods This prospective observational cohort study was conducted in the rheumatology center of a local tertiary hospital. All patients were incident cases. Compliance to ULT was assessed by the clinic nurses through pill counts at the scheduled visits and non-compliance was defined as less than 80% of the prescribed dose taken. Non-persistence was defined as discontinuation of ULT longer than a month. Several variables that might affect adherence were examined and serum urate levels and frequencies of acute gouty attack were checked. Results A total of 132 male patients with gout were recruited. The 94 (71.2%) was compliant. The medical history of hypertension and chronic kidney disease (CKD) was fewer in the non-compliant patients. The number of comorbidities of non-compliant patients was significantly lower. The previous history of non-persistence of ULT was significantly higher in the non-compliant patients. The absence of CKD and the previous history of non-persistence of ULT are the independent factors associated with non-compliance. The 81 (61.4%) was found to be persistent. The non-persistent patients were significantly younger and a medical history of CKD was fewer. The number of comorbidities of non-persistent patients was significantly lower. The absence of CKD is an independent factor associated with non-persistence. The average serum urate levels of non-compliant and non-persistent patients were significantly higher. Conclusion Accurate assessment of adherence and its associated factors in a routine clinical setting is a necessary first step towards improving effectiveness to gout treatment.

ICW-C13-1

Trend of total joint arthroplasties in our institutes in last decade of super-aging society

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Conflict of interest: None

[Objectives] The trend of total joint arthroplasties (TJA) has increased year by year because the elderly people has also increased in Japan. In fact, the rate of elderly people over 65 year-old increased from 18.5 % in 2004 to 25.1% in 2014 in Japan. The rapid increase of TJA may reflect the management of health care and economic conditions of social system. [Methods] We surveyed the number and rate of TJA in our institutes in the last decade. The cause of revision TJA was analyzed in 2005-09 vs in 2010-14. [Results] We had 19,849 cases of orthopaedic surgery, including 6,978 TJA from 2005 to 2014. The case of TJA increased from 444 in 2004 to 2,309 in 2014 year by year. The cause of TJA contained 5,126 osteoarthritis (OA, 82 %), 355 traumas (6 %), 250 loosening of TJA (5 %), 162 rheumatoid arthritis (RA, 2 %), 105 osteonecrosis (2 %), 46 infections (1 %), 25 dislocations (0.4 %). They contained 2,838 cases of total hip arthroplasties (THA, 41 %), 2,201 cases of total knee arthroplasties (TKA, 32 %), 416 cases of bipolar hip arthroplasties (6 %), 300 cases of revision THA (4 %), 265 cases of unilateral knee arthroplasties (UKA, 4 %), 26 cases of revision TKA (0.4 %). The increase of TJA was correlated to OA (r= 0.9, p< 0.05), osteonecrosis (r= 0.8), infections (r= 0.8), RA (r= 0.6), and THA (r= 0.9), TKA (r= 0.9), UKA (r= 0.9), Revision TKA (r= 0.8). The cause of 381 revision TJA contained 294 loosening (77 %), 63 infections (17 %) and 25 dislocations (7 %). The value of infections as cause of revision TJA was larger compared to the value of all revision TJA between in 2005-09 and in 2010-14 (1.5 vs 2.2 times). [Conclusion] The number and rate of TJA increased year by year, because of expansion of elderly people affected by OA in the super-aging society. Revision TJA due to infections may be increasing year by year.

ICW-C13-2

Identification Of Factors Leading To Total Knee Replacement - Data from the Osteoarthritis Initiative (OAI)

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Conflict of interest: None

To investigate the driving clinical and imaging based factors leading to total knee replacement (TKR) surgery in patients with knee osteoarthritis. 165 participants (64.5±8.4yrs, BMI 29.7±4.7kg/m^2, 60% females) were identified from the Osteoarthritis Initiative (OAI) who received a TKR during a 4-year period. Annual publicly available patient and knee specific data were obtained from 165 knees in the visit before TKR, for 140 knees 1 year before the TKR, for 107 knees 2 years before TKR, for 68 knees 3 years before TKR and for 30 knees 4 years before the TKR

surgery. Between these timepoints we compared the participant's quality of life (QoL; measured by the Knee Injury and Osteoarthritis Outcome Score [KOOS]), the knee specific Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score, WOMAC pain subscore, knee pain intensity score (measured on a numerical rating scale) and the x-ray based Kellgren and Lawrence (KL) grades. The overall distribution of KL grades, changed significantly each successive year prior to the TKR surgery ($p<0.045$). For measures of QoL, WOMAC pain score, WOMAC total score a significant change was only observed in the year before ($p<0.0001$), whereas in the years more than 1 year prior to TKR ($p<0.0001$), no significant difference between the scores was noticed ($p>0.06$). Scores for pain intensity changed significantly starting 2 years prioir to TKR surgery ($p=0.014$). The results of this study indicate, that albeit a significant change in KL grades is present between each year before TKR surgery, the driving factors for surgery are based on patients quality of life and knee specific pain and functional scores. Based on these results KL grades seems to be a less strong predictive factor for TKR surgery compared to change in participants global and knee specific measures like pain and quality of life.

ICW-C13-3

How precisely does ultrasonographic evaluation reflect the histological status of the articular cartilage in the knee joint?

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Conflict of interest: None

Objective: Ultrasonographic evaluation of the joints has gained stable credibility, especially for assessment of joint inflammation and destruction. However, its concordance with histological evaluation is not fully confirmed. In order to assess the reliability of ultrasonography (US) in evaluation of the articular cartilage, we evaluated the thickness and the status of the distal femoral condylar cartilages by US, and compared the results with those of histological evaluation. Patients and method: We examined 35 knees of 34 patients who underwent total knee arthroplasty (TKA) due to rheumatoid arthritis (RA) or osteoarthritis (OA). Before operation, US evaluation of the knee joint was performed and the status of the lateral and medial femoral condylar cartilages was assessed. Then, bone fragments of the distal femoral condyles were collected and histologically evaluated. Results: The thickness measured by US was significantly correlated with that evaluated by the histology in the medial condylar cartilages ($p=0.0006$) while the tendency did not reach to statistical significance in the lateral condylar cartilages ($p=0.0861$). The lateral condylar cartilages tended to be thinner in the US evaluation than in the histological evaluation ($\mu=0.837$ in US, $\mu=1.71$ in histology). When the cartilages evaluated by histology were divided into thick group (>1mm in histological evaluation) and thin group (<1mm), the thickness of the cartilages in the thick group significantly appeared thinner in US evaluation than in histological evaluation ($p<0.0001$). Discussion: Knee US could be effective to measure the thickness and the status of the distal femoral condylar cartilages, but the severer the cartilage damage becomes, the more imprecise the examination might be.

ICW-C13-4

Are denuded areas of subchorndral bone related to localized knee or regional pain as evaluated by the Knee Pain Map? - Data from the Osteoarthritis Initiative

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Conflict of interest: None

To evaluate the relationship between the presence and size of denuded areas of subchondral bone (dABs) and locations of pain as indicated on the knee pain map (KPM) and thus to provide spatial patterns of structure-pain-correlates in knee OA. 440 participants (244 females, 62.5 ± 9 years, 30.1 ± 4.9 kg/m^2) from the Osteoarthritis Initiative (OAI) were included in this study. Participants used the KPM to identify the presence of localized and regional knee pain. dABs were measured in subregions of the femorotibial cartilages. Localized pain in the medial joint line was significantly associated with moderate dABs in the external cMF OR 2.02 [95% CI 1.26-3.21] and external MT OR 1.69 [95% CI 1.08-2.67] but not with the internal cMF OR 1.03 [95% CI 0.53-2.01] or with internal MT OR 1.29 [95% CI 0.25-6.77]. Medial regional pain was significantly associated with moderate dABs in cMF OR 2.03 [95% CI 1.30-3.19] and in MT OR 2.46 [95% CI 1.53-3.95] but not associated with dABs in cLF OR 0.47 [95% CI 0.25-0.89 or in LT OR 0.60 [95% CI 0.36-1.00]. This cross-sectional analysis reveals a spatial pattern of structure-pain-relationships in knee OA. Knee pain was associated with medially located dABs but not with those located in the lateral compartment.

ICW-C13-5

Adipokine profile of synovial fluid in end-stage knee osteoarthritis - An investigation across racial groups

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Conflict of interest: None

Object: Osteoarthritis (OA) associated clinical and epidemiological differences have been identified across races. Whether these variations are related to adipokines in joint synovial fluid (SF) remains unknown. We examined whether the SF adipokines and infrapatellar fat pad (IFP) gene expression among patients with end-stage knee OA varied by race. **Method :** Age, sex, body mass index (BMI) and race (White, Asian and Black) were elicited through self-report questionnaire prior to surgery. SF and IFP samples were collected at the time of total knee replacement. Adipokines were examined using multiplex platform and differences in concentrations were tested across racial groups. IFP was profiled using Adipogenesis PCRArray and genes of interest were validated via qPCR using Student's t-test. Linear regression modeling was used to investigate the association between each adipokine (outcome) and race (predictor; referent group: White); adjusting for age, sex and BMI. **Results**: 67 patients (18 White, 33 Asian, 16 Black) were included. Mean SF adiponectin concentration was greatest in Whites (1175.05 ng/mL), followed by Blacks (868.53 ng/mL) and Asians (702.23 ng/mL) ($p=0.034$). The mean SF leptin concentration was highest in Blacks (44.88 ng/mL), followed by Whites (29.86 ng/mL) and Asians (20.18 ng/mL) ($p=0.021$). Regression analysis showed Asians had significantly lower adiponectin concentrations compared to Whites ($p<0.05$). However, leptin concentrations did not differ significantly by race in adjusted analyses. Testing the IFP showed significantly higher expression of LEP gene (leptin, $p=0.03$) in Asians compared to Whites ($n=4$). **Conclusions**: There appears to be important racial differences in SF adipokine profile and IFP gene expression among individuals with end-stage knee OA. Further work to determine the source and function of these adipokines in knee OA pathophysiology across racial groups is warranted.

ICW-C14-1

Anti-cyclic citrullinated peptide antibody (anti-CCP) positivity in non-arthritic individuals with up to ten years of observation

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Conflict of interest: Yes

Objectives: Anti-CCP was included as part of the comprehensive health screening in non-arthritic individuals in order to determine positivity rates in the general population. The development of arthritic symptoms and the diagnosis of rheumatoid arthritis (RA) in this population was prospectively followed up to 10 years. **Methods:** Commercial anti-CCP assay (SRL, Inc.) was included as part of comprehensive wellness screening. Subjects with active arthritic symptoms and/or prior history of RA or any systemic inflammatory arthritides were excluded from analysis. **Results:** Among the 1879 individuals (788 men; 1091 women; mean age 51.8yrs) with at least one screening visit, 30 (1.6%) were found to be anti-CCP positive at first visit, with 3 out of the 30 (10%) becoming symptomatic and meeting the 2010 ACR/EULAR Classification Criteria for RA after an average of 3.5yrs. Additionally, six individuals (2%) were found to newly develop anti-CCP positivity at a subsequent visit. **Conclusion:** Individuals without arthritic symptoms have low rates of anti-CCP positivity. However, anti-CCP positivity seems to confer relatively high rates of symptom onset and development of RA. The utility of anti-CCP as a screening modality needs further evaluation in larger populations.

ICW-C14-2

Anti-centromere antibodies (ACAs) exhibits a specific distribution of titers among anti-nuclear antibodies (ANAs), and ACA-positive rheumatoid arthritis (RA) is a distinct clinical subset

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Conflict of interest: None

Objective. Anti-centromere antibodies (ACA) is one of anti-nuclear antibody (ANA). Here, we characterize the titer distribution of ACAs and analyze clinical and genetic features of ACA-positive rheumatoid arthritis (RA). *Methods*. We examined ANA by indirect immunofluorescence for 9,575 healthy volunteers and 1,278 RA patients without systemic sclerosis. HLA-DRB1 was genotyped for 285 RA patients. We compared distributions of titers among ANA and analyzed associations between ACA and clinical or genetic features in the subjects. *Results.* ACA demonstrated a significant higher distribution levels than other ANAs ($p<0.0001$). ACA-positivity was associated with old age and females. ACA-positive patients with RA showed lower positivity of rheumatoid factor ($p=0.0011$). ACA positivity was a risk factor of high Total Sharp Score independently of known factors. ACA was associated with Raynaud's phenomenon and complication of Sjogren's syndrome and primary biliary cirrhosis ($p\leq0.0052$). No HLA-DRB1 alleles were significantly associated with ACA. *Conclusions.* ACA showed a specific distribution of levels among ANA. ACA-positive RA is a distinct subset with specific clinical features and complications. ACA is a possibly new risk factor of bone destruction in RA.

ICW-C14-3

Handedness influences the laterality of clinical and radiological articular involvements in rheumatoid arthritis

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Conflict of interest: None

Background: Mechanical stress would play an important role on inflammation of rheumatoid arthritis (RA). Some studies reported that the dominant hand joints were more affected than the non-dominant ones, but many of them led to the conclusion by evaluating only right-handed subjects. Thus, it is still inconclusive whether right or dominant hand gets more damaged in RA. ***Objective***: To clarify the relationship of handedness with clinical and radiological joint involvements in RA. ***Methods***: We enrolled a total of 334 patients. Clinical and radiological joint involvements were compared between right and left sides using the data of the 28 joints evaluated for DAS28 and X-rays scored by the modified Total Sharp Score (mTSS). ***Results***: We found 322 and 12 patients right- and left-handed, respectively. In both groups, clinical and radiological involvements tended to be worse in dominant hands than in non-dominant ones ($p=0.0015$, mTSS in right-handed subjects). On the contrary, non-dominant foot showed more damage than dominant foot in right-handed subjects ($p=0.031$, mTSS). **Conclusion**: Handedness influences the laterality of clinical and radiological joint involvements in RA. Laterality of damage in foot may be different from that in hand.

ICW-C14-4

The relationship between rheumatoid arthritis disease activity and recurrence after arthroplasty for rheumatoid forefoot deformity

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Conflict of interest: None

【Object】While resection arthroplasty is a useful means to treat forefoot deformities caused by rheumatoid arthritis (RA), the outcomes are poor in some patients. We extracted patients with recurrent deformity, and examined the relationship with RA disease activity.【Methods】The study included 46 feet in 25 RA patients who underwent resection arthroplasty of the hallux and 4 lesser toes from 2008 to 2013. According to gender, there were 40 female feet, and 6 male feet, with a mean age at the time of surgery of 70 years, and mean follow-up period of 31 months. As endpoints, we examined the presence and number of dislocated metatarsophalangeal (MTP) joints prior to surgery and at the time of the final follow-up, hallux valgus angle (HVA), and Disease Activity Score 28-CRP (DAS), then analyzed factors that affected recurrent deformity following surgery.【Results】The mean DAS was 2.9 prior to surgery, and 2.5 at the time of the final follow-up, with a significant improvement observed. When feet with recurrent dislocation of the MTP joint or HVA > 25 degrees at the time of the final follow-up were defined as the recurrent deformity group, there were 25 patients (26 %) allocated to the recurrent deformity group. Compared to the non-recurrent deformity group, the recurrent deformity group showed significantly higher DAS at the time of the final follow-up (3.6 vs 2.1, $p<0.001$). When patients with DAS < 2.6 prior to surgery and at the time of the final follow-up were defined as the improvement maintained group, there were 20 patients (43 %) who corresponded. Compared to the non-maintained group, the improvement maintained group showed a higher preoperative HVA with more MTP dislocations, however only 1 patient developed recurrent deformity, which was significantly low compared to the group without maintained improvement ($p<0.001$).【Conclusion】The control of RA disease activity prior to and following resection arthroplasty is important for the prevention of recurrence.

ICW-C14-5

Ageing is independent factor of Health Assessment Questionnaire Disability Index in rheumatoid arthritis patient who is older than sixty-five year old

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Conflict of interest: None

[Objectives] In order to verify influence of ageing in Health Assessment Questionnaire Disability Index (HAQ-DI) in rheumatoid arthritis (RA) patient, correlation among HAQ-DI, 28 joints disease activity index with C-reactive protein (DAS28-CRP), Sharp/van der Heijde score (SHS), and age was investigated and evaluated statistically with multiple linear regression analysis. [Methods] 363 RA patients who have been followed up more than 3 years were analyzed. Their average age, DAS28-CRP, HAQ-DI, SHS, and age at third year were calculated, and their correlations between HAQ-DI and the other factors were evaluated. Patient was divided according to age at 65-years-old (G-Y; younger and G-O; older). Correlations between two facotors were evaluated for all the patients (G-All) and for each age group statistically. Patients with DAS28-CRP less than 2.3 and SHS less than 50pts, were picked up (G-Rem). Correlations between HAQ-DI and the other factors for each age group were evaluated statistically. Significance level was set within 0.01%. [Results] For G-all, HAQ-DI has correlated with all of three factors significantly. In G-Y, HAQ-DI has correlated with DAS28-CRP and SHS significantly, but not significant with age. In G-O, HAQ-DI has demonstrated significant correlation with all of the three. In 192 G-Rem patients, HAQ-DI has demonstrated no significant correlation with age for G-Y, however for G-O significant correlation between the two has demonstrated. In correlation between the two, all combinations except DAS28-CRP and age have demonstrated significant correlations for G-all and for G-O, however for G-Y, there demonstrated statistically significant correlation only between HDAQ-DI and DAS28-CRP. [Conclusions] These results suggested that ageing has close influence on HAQ-DI. This effect applies when patient's age becomes over 65-year-old independently. Thus, age related HAQ-DI, AGE-HAQ for short, should be considered when evaluate HAQ-DI in RA patient older than 65.

ICW-C14-6

The effect of medication on development of cardiovascular disease in patients with rheumatoid arthritis

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Conflict of interest: None

Objectives To evaluate the effects of medication on the development of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) **Methods** A retrospective cohort of RA patients was established using Korean national healthcare claims database between Jan 2009 and Dec 2013. There was 6 months disease-free period of CVD to determine the incident cases. After excluding the patients with CVD history, patients were followed for the development of CVD or the last observational date (Dec 31, 2013). We performed a nested case-control study of RA patients without previous CVD. Cases who developed CVD were identified and matched with up to 4 controls without CVD. Controls were matched for age, gender, RA index date, comorbidities including hypertension, diabetes, hyperlipidemia, chronic kidney disease, and drugs such as antiplatelet agent, cholesterol lowering agent. Information on drugs exposure: non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs (DMARDs), biologic DMARDs, corticosteroids, calcium which was used more than 30 days during 1 year before CVD was collected. Using the multivariate regression model, we evaluate the effect of each drug on the development of CVD with adjusting other risk factors. **Results** We identified 7,102 cases and 27,018 controls. In models adjusted for other risk factors for CVD, DMARDs (OR 0.79, 95%CI 0.73-0.85) were protective effect for CVD, while biologic DMARDs were not significant (OR 0.85, 95%CI 0.56-1.28). Corticosteroids (OR 1.26, 95%CI 1.19-1.34) and NSAIDs (nonselective NSAIDs: OR 1.32, 95%CI 1.22-1.41, Cox-2 inhibitor: OR 1.31, 95%CI 1.18-1.45) were risk factors for CVD. These results were consistent in subgroup analyses stratified by various CV events; coronary artery disease, stroke, and cerebral hemorrhage. **Conclusions** The use of DMARDs showed protective effect for CVD, while corticosteroids and NSAIDs increase the risk of CVD in RA patients.

ICW-C15-1

A prospective study of glutamates of methotrexate and its efficacy

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Conflict of interest: None

Objective: To determine the levels of erthrocyte methotrexate polyglutamate (1-5) levels in patients with rheumatoid arthritis and assess their relationship to efficacy and adverse effects.Methods: This study included patients of RA (fulfilling 1987 ACR), aged 18-65 years who had active disease (DAS28>3.2) and were not on methotrexate. Patients were started on MTX at 15 mg/week and increased to 25 mg/week by 8 weeks that was continued till 24 weeks. At 24 weeks, patients were classified by EULAR response criteria into responders (good or moderate response) or non-responders. MTX-PG levels (Pgs 1-5) were assayed in packed RBCs using HPLC using post-column derivitization using UV photo-oxidation and then fluorescent detection. Results: This study included 117 patients, with mean (±SD) age of 42.7±11.9 years, disease duration 2.0±1.7 years, 71.8% RF+ and 85.7% CCP+. At 24 weeks, among completers, 57 patients were responders and 33 were non-responders with the mean (±SD) MTX dose being 21.7±3.9 and 22.7± 4.1 mg/week. There was no difference in the mean methotrexate polyglutamate levels (pgs 1-5) between responders and non-responders at any of the visits (4, 8, 16 and 24 weeks). At 24 weeks the MTX PG levels were 158.5 and 160.2 nM respectively. In addition, there was no difference in the mean methotrexate polyglutamate levels between those with adverse effects and those without any adverse effects.Conclusions: Our study suggests that MTX-PG levels are not determinants for response to MTX,or their adverse effects..

ICW-C15-2

Analysis of non-responders to infliximab: a retrospective cohort study of rheumatoid arthritis patients

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Conflict of interest: Yes

Introduction Biologics are highly effective treatment for rheumatoid arthritis (RA). However, a small proportion of patients showed worsened disease activity after initiation of biologics. As treatment failure may lead to reduced adherence to the following treatment, identifying factors that affect refractory status to biologics is important. **Method** Clinical data was obtained from RA patients who were treated with infliximab (IFX) during the period of August 2003-April 2014. Patients who fell into either of the following condition were defined as non-responder. 1. Ifx was stopped within 22 week due to non-response. 2. DAS28-CRP at 22 week increased by >0.6 from that at week 0. **Results** Sixteen out of 582 patients were identified as non-responder. Age, duration of disease, dose of MTX, disease activity were not associated with non-response, and treatment with prednisolone (PSL) was the only factor identified as a risk factor of non-effective outcome (Odds ratio 4.8, 95% CI 1.5-15.3). **Discussion** This result showed PSL usage might be a risk factor for poor outcome of IFX. Although transient treatment with low dose corticosteroid is reported to be beneficial to prevent bone destruction, this result suggests that corticosteroid usage requires careful consideration to avoid poor outcome of IFX in RA patients.

ICW-C15-3

Evaluation of the binding kinetics and functional bioassay activity of sarilumab and tocilizumab to the human il-6 receptor alpha (il-6rα)

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Conflict of interest: Yes

Objectives: To evaluate the kinetic binding parameters and in vitro functional activity of sarilumab, a human monoclonal antibody (mAb) directed against human interleukin 6 receptor alpha (IL6-Rα), and tocilizumab, a humanized anti-IL6Rα mAb. Sarilumab was developed using VelocImmune® mice immunized with human IL6Rα. It is currently being explored as a therapeutic treatment for rheumatoid arthritis. **Methods:** Kinetic binding parameters of sarilumab and tocilizumab (EU commercial source) were measured using surface plasmon resonance (SPR). Sarilumab and tocilizumab blockade of IL-6/IL-6-Rα "classical" activation in cells expressing IL6Rα were compared in a HepG2/STAT3 luciferase reporter assay and a DS-1 proliferation assay. Sarilumab blockade of *trans*-signaling in the presence of soluble IL6Rα was evaluated using HEK293/gp130/STAT3-luciferase reporter cells which do not express IL6Rα. An ELISA assay was used to evaluate sarilumab blockade of hIL-6Rα binding to IL6. **Results:** Sarilumab bound with high affinity to monomeric human and monkey IL6Rα(K_D = 62 pM and 72 pM, respectively) and to the dimeric human IL-6Rα-hFc with a K_D value of 13 pM. Sarilumab blocked luciferase activity in HepG2/STAT3-Luc cells induced by 50 pM IL-6 with an IC_{50} of 146 pM and blocked proliferation in DS-1 cells induced by 1 pM IL6 with an IC_{50} of 226 pM. In both the SPR and functional assays, sarilumab was several-fold more potent than tocilizumab. Sarilumab blocked *trans*-signaling in HEK293/gp130/STAT3-Luc cells induced by 1 nM IL-6Rα and 10 nM IL-6, with an IC_{50} value of 860 pM. In an ELISA assay, sarilumab blocked 100 pM IL-6Rα-hFc from binding to human IL-6 with an IC_{50} value of 108 pM. **Conclusion:** Sarilumab has a higher binding affinity for IL-6Rα, blocks IL6Rα activation, and inhibits IL6 induced cell proliferation at lower concentrations than tocilizumab. Sarilumab inhibits activation in both *cis*- and *trans*-signaling assays via direct blockade of IL6 binding to IL-6Rα.

ICW-C15-4

Efficacy of denosumab added to a biologic agent on radiographic progression in rheumatoid arthritis

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Conflict of interest: None

Object. Accumulating evidences have shown that RANKL and inflammatory cytokines are essential in osteoclast differentiation and activation, which leads to bone destruction in rheumatoid arthritis (RA). The aim of this study was to elucidate the efficacy of concomitant use of denosumab and a biologic agent on radiological progression in RA patients. **Methods.** 40 RA patients on biologic agents who have initiated denosumab 60mg injections every 6 months for osteoporosis between 2013 -2015 in our institution with hand and foot X-rays available were enrolled in this study. Control group comprised of age-, sex-, disease duration-, disease activity-, and modified total Sharp score (mTSS)-matched 40 patients with a biologic treatment without denosumab. Disease activity and radiographic progression 12 months later was compared between the two groups. **Results.** The increase in modified Sharp erosion scores was significantly smaller in the denosumab+biologics group than in the biologics group (0.16 vs 0.64, P=0.038). Clinically relevant radiological progression (CRRP; mTSS≥3) rate was also lower in the denosumab+biologics group (2.5% vs 15%, P=0.048). Denosumab had no evidence in suppressing RA disease activity and progression of joint space narrowing. Patients who were young, had moderate disease activity, and showed greater preexisting joint damage were prone to experience CRRP in the biologics group. The rate of overall adverse events were comparable between the two groups. **Conclusions.** Concurrent use of denosumab and a biologic agent in RA patients is efficacious in inhibiting structural damage and preventing CRRP without increasing adverse events compared with the treatment of a biologic agent alone.

ICW-C15-5

Safety, Pharmacokinetics and Efficacy of E6011, an Anti-Fractalkine Monoclonal Antibody, in a First-in-Patient Phase 1/2 Study in Japanese Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

Background/Purpose: We developed E6011, a novel humanized anti-Fractalkine (CX3CL1, designated as FKN hereafter) monoclonal antibody, and its safety and tolerability were assessed in a Phase 1/2, open-label, multiple ascending dose study in RA patients for the first time (NCT02196558). **Methods**: Active RA patients with inadequate response to MTX or TNF inhibitors were received 7 consecutive doses (subcutaneous) of E6011 at week 0, 1, 2 and thereafter every 2 weeks up to week 10. The primary objective was safety and tolerability of E6011 in Japanese RA patients while the efficacy of E6011 was also explored. **Results**: Twelve subjects were enrolled in the cohort of 100 mg and subsequently 15 subjects were enrolled in the 200 mg cohort, in total, 27 subjects received repeated subcutaneous administrations of E6011. As a result, repeated dose of E6011 was found safe and well tolerated. The incidence of AE, treatment-related AE and SAE was 59.3%, 29.6% and 7.4%, respectively. There were no severe AE or deaths, and no significant differences were observed in the incidence or severity of AE between the 100 mg and 200 mg cohorts. After starting multiple dose administration of E6011, the steady state was achieved at week 2, and was held to week 12. Clinical outcome was also available in the study in which response rates of ACR20, 50 and 70 at week 12 were 75.0%, 33.3%, 8.3% and 80.0%, 26.7%, 20.0% in the cohort of 100 and 200 mg, respectively. At week 12, 33.3% of subjects achieved DAS28-CRP remission in both cohorts, 16.7% and 20.0% for SDAI remission and 8.3% and 26.7% for Boolean remission were observed in the 100 mg and 200 mg cohorts, respectively. **Conclusion**: E6011 was safe and well tolerated, and demonstrated a promising efficacy in active Japanese RA patients with MTX or TNFi-IR. While further clinical studies are required, the results obtained indicate that a novel biological DMARD targeting FKN/CX3CR1 interaction will be clinically beneficial for active RA patients.

ICW-C15-6

Joint preserving surgery for hallux valgus in rheumatoid arthritis with minimum 2-year follow-up

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Conflict of interest: None

Objectives Ninety percent of patients with rheumatoid arthritis (RA) have suffered from feet deformities, including hallux valgus. Previous studies reported that arthrodesis and resection arthroplasty of the first MTP joint were major procedures for RA patients. However, those procedures sacrifice the function of the first MTP joint. Recently, because of the introduction of biologics, RA can be well controlled and the function of joints can be preserved. Therefore, we perform joint-preserving surgery (Scarf osteotomy) for hallux valgus in RA patients including severe deformities. We aimed to investigate clinical results of Scarf osteotomy for hallux valgus in RA patients. Methods A retrospective study was undertaken to review a series of 55 feet with hallux valgus in 44 RA patients who underwent Scarf osteotomy. The mean age at surgery and duration of RA affliction were 65.0 (range 45-81) years and 21.3 (range 5-45) years, respectively. There were 42 women and 2 men. They were followed up for a mean duration of 28 months and all of them were available for follow-up for at least 2 years. The angles of the hallux valgus (HVA), the angles of M1M2 (M1M2A), the angles of M1M5 (M1M5A), Hardy's classification, and DAS28-CRP were examined pre- and postoperatively at the final follow-up. Complications were also examined. We defined a recurrence of hallux valgus as more than 25 degrees of HVA.

Results The mean HVA improved from 48.7 degrees preoperatively to 14.1 degrees at the final follow-up. The mean M1M2A and M1M5A improved from 13.8 degrees to 8.8 degrees and from 32.4 degrees to 22.0 degrees, respectively. The median Hardy's classification improved from 6 to 3. The mean DAS28-CRP improved from 3.1 to 2.8. There were 8 (15%) recurrences of hallux valgus, 3 (5%) hallux varus, and 5 (9%) delayed wound healing. Conclusions Our results show that Scarf osteotomy is a beneficial procedure for hallux valgus in RA patients.

International Concurrent Workshop Basic

ICW-B1-1

Internalization of anti-DNA antibodies into live cells: one of the possible pathogenic mechanisms in SLE

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Conflict of interest: None

Objective: We previously reported that monocytes of patients with systemic lupus erythematosus (SLE) secrete higher amount of BAFF (B cell activating factor) by stimulation with IFN-g than those from healthy controls, suggesting that patient monocytes might be in a pre-activated state. We observed later that incubation of monocytes with anti-DNA antibodies induced expression of BAFF, which urged us to study how anti-DNA antibodies interact, stimulate, and/or damage the cells. **Methods:** Mouse monoclonal IgG anti-DNA antibodies (MoAbs) 2C10, H241 and WB-6 were purified with a protein A column. Human epithelial cell lines HeLa and HEp-2, or monocytic THP-1 cells were incubated with one of the MoAbs, or serum samples from patients with SLE for 2 hours at 37℃. Fluorescence-labeled second antibody was added after wash, fixation, permiabilization and blocking, and the cells were analyzed by fluorescence microscopy or flowcytometry. **Results:** Anti-DNA MoAbs, but not isotype-matched IgG, entered the cytoplasm and/or nucleus of live cells. Two hours after incubation with MoAbs, the cells were not stained by annexin V suggesting that the cell membrane was intact at this point. The second antibody did not enter the cells without fixation and permiabilization, which also suggested the integrity of the cell membrane. Incubation at 4℃ significantly reduced the internalization of MoAbs indicating that the process was resulted from active cellular function. Polyclonal IgG from some patient sera, but not from healthy subjects, also entered live cells, and induced apoptosis by 4-hour or longer incubation. **Conclusion:** Some anti-DNA antibodies enter live cells, and stimulate or damage the cells.

ICW-B1-2

Anti-enolase 1 autoantibodies in SLE with pulmonary hypertension induce migration of pulmonary artery smooth muscle cells

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Conflict of interest: None

Objective: The process of pulmonary vascular remodeling in pulmonary arterial hypertension (PAH) in systemic lupus erythematosus (SLE) largely depends on migration of pulmonary artery smooth muscle cells (PASMCs). Since some SLE patients have autoantibodies to enolase 1 (ENO1), which is reported to be involved in cell migration, we tested whether IgG from SLE with PAH have stimulatory effects on PASMC migration. **Methods:** Sera from 6 SLE patients, including 1 with PAH, and 7 healthy subjects were collected, and IgG was purified using Melon Gel or protein G. PASMC migration was examined by a Boyden chamber method. Lamellipodia formation and antibody binding sites in the cells were determined by immunocytochemistry. Identification of anti-ENO1 antibodies was performed by immunoprecipitation, western blotting, mass spectrometry, and ELISA. **Results:** IgG from SLE with PAH, significantly increased migration of PASMCs, which was 2.0-fold greater in SLE patients with PAH than those without PAH (p<0.01, n=3, 12). After incubation with IgG, the number of cells with lamellipodia, which represents rearrangement of the cytoskeleton necessary to migration, was 1.4-fold higher in SLE patients with PAH than those without PAH (p<0.01, n=8, 21). In immunocytochemistry, IgG from SLE with PAH were colocalized with b-tublin in the cytoplasm of PASMCs, and western blotting showed that the antibodies bound to a ~50 kD protein in the lysates, which was subsequently identified as ENO1. Furthermore, the titer of IgG anti-ENO1 antibodies was 1.5-fold higher in SLE patients with PAH than those without PAH. **Conclusion:** Anti-ENO1 antibodies in SLE with PAH induce migration of PASMCs, and possibly play a pivotal role in the pathogenesis.

ICW-B1-3

Curcumin Prevented the Progressivity of Nephritis in Pristane Induced Lupus Mice

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Conflict of interest: None

Objective: Curcumin is an immune modulator compound which rarely discussed for systemic lupus erythematosus (SLE) treatment. The aim of this research was to investigate the effect of curcumin treatments in preventing the progressivity of nephritis in pristane induced lupus mice model. **Methods:** Female Balb/c mice (n=24) were injected by single 0.5 cc pristane intraperitoneally to induce lupus manifestations. Mice were divided into four groups, based on curcumin doses: control (no curcumin). C1 (12.5 mg/kgBW/day), C2 (50 mg/kgBW/day), and C3 (200 mg/kgBW/day). Curcumin were given orally every day from fourth to eight months after pristane injection. The progressivity of nephritis was monitored by measuring proteinuria and histopathologic analyses of the kidney, including class, activity index, and chronicity index of lupus nephritis. **Results:** Presence of proteinuria (>500 mg/dl) was significantly lower in C3 group compared to control (p=0.000). Most of mice in control, C1, and C2 group had class IV lupus nephritis (66.6%, 66.6%, and 50% respectively) while most of the mice in C3 group had class II lupus nephritis (50%). Lupus nephritis activity index was significantly lower in C3 group compared to control (p=0.000). However, no significant difference of lupus nephritis chronicity index was found from C1, C2, and C3 group compared to control. **Conclusion:** Curcumin treatment can prevent proteinuria, progressivity of lupus nephritis class, and activity index of lupus nephritis. Therefore, curcumin is a potential compound that can be developed as a complementary therapy in the treatment of SLE, especially by preventing the progressivity of lupus nephritis.

ICW-B1-4

Association between macrophages and proteiuria in lupus nephritis

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Conflict of interest: None

Introduction Number of macrophages (Mφ) in glomeruli correlate with proteinuria in lupus nephritis (LN). Recently, polarity of Mφ has gained attention in inflammatory diseases. Macrophages can be classified into two functional subsets: classically activated Mφ(M1), which are characterized by cytotoxic properties; and alternatively activated Mφ(M2), which are involeved in resolution of inflammation. We have previously reported that induction of heme oxygenase (HO)-1, which are predominantly expressed in M2, led to a significant reduction of proteinuria in MRL-Fas_{lpr} mice. Object To analyze association between proteinuria and Mφ polarity in LN. Methods M1Mφ and M2Mφ were generated from peripheral monocytes with M-CSF/GM-CSF. In renal biopsies from 20 cases with LN, immunohistochemistry was performed using Abs for CD68, CD163 (a marker of M2Mφ), and HO-1. And average cell number per glomeruli of M1Mφ, M2Mφ and HO-1 positive cells were counted. Retrospectively, we analyzed association between average cell number per glomeruli and proteinuria at the time of diagnosis. In addition, we generated congenic mice MRL/Fas_{lpr}.C57BL/6J-$^{Bach1-/-}$(a transcriptional repressor of HO-1) and analyzed difference of survival rate and proteinuria. Result Histological examination revealed that M2Mφ was predominantly present in LN glomeruli compared with M1Mφ(M2Mφ 7.95 vs M1Mφ 1.57). In vitro analysis of GM- and M-CSF induced human Mφ, M2Mφ showed highly expressed CD163, HO-1, and ferritin in M2 subset. Interestingly, correlation between HO-1 and CD163 were absent, suggesting aberrant regulation of HO-1 in M2Mφin LN. There were significant positive correlation between M1/M2 Mφ number and proteinuria. Phenotype analysis of MRL/Fas_{lpr}. C57BL/6J-*Bach1-/-* is under way. Conclusions There were significant positive correlation between M1/M2 cell number and proteinuria in LN. Immunohistochemistry showed possible M2 dysfunction in LN.

ICW-B1-5

Monocyte Chemoattractant Protein - 1 in urine as biomarker of disease activity in lupus nephritis: cross sectional and longitudinal study

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Conflict of interest: None

Objectives: Monocyte Chemoattractant Protein-1 (MCP-1) is involved in pathogenesis of lupus nephritis (LN). However, large prospective studies evaluating its role as a biomarker in LN are lacking. **Methods**: SLE patients with active nephritis (AR), active disease without nephritis (active non-renal; ANR) and inactive disease (ID) were enrolled. Patients were treated according to the ACR guidelines and AR group was followed up every 3 months for 1 year. Urine and serum samples were collected at baseline and follow up visits. Urine samples from 20 healthy subjects (HC) and 20 patients each of rheumatoid arthritis (RA) and diabetic nephropathy (DM) served as controls. Serum (sMCP-1) and urinary MCP-1 were measured using ELISA and urinary values were normalized for creatinine excretion. Non-parametric tests were used for statistical analysis. **Results:** A total of 121 SLE patients (females 113) were enrolled. At baseline, normalized urinary MCP-1 (uMCP-1) was significantly higher in AR group as compared to ANR, ID, HC and RA ($p<0.001$for all) but it was not different from DM. At baseline, uMCP-1 showed good correlation with rSLEDAI and SLEDAI ($r=0.5$ and 0.4, $p<0.001$) but not with sMCP-1. On ROC analysis to differentiate between AR and ANR, uMCP-1 performed better than sMCP-1, anti-ds DNA antibodies, C3 and C4. In the longitudinal study, uMCP-1 decreased significantly at all visits as compared to baseline ($p<0.001$) whereas sMCP-1 showed an irregular erratic trend with significant variability in follow up levels. uMCP-1 rose before conventional markers in 2 patients who had a relapse of LN at 11 and 12 months respectively and its levels remained persistently high in another patient who developed chronic kidney disease. **Conclusion:** uMCP-1 is derived from kidneys and helps differentiate between AR and ANR patients. It shows good correlation with disease activity and its levels fall with treatment. It may have a potential to predict poor response to therapy and relapse of LN.

ICW-B1-6

Vitamin D increases bactericidal function of neutrophil independent to cathelicidin in patient with systemic lupus erythematosus

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Conflict of interest: None

Object: to examine the effect of vitamin D {1,25 $(OH)_2D_3$} in increasing bactericidal function of neutrophil against *Escherichia coli*(*E. coli*) in patient with systemic lupus erythematosus (SLE). **Methods:** six groups culture of neutrophil cells from SLE patient with hypovitamin D were given six different dose of 1,25 $(OH)_2D_3$: 0, 10^{-10}M, 10^{-9}M, 10^{-8}M, 10^{-7}M, and 10^{-6}M. Every group was induced by phorbol 12-myristate 13-acetate (PMA) to form neutrophil extracellular traps (NETs) as the last defense of neutrophils against bacteria. Intracellular flowcytometry was done to measure the expression of antibacterial cathelicidin. The cultures were infected with 10^3 *E.coli* O157 (bacteria to cell ratio: 100), centrifuged, and further incubated for 20 minutes with medium speed at 37°C. The harvested pellet and supernatant was plated into eosin-methylene blue (EMB) medium to determine colony forming unit (CFU). **Results:** expression of cathelicidin was increased among 10^{-10}M, 10^{-9}M, 10^{-7}M, 10^{-6}M and decreased among 10^{-8}M compared to 0 ($p>0.05$). There were significant higher mean of bacteria survival among 10^{-9}M, 10^{-7}M, 10^{-6}M, 10^{-10}M on pellet and 10^{-9}M, 10^{-7}M, 10^{-6}M on supernatant compared to 0 ($p<0.05$). This means in the dose of 10^{-8}M vitamin D, the bacteria survival was not increased significantly or in other word the bactericidal function of neutrophil become more efficient however the cathelicidin expression was decreased. **Conclusion:** vitamin D increases bactericidal function of neutrophil independent to cathelicidin in patient with SLE. ***Key Word:*** Vitamin D, neutrophil, *Escherichia coli*, SLE.

ICW-B2-1

Effect of anti-High mobility group box 1 antibody for nephritis in MRL/*lpr* lupus-prone mice

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Conflict of interest: None

[Objectives] High mobility group box 1 (HMGB1) is a ubiquitous non-histone nuclear protein that exerts proinflammatory functions in the extracellular milieu. Here we evaluate the efficacy of neutralizing anti-HMGB1 monoclonal antibody (mAb) whether it ameliorates nephritis in MRL/*lpr* lupus-prone mice. [Methods] We administered the anti-HMGB1 mAb (5 mg/kg weight) neutralizing ICAM-1-inducing activity of HMGB1 *in vitro* or class-matched control IgG2a intravenously twice a week from 4 to 15 weeks. Urine albumin was monitored every 2 weeks and histological evaluation of kidneys was conducted at 16 weeks. Anti-ds DNA antibody titers, cytokines and chemokines were also evaluated. [Results] Anti-HMGB1 mAb tended to reduce the albuminuria compared to an isotype control at 16 weeks. Consistent with the urinary albumin excretion, histological score of the kidney also tended to be attenuated and the complement deposition was improved. There're no significant differences in the glomerular infiltrations of F4/80 positive cells, while the infiltrations of Ly-6B positive neutrophils were significantly suppressed. Despite its effectiveness in nephritis, antagonizing HMGB1 treatment didn't show significant reductions of serum cytokine and chemokine levels and their mRNA expressions in kidney, such as IFN-alpha, TNF-alpha and IL-6. Moreover the anti-dsDNA antibody titer increased by anti-HMGB1 antibody treatment. The glomerular depositions of whole IgG, IgG2a and IgG3 were similar in the two groups. The serum HMGB1 level and the renal gene expression were not altered. The weights of lymphoid tissues were almost similar and ^{18}F-FAC-PET/CT also showed the similar accumulation in cervical and axilla lymph nodes in the two groups. [Conclusion] Anti-HMGB1 mAb demonstrated therapeutic potential against lupus nephritis through inhibiting neutrophil recruitments, but serological deterioration might blunt the effectiveness.

ICW-B2-2

The $CD4^+CD52^{low}$ T cell Contributes to Disease Activity and Autoantibody Production in Systemic Lupus Erythematosus

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Conflict of interest: None

Object: CD52 is a cell-surface glycoprotein that is widely expressed in lymphocytes, monocytes and eosinophils. $CD4^+CD52^{high}$ T cells inhibit the activation of $CD4^+CD52^{low}$ T cells through the release of cell-surface CD52. Soluble CD52, which is cleaved from $CD4^+CD52^{high}$ T cells, works as a ligand of siglec-10 on $CD4^+CD52^{low}$ T cells (Nat Immunol. 2013: 14:741-8.). $CD4^+CD52^{high}$ T cells were reported as distinct population from conventional regulatory T cells. The role of the immune regulation of these cells in systemic lupus erythematosus (SLE) is unknown. We evaluated the $CD4^+CD52^+$ T cells in the human peripheral blood mononuclear cells (PBMCs) of SLE patients and clarified their roles in the pathogenesis of SLE. Methods: We isolated the PBMCs of 58 SLE patients, 22 non-SLE patients (19 with rheumatoid arthritis, 3 with mixed connective-tissue disease) and 33 healthy controls (HCs). The expressions of $CD4^+CD52^{high}$ T cells and $CD4^+CD52^{low}$ T cells were analyzed by flow cytometry. We also analyzed the correlations with clinical parameters including SLEDAI, anti-ds-DNA antibodies and complement. We then analyzed circulating follicular helper like T cells (Tfh like cells) identified as $CD4^+CXCR5^{high}ICOS^{high}PD\text{-}1^{high}$ and plasmablast identified as $CD3^-CD19^+CD38^+CD27^+$. Results: We found that the expression of $CD4^+CD52^{low}$ T cells in the SLE was significantly higher than HC and non-SLE. The expression of $CD4^+CD52^{low}$ T cells of the SLE were positively correlated with SLEDAI, anti-ds-DNA antibodies and IgG. The $CD4^+CD52^{low}$ T cells were reduced after induction of intravenous cyclophosphamide therapy for SLE (N=5). The population of Tfh like cells were increased in SLE and its expression was positively correlated with $CD4^+CD52^{low}$ T cells. Conclusions: Collectively, our data suggest that increased $CD4^+CD52^{low}$ T cells along with increased Tfh like cells are involved in the pathogenic autoantibodies production highlighting its potential as a therapeutic target for SLE.

ICW-B2-3

miR-200a-3p regulates IL-2 production in SLE derived T cell by targeting C-terminal binding protein-2 (CtBP2)

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Conflict of interest: None

【Objective】MicroRNAs are involved in epigenetic mechanism and play an important role as post-transcriptional regulators in the pathogenesis of SLE. IL-2 hypoproductivity in SLE has been reported and we hypothesized that miRNAs may be involved in the pathobiology. In this study, CD4+T cells were isolated from spleen of MRL/lpr lupus model mice and C57BL/6J mice as a control. Total RNAs were purified and analyzed by next generation sequencing to compare miRNA and mRNA profiles between two groups, respectively. The number of leads for miR200a-3p was significantly downregulated in MRL/lpr mice (0.10) compared to control (5.32) (p=0.03). CtBP2 was identified as a possible target of miR200a-3p since it was significantly upregulated in mRNA level in MRL/lpr mice with 53-fold change. CtBP2 has been reported as a negative transcription factor of IL-2, thus we examined the role of miR200-3p in increased expression of CtBP2 and subsequent defects of IL-2 production in lupus T cells.【Methods】MiR200a-3p was transfected in EL4 mice T cell line and the level of mRNA and protein of CtBP2 were examined by real time PCR (RT-PCR) and western blotting, respectively. MiR200a-3p overexpressed cells were stimulated with phorbol 12-myristate 13-acetate (PMA) (10ng/ml) and ionomycin (1uM). After 6 hours stimulation, cells and supernatant were harvested and IL-2 level were examined by RT-PCR and ELISA. Luciferase plasmid containing IL-2 promoter region was transfected with miR200a-3p, then luciferase activity was evaluated after 24 hours stimulation.【Results】 In EL4 cell with miR200a-3p overexpression, CtBP2 was significantly downregulated while mRNA and cytokine level of IL-2 was upregulated. IL-2 promoter activity was also elevated under the miR200a-3p overexpression.【Conclusion】IL-2 production was elevated after miR200a-3p overexpression. Our data suggested that reduction of miR200a-3p is functionally associated with suppression of IL-2 production through CtBP2 in SLE T cell.

ICW-B2-4

Decreased frequency and activated phenotype of blood CD27+IgG+B lymphocytes in systemic lupus erythematosus patients

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Conflict of interest: Yes

Objective: In systemic lupus erythematosus (SLE) patients, the char-

acteristics of blood IgG+B cells that associated with IgG production were not well clear. And, whether follicular helper T (Tfh) cells are associated with IgG+B cells remains largely unknown. *Methods:* A total of 37 newly-diagnosed SLE patients and 21 healthy controls (HC) were enrolled for this study. B lymphocyte subsets (analysed by flow cytometry) were compared. The frequency of IgG+B cells including CD27-IgG+B cells and CD27+IgG+B cells, the expression of activation makers including CXCR3, CD86 and CD95 on IgG+B cells, and the percentage of circulating Tfh cells as well as its subsets were analyzed by flow cytometry. The role of Tfh cells on the activation of IgG+B cells was investigated in a co-culture system. *Results:* A subset of activated memory B cells with an activated phenotype was increased in patients with SLE and correlated with disease activity and serologic abnormalities. The frequency of CD27+IgG+B cells reduced in SLE patients in comparison with HC, while the activation of CD27+IgG+B cells increased with elevated expression of CD95, CD86 and CXCR3. Meanwhile, circulating Tfh cells (CD4+CXCR5+PD-1+), Tfh2 cells (IL-4+CXCR5+) and Tfh17 cells (IL-17+CXCR5+) as well as Tfh21 cells (IL-21+CXCR5+) were significantly expanded in SLE patients. Circulating Tfh cells from SLE patients were better able to promote the expressions of CD86 and CD95 on CD27+IgG+B cells compared with those in HC in co-culture system. Blocking with IL-21 with IL-21R FC Chimera, the expression of CD86 and CD95 on CD27+IgG+B cells induced by Tfh cells decreased in SLE patients. *Conclusion:* The immune dysfunction of SLE patient is associated with reduction and activation of CD27+IgG+B cells as well as balance disorders of Tfh subsets. The Tfh cells contribute to the activation of CD27+IgG+B cells by producing IL-21 in patients with SLE.

ICW-B2-5

Characteristic expression of chemokine receptor and its relevance to differentiation of B cells in patients with Systemic lupus erythematosus (SLE)

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Conflict of interest: None

Objectives: SLE is characterized by an expanded population of peripheral memory B cells. However, little is known about the qualitative abnormality of B cells associated with pathogenesis of SLE. We assessed the subset classification of B cells by chemokine receptor expression and differentiation mechanisms of those subsets. **Methods:** PBMCs obtained from subjects with 56 SLE, 31 patients with rheumatoid arthritis (RA) and 8 healthy donors (HD) were analyzed. B cell subsets were categorized by expression of chemokine receptors such as CXCR3 and CXCR5. Additionally, pan B cells obtained from HDs were cultured 4 days under stimulation with B cell receptor, co-stimulatory molecules and cytokines such as IL-21 and type I/II interferons (IFNs), and we assessed the expression of chemokine receptors and transcription factors by multi-color flow cytometry. **Results:** 1) The proportion of $CD19^+CD20^+IgD^-CD27^-$ effector memory B cells has significantly increased in SLE compared to HD and RA ($p<0.01$). 2) The proportion of $CD19^+CD20^+CXCR5^-$ B cells and $CD19^+CD20^+CXCR3^+$ B cells has significantly increased in SLE compared to HD and RA. Those tendencies were remarkably noted in $CD19^+CD20^+IgD^-CD27^{+/-}$ memory B cells ($p<0.01$). 3) CXCR5 expression was decreased in cultured B cells stimulated by BCR, CD40 ligands and IFN-β($p<0.05$). 4) CXCR3 expression was increased in cultured B cells stimulated by BCR, CD40 ligands and IFN-γ($p<0.01$). **Conclusion:** The results indicated that B cell abnormality in SLE is characterized by not only quantitative increase of peripheral memory B cells but abnormal expression pattern of chemokine receptors with lost of CXCR5 and up-regulation of CXCR3, indicating a potential of preferential migration into peripheral organs. Furthermore, in vitro experiments revealed that type I/II IFNs are a potent inducer of effector memory B cells involving abnormal chemokine receptor expression, suggesting an importance of these cytokines for the pathogenesis of SLE.

ICW-B2-6

Anti-Suprabasin Antibody: Identification of a Novel Antibody for neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

[Objectives]: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious complication in systemic lupus erythematosus (SLE). It is often difficult to diagnose and distinguish from those of other diseases, because no specific antibodies for NPSLE have yet been detected. **[Methods]**: We developed a novel proteomic strategy for identifying and profiling antigens in immune complexes (ICs) in the cerebrospinal fluid (CSF) of 26 NPSLE patients. We used the CSF of 15 patients with multiple sclerosis (MS), 16 patients with neuromyelitis optica (NMO) and 13 patients with viral meningitis (VM) as a disease control group. We performed *in vitro* experiments using astrocytes and analyzed functional change by microarray.**[Results]**: We identified ICs of suprabasin (SBSN), a molecule which is thought to play a role in epidermal differentiation. We assessed the antibody titer of SBSN using the Gaussia luciferase (GL) immunoprecipitation method, which uses a fusion protein of SBSN and GL as a reporter. We found that the titer of CSF/serum antibody titer of SBSN is significantly higher in NPSLE compared to other groups. The astrocytes exposed to anti-SBSN antibody with lipopolysaccharide (LPS) for 24 h induced interleukin (IL)-6. Microarray data showed that the senescence and autophagy pathways, as well as the transforming growth factor beta (TGF-beta) signaling pathway, were significantly changed in astrocytes with anti-SBSN antibody exposure compared to normal immunoglobulin G (IgG) exposure.**[Conclusion]**: These findings indicate that SBSN could be a novel autoantibody for the evaluation of suspected NPSLE, and may help elucidate the pathogenesis underlying this disease.

ICW-B3-1

Gelsolin level correlates with the progression of rheumatoid arthritis, maybe a new biomarker for prognosis and treatment

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Conflict of interest: None

Objectives Gelsolin, an actin scavenging protein, was involved in many inflammatory diseases, including rheumatoid arthritis (RA). However, the mechanism of gelsolin in RA was poorly understood. In the present study, we aimed to investigate the relationship between gelsolin expression and RA progression, and the effect of treatment on gelsolin expression. Methods Serum and synovial fluid were collected from 27 cases of active RA patients, including 11 cases of patients with effective DMARDs treatment (DAS28<3.2) and 16 cases of untreated patients, and 15 cases in remission of RA. Western blot was performed to measure gelsolin expression, using osteoarthritis (OA) samples as control. Results In active RA, gelsolin expression was significantly decreased in both serum and synovial fluid, compared with that in OA (62.56 ± 31.36 versus 92.17 ± 18.59 mg/L, p=0; 44.73 ± 21.41 versus 59.14 ± 16.88 mg/L, p=0.008). Gelsolin expression in serum of active RA was dramatically lower than that of patients in remission (62.56 ± 31.36 versus 83.24 ± 29.02 mg/L; p=0.042), but there was no difference of gelsolin expression in serum of RA in remission compared with that from OA patients (83.24 ± 29.02 versus 92.17 ± 18.59 mg/L; p=0.28). Interestingly, in effective DMARDs-treated group (DAS28<3.2), gelsolin expression in serum and

synovial fluid was dramatically higher than those in untreated group (81.30 ± 27.77 versus 49.67 ± 27.48 mg/L, p=0.0072; 55.64 ± 25.88 versus 37.24 ± 14.17 mg/L, p=0.05). Conclusions Gelsolin expression was decreased in both serum and synovial fluid from active RA patients, but was increased with effective DMARDs treatment. In the remission phase of RA, gelsolin expression was consistent with that in OA. These data suggest that gelsolin is a promising biomarker for therapy and prognosis of RA.

ICW-B3-2

T cell and B cell responses to Mycobacterium heat shock protein 70 in rheumatoid arthritis and their corellation with autoimmune responses to BiP.

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Conflict of interest: None

Objective. The immunological linkage between human heat shock proteins (HSPs) and Mycobacterium (Myc) HSPs was examined in rheumatoid arthritis (RA). Methods. Serum antibodies (Abs) to human and MycHSPs in RA were measured by ELISA. Proliferations of PBMCs from HLA-DR4+ RA in response to MycHSP70 and BiP epitopes were examined by ^{3}H-thymidine uptake and cytokine (IL-17 and IFN-gamma) secretions were measured by ELISA. HLA-DR4-Tg mice were immunized with MycHSP70 and immune responses to BiP was analyzed. MycHSP70 epitope was orally administered to collagen-induced arthritis (CIA). Results. Serum anti-MycHSP70 Abs were significantly elevated in RA and correlated with anti-BiP Abs. The major HLA-DR4 epitope, MycHSP70$^{287\text{-}306}$, was identified as a potent inducer of PBMC proliferation and cytokine secretion, and was located at the corresponding position in the human BiP major epitope, BiP$^{336\text{-}355}$. PBMC proliferations in response to these epitopes were highly correlated. Immunization with MycHSP70 induced T cell proliferation to BiP and anti-BiP Abs. Oral administration of MycHSP70$^{287\text{-}306}$ resulted in amelioration of CIA and suppressed immune responses to BiP. Conclusion. Immune responses to MycHSP70 were associated with autoimmunity to BiP based on molecular mimicry of T cell epitopes.

ICW-B3-3

Therapeutic application of human mesenchymal stem cells with a novel delivering scaffold for the treatment of rheumatoid arthritis

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Conflict of interest: None

Objectives. Mesenchymal stem cells (MSCs) differentiate into a variety of cells which constitute joint tissues, and exhibit immunoregulatory property. The aim of this study is to clarify regulatory mechanism of nano-fiber scaffold as a novel delivery system of MSCs for treatment of rheumatoid arthritis (RA). **Methods.** Human bone marrow-derived MSC was injected into collagen-induced arthritis (CIA) rats intra-articularly (IA) or implanted into ankles after seeded on nano-fiber (Nano-hMSC). After 6 weeks, effect of MSC on CIA by arthritis score and X-ray image, serum anti-collagen antibody level, and distribution of MSC in rat tissue of inoculation of GFP-labeled MSC were assessed. We further measured transforming growth factor (TGF) -β1 level after cultivating MSC seeded on nano-fiber. **Results.** Treatment with nano-hMSC significantly suppressed arthritis score in CIA rats, whereas IA treatment showed no effects. Furthermore, Nano-hMSC rat improved bone destruction, which is evaluated by X-ray images or HE staining, to be similar level as those from wild-type (WT) rat. Serum anti-collagen antibody level was markedly decreased in Nano-hMSC rat compared to IA-treated CIA rat. The size and weight of spleen or lymph nodes (LN) and germinal center formation from Nano-hMSC rat was comparable with that from WT rat. Inoculation of MSC transfected with GFP showed that MSC remained within implanted ankles and did not migrate to other organs. MSC cultured on nano-fiber showed increased TGF-β1 production compared to MSC cultured on plate. **Conclusion.** The data indicated that implanted Nano-hMSC remains around local joint tissues and efficiently suppressed arthritis and joint destruction through a remote anti-inflammatory and immunoregulatory action via TGF-β1 production. These results suggested a potential clinical application of MSC-based treatment by utilizing nano-fiber scaffold for treatment of RA.

ICW-B3-4

Comprehensive Novel Proteomic Analysis of Untreated RA Synovial Fluid Identified Distinct Protein Profiles of Bone and Cartilage Metabolism and Relationships with Inflammatory Cytokines

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Conflict of interest: None

Object: To clarify the synovial fluid (SF) specific protein profiles. **Methods:** SF was collected from untreated 10 RA and 10 OA patients. A total of 1128 proteins were quantitatively measured by comprehensive high-throughput proteomics assay using nucleic acid aptamers. (SOMAscan™ Assay; Somalogic Inc., CO, USA). We statistically extracted differentially expressed proteins (DEP) in RA SF and OA SF. Ontology analysis was underwent using Ingenuity Pathway Analysis (IPA) Knowledge database (Ingenuity® Systems, www.ingenuity.com). **Results:** A total of 309 DEP and 122 of known protein ontologies were extracted from RA SF. RA SF proteins were not only associated with inflammatory signals but also strongly associated with "role of osteoblasts, osteoclasts and chondrocytes", "IL-6 signaling" and "STAT3 pathway". Next, we focused on the SF inflammatory cytokines and proteins associated with bone and cartilage metabolism. SF IL-6 was significantly increased in RA SF but TNF-α was not significant. (IL-6; p<0.001, TNF-α; p=0.406) Bone morphogenic protein (BMP) -7 which promote osteogenesis and RANKL-RANK signaling proteins including osteoprotegerin were significantly decreased in RA SF than OA SF. (BMP-7; p<0.001, soluble RANKL; p=0.025, osteoprotegerin; p=0.032.) Remarkably, dickkopf (Dkk)-1 which negatively regulated Wnt signaling pathway were also suppressed in RA SF. (p<0.001) Furthermore, Dkk-1, soluble RANKL and OPG were negatively correlated with SF IL-6 levels but not associated with TNF-α in RA SF. (IL-6 and DKK-1; rho=-0.64, p=0.047, soluble RANKL; rho=-0.66, p=0.038, OPG; rho=-0.66, p=0.038) **Conclusion:** Our results from proteomic analysis has thrown light distinct human RA SF protein profiles of bone and cartilage metabolism and relationships with IL-6 in affected joint.

ICW-B3-5

Significant impact of miRNA-target gene networks on the genetics of rheumatoid arthritis

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Conflict of interest: None

Objective MicroRNA (miRNA), a short endogenous noncoding RNA, plays major roles in a variety of biological processes. However, its impact on the genetics of human complex traits has not been fully assessed. We aimed to develop a novel analytical method to comprehensively evaluate the enrichment of genome-wide association study (GWAS) signals in miRNA-target gene networks, which was implemented as **MIGWAS** software. **Methods** We obtained GWAS results of the

18 human complex traits, that comprises in total >1.75 million subjects. Relative enrichment of the association signals between miRNAs and target genes predicted by the multiple public databases (miRDB, miRmap, PITA, and TargetScan) was evaluated through permutation test (×10,000 iterations). **Results** Of the 18 evaluated traits, rheumatoid arthritis (RA), kidney function (eGFR), and adult height exhibited significant enrichment of the association signals in miRNA-target gene networks ($P < 0.05/18 = 0.0028$, most significant enrichment in RA with $P = 1.7 \times 10^{-4}$), which were generally consistent with current literature-based knowledge obtained from NCBI PubMed database (adjusted $P = 0.024$). Our method provided a list of miRNA and target gene pairs with excess genetic association signals, part of which included drug target genes. **Conclusions** Our study indicated significant impact of miRNA-target gene networks on the genetics of human complex traits, especially on RA, and provided resources which should contribute to drug discovery and nucleic acid medicine.

ICW-B3-6

Cell-type-specific Effects of the Risk Alleles of Rheumatoid Arthritis and Systemic Lupus Erythematosus in Primary Human Immune Cells

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Conflict of interest: Yes

Objectives: Genome-wide association study (GWAS) identified multiple risk alleles of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is broadly accepted that majority of GWAS risk alleles affect gene expression and the consequent modulations in the transcriptome increase the risk of developing diseases, because they are enriched in the enhancer regions. Contrary to the robustness of the associations between the GWAS risk alleles and disease development, the detailed mechanisms how they disturb the immune system and cause autoimmunity is not well elucidated. In order to unveil those mechanisms, we investigated the linkage between genetic polymorphisms and transcriptome variations of primary human immune cells. Methods: We performed RNA-seq of FACS-sorted $CD4^+$ T cells (CD4T), $CD8^+$ T cells (CD8T), B cells, monocytes and NK cells and whole peripheral blood (PB) of 110 Japanese healthy volunteers. We also genotyped those volunteers. By examining the associations between individual genotype and transcriptome in each sample, we searched for cell-type-specific expression quantitative trait loci (eQTLs) whose variants regulate gene expressions. Results: We identified on average 6384 genes whose expression was influenced by genotypes of eQTLs. We assessed the enrichment of GWAS risk alleles (including SNPs linkage disequilibrium with $r^2>0.8$) within eQTLs in each cell type, and found 31 out of 75 RA risk alleles and 18 out of 42 SLE risk alleles were overlapped with eQTLs in at least one of six cell types (enrichment p-values were $4.5\text{x}10^{-6}$ and $2.7\text{x}10^{-4}$, respectively), indicating those GWAS risk alleles were linked to overlapped eQTLs and exert a pathogenic function though modulating corresponding gene expression in associated cell types (e.g. CCR6 in B cells of RA and IRF5 in B cells of SLE). Conclusion: By combining the results of GWAS and eQTL analysis, we found several candidates of causal genes and cell types in RA and SLE.

ICW-B4-1

The epigenetic mechanism of constitutive and IL-6-induced MMP gene activation in rheumatoid arthritis synovial fibroblasts

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Conflict of interest: None

Objectives. Rheumatoid arthritis (RA) synovial fibroblasts (SFs) produce matrix metalloproteinases (MMPs) that degrade articular cartilage. Epigenetic mechanisms, including histone modifications, are considered to be important regulators in gene transcription. We hypothesized that epigenetic dysregulation might activate RASFs. Here we examined whether the IL-6 signal upregulated MMP expression in RASFs and whether the histone modifications were associated with the MMP gene activation in RASFs. Methods. We examined MMP expression and histone methylation in their promoters after IL-6 stimulation in RASFs and osteoarthritis (OA) SFs. We investigated the change in the MMP gene expression after the silencing of WDR5 that is required for the histone modification of H3K4me3, an active histone marker. We examined the IL-6 signaling pathway and binding of STAT3 to the MMP promoters after IL-6 stimulation in RASFs and OASFs. Results. MMP1, 3, 9 and 13 genes were actively transcribed in RASFs. The histone methylation profiles (H3K4me3 and H3K27me3) and the result of micrococcal nuclease assay indicated that the chromatin structure was open in the MMP1, 3, 9 and 13 promoters in RASFs. The depletion of WDR5 reduced the levels of H3K4me3 and the MMP1, 3, 9 and 13 gene expression. Interestingly, the IL-6 signal significantly increased the expression of MMP1, 3 and 13, but not MMP9, in RASFs. Although cell surface expressions of gp130 and IL-6Rα were comparable and STAT3 was similarly phosphorylated after IL-6 stimulation in RASFs and OASFs, STAT3 bound to the MMP1, 3 and 13 promoters, but not the MMP9 promoter, after IL-6 stimulation only in RASFs. It was suggested that binding of STAT3 to the promoters resulted in MMP1, 3 and 13 gene activation after IL-6 stimulation in RASFs. Conclusion. Histone methylation and binding of STAT3 to the promoters regulate constitutive and IL-6-induced MMP gene activation in RASFs and possibly arthritogenic properties of RASFs.

ICW-B4-2

A Novel Transcription Factor NFAT5 Plays an Important Role in Toll-like Receptor 4 signaling pathway of the activity of Rheumatoid Arthritis Synovial Fibroblasts

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Conflict of interest: None

Objectives: To investigate the role of novel transcription factor NFAT5 in Toll-like receptor (TLR) 4 signaling pathway in the inflammatory response of RA synovial fibroblasts (RASF). **Methods:** Recombinant human neutrophil-derived lactoferrin (LTF) was used as one of TLR4 ligands. RASF were treated with LTF and/or TNFα, and the expression of proinflammatory cytokines, such as IL-6, IL-8 and CCL20 in RASF was measured by RT-qPCR and ELISA. To repress the TLR4 signaling pathways, a small molecular inhibitor of TLR4 (TAK242), NF-kB inhibitor (BMS345541), and p38MAPK inhibitor (SB202190) was used. The role of NFAT5 in the TLR4 signaling pathway in RASF was investigated using a small interfering RNA targeting NFAT5. **Results:** Stimulation of RASF with LTF significantly increased the expression of IL-6, IL-8 and CCL20 mRNA and the levels of protein (p=0.01). Furthermore, LTF enhanced the expression of these cytokines mRNA in RASF stimulated by TNFα. TAK242 repressed the expression of these cytokines and chemokines in RASF stimulated by LTF. BMS345541, but not SB202190, repressed the expression of IL-6 and IL-8 mRNA induced by LTF. However both BMS345541 and SB202190 did not repress the expression of CCL20 mRNA. On the other hand, silencing of NFAT5 significantly decreased the expression of not only IL-6, IL-8 but also CCL20 mRNA in RASF treated by LTF. **Conclusion:** These findings suggest that NFAT5 play important role as critical regulator in the proinflammatory response of RASF mediated by TLR4 signaling pathway.

ICW-B4-3

IL-17A promotes rheumatoid fibroblast-like synoviocytes migration and proliferation by increasing the accumulation of p62

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Conflict of interest: None

Objectives: Both autophagy and interleukin-17A (IL-17A) promote the migration and proliferation of fibroblast-like synoviocytes (FLS), which are critical for the pathogenesis of rheumatoid arthritis (RA). However, IL-17A induced autophagy is not reported on the effect on cell proliferation and migration in RA-FLS. In this study, we observed that RA-FLS exposed to IL-17A experienced autophagy flux, with cell migration and proliferation. **Methods:** RA synovial tissue and fibroblast were obtained from patients during total knee replacement surgery or arthroscopy. Primary cultured FLS was cultured under IL-17A, autophagy inducer or inhibitor. Autophagy flux (LC3B, Beclin1, Atg5, p62) and autolysosome marker LAMP1 protein expression were analyzed by western blot. Functional mechanisms were quantified by proliferation and migration assays. **Results:** The expression of autophagosome markers (LC3B, Atg5, Beclin1) was increased in RA-synovium than in that of OA-synovium. Similarly, RA-FLS showed a high expression of autophagy flux compared with OA-FLS. The accumulation of p62 was more prominent in RA-FLS than in OA-FLS. Moreover, IL-17A was augmented the accumulation of p62 in RA-FLS. Treatment of autophagy inhibitor bafilomycin A1 were decreased cell migration and proliferation in FLS by decreasing the accumulation of p62. **Conclusions:** Our results suggest that regulation of autophagy flux suppresses RA progression by recovering dysfunction of autophagy flux. Thus, autophagy will be used as a tool for the management of autoimmune diseases such as rheumatoid arthritis.

ICW-B4-4

The epigenetic induction of aggressive phenotype of fibroblast-like synoviocytes (FLS) in rheumatoid arthritis (RA), the role of DNA demethylation enzyme TET3

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Conflict of interest: None

【**Objective**】FLS plays an important role in joint destruction in RA, but its epigenetic control of the FLS remains unknown. We here assessed a novel DNA demethylation enzyme, TET, in cytokine-mediated activation of FLS during pathological processes of RA. 【**Methods**】Gene expression was determined by qPCR and protein expression by WB and immunostaining. 5-hmC was determined by dot blot. Cell migration was assessed using a scratch assay. TET3 KO and WT C57BL/6J mice were injected with K/BxN KO and WT C57BL/6J mice were injected with K/BxN sera to induce arthritis. 【**Results**】TET3 is co-expressed with CD55 in the intimal lining layer of synovium in patients with active RA. In vitro stimulation with TNFa and IL-1b for 2 hrs significantly increased TET3 mRNA expression in FLS. TET3 protein expression and 5-hmC in RA FLS was significantly increased by stimulation with TNFa within 48 hrs and 96hrs, respectively. TET3-knockdown of FLS with siRNA not only inhibited TNF-induced expression of key migratory genes, including CCL2 and ICAM-1, but also reduced TNF-induced FLS-migration completely. Although there was no significant difference in arthritis score between each group, Tet3 KO mice showed reduced joint destruction. 【**Conclusion**】Our findings indicate that persistent exposure to pro-inflammatory cytokines in the synovium increases TET3 expression, resulting in aggressive phenotype of FLS via DNA demethylation and severe joint destruction. Targeting TET3 may be a therapeutic strategy for preventing FLS from cytokine-mediated imprinting in RA.

ICW-B4-5

Osteogenic differentiation of fibroblast-like synovial cells in Rheumatotid arthritis is induced by microRNA-218 through ROBO/Slit pathway

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Conflict of interest: None

Background Inhibition of fibroblast-like synovial cells (FLS) proliferation is one of the therapeutic targets of RA. Moreover FLS have multilineage differentiation potential including osteoblasts. Therefore induction of osteogenic differentiation in proliferated FLS might become superior treatment. **Objective** To investigate the role of microRNAs during osteogenic differentiation of RA-FLS. **Methods** RA-FLS was differentiated in osteogenic medium for up to 3 weeks. Osteogenic differentiation was evaluated by ALP staining and alizarin red staining. Expression of miR-218 during osteogenic differentiation of RA-FLS was analyzed by quantitative real-time PCR. To identify target of miR-218, RA-FLS was transfected with miR-218 precursor and inhibitor. Then, we analysed osteogenic differentiation after overexpression/knockdown of miR-218. ELISA was used to measure DKK-1 from FLS transfected with miR-218 precursor/inhibitor or ROBO1 knockdown FLS using ROBO1-siRNA. **Results** Differentiation of RA-FLS into osteoblast was evidenced by ALP staining, alizarin red staining and up-regulation of ALP and RUNX2 mRNA expression. The miRNA array revealed that 12 miRNAs were up-regulated and 24 miRNAs were down-regulated during osteogenic differentiation. Among them, miR-218 was further characterized because of its consistent differential expression. MiR-218 was down-regulated during osteogenic differentiation of RA-FLS ($20 \pm 5\%$, $p<0.0001$, $n=5$). Induction of miR-218 in RA-FLS decreased ROBO1 expression. Conversely, the knockdown of miR-218 increased the expression of ROBO1. Finally, miR-218 promoted osteogenic differentiation of RA-FLS through DKK-1 suppression caused by down-regulation of ROBO1. **Conclusion** This is the first demonstration to our knowledge that microRNAs regulate osteogenic differentiation of RA-FLS. Our results showed that miR-218 modulate osteogenic differentiation of RA-FLS through ROBO1/DKK-1 axis. This attractive hypothesis needs to be further tested in animal models.

ICW-B4-6

Glutaminase1 inhibitor inhibits synoviocytes proliferation and ameliorates inflammatory arthritis in mice

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Conflict of interest: None

【Objectives】Cancer cells consume glucose and glutamine at a high rate compared to normal cells. Synovial fibroblasts from RA patients (RASFs) is known to have several tumor-like characteristics. However, whether RASFs show enhanced glycolysis and glutaminolysis or not, is unknown. We aimed to elucidate the metabolic characteristics of RASFs, and discover a novel therapeutic target of RA by metabolomic approach. 【Methods】The intracellular metabolites in synoviocytes were analyzed by gas chromatograph mass spectrometer (GC/MS). The expression of metabolic enzymes was evaluated by real-time PCR and Western blotting. siRNA and compound 968 were used to inhibit glutaminase (GLS)1. Arthritis was induced in SKG mice by zymosan A injection. SKG mice were treated with compound 968. 【Results】GC/MS-based metabolome analysis revealed that the levels of many metabolites were different between RASFs and OASFs, and suggested that glutamine metabolism was increased in RASFs. The levels of GLS1 mRNA and protein were increased in RASFs. The expression of GLS1 mRNA in RASFs was increased after stimulation with IL-17 or PDGF. Cell proliferation of RAS-

Fs was suppressed by knocking down the GLS1 or treatment with compound 968, an inhibitor of GLS1. Furthermore, i.p. injection of compound 968 ameliorated autoimmune arthritis in SKG mice.【Conclusion】Glutamine metabolism was involved in the pathogenesis of RA. GLS1 could be a novel therapeutic target in rheumatoid arthritis.

ICW-B5-1

Involvement of M2 Macrophages in the Pathogenesis of Arthritis in a Mouse Model

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Conflict of interest: None

Background: Synovial macrophages play an important role in initiating and maintaining joint inflammation in arthritis. Classically activated pro-inflammatory macrophages and alternatively activated anti-inflammatory macrophages are generally referred to as M1 and M2 macrophages, respectively. The CD163, CD204, and CD206 proteins are predominantly expressed by M2-phenotype macrophages. The restrictive expression of CD163 by the monocyte-macrophage has been confirmed and it has been demonstrated to be expressed in the affected joint tissues obtained from patients with RA and spondyloarthropathy; However, the pathogenic role of M2 macrophages in inflammatory arthritis remains unclear. We investigated the involvement of M2, CD163 and CD 204 positive macrophages in the development of arthritis in mice. **Methods:** Collagen antibody-induced arthritis (CAIA) was induced using a combination of anti-collagen antibodies and LPS. C57BL/6 (B6) background CD163 KO mice and BALB/c background CD204 KO mice were used for CAIA. Histological grading of cartilage and bone erosion in the ankle sections were performed. Total RNA was isolated from mouse ankle joints. Gene expression of IL-1β and IL-6 was determined by RT-PCR. **Results:** CD163 KO mice exhibited significantly higher clinical scores for arthritis than did control mice. Histomorphometric quantification of arthritic changes in the joint tissues confirmed the clinical assessment, with significantly higher erosion scores in CD163 KO mice. Correspondingly, mRNA expression of IL-1β and IL-6 was significantly up-regulated in inflamed ankle joints of CD163 KO mice. CD204 KO mice were found to be normally susceptible to arthritis. **Conclusion:** Our present study is to identify the involvement of M2, CD163-positive macrophage in CAIA. CD163 deficiency exacerbates disease severity via up-regulation of synovial tissue IL-1β and IL-6 expression. CD163-positive M2 macrophage may play as an inhibitor in the pathogenesis of RA.

ICW-B5-2

MicroRNA-34a exacerbates murine collagen-induced arthritis via extensive T lymphocyte activation

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Conflict of interest: None

Objective: Rheumatoid arthritis (RA) is a systemic disease involving synovium hyperplasia and bone resorption. MicroRNA-34a (miR-34a), may participate in immune activation, bone metabolism and cell apoptosis. In this study, we aimed to investigate the effect of miR-34a on RA. **Material and Methods:** PBMC were obtained from RA patients and healthy donors. MiR-34a expression in PBMC was performed by real-time PCR analysis. The collagen-induced arthritis (CIA) mice were divided into two groups which were administered with miR-34a agomir and negative control respectively by iv injection. Arthritis severity was determined by clinical score, while joint destruction was determined by histopathology. Flow cytometry was performed to detect the subgroups of T lymphocyte, including Th1/Th2/Th17/Treg. Bone marrow osteoclastogenesis assays were utilized to value the effect of miR-34a on osteoclast differentiation. Expression of inflammatory cytokines in joints was assessed by real-time PCR. **Results:** Levels of miR-34a in the PBMC from RA patients were significantly lower than that in the healthy controls. However, *in vivo* administration of miR-34a exacerbates murine CIA. The incidence of arthritis in miR-34a agomir-treated mice was dramatically higher, accompanied with early onset of symptoms. The arthritis scores were elevated with miR-34a treatment with upregulated expression of inflammatory cytokines. MiR-34a-agomir delivery led to dramatically extensive T- lymphocyte activation. Nevertheless, bone marrow cells from miR-34a agomir-treated CIA mice exhibited the impaired osteoclastogenesis capacity. **Conclusion**: Although miR-34a expression was down-regulated in RA patients, *in vivo* delivery of miR-34a exacerbated the murine arthritis via extensive T cell activation, in despite of the impaired osteoclastogenesis capacity of bone marrow cells beneficially. Further cellular and molecular investigation is undertaken in order to explore more roles of miR-34a in autoimmune arthritis.

ICW-B5-3

Increased circulating CD14^{bright}CD16+ intermediate monocytes are regulated by TNF-α and IL-6 axis in patients with rheumatoid arthritis

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Conflict of interest: None

Objectives: Monocytes are divided into 3 subsets by the level of CD14/CD16 expression. CD16 is immunoglobulin gamma Fc region receptor III(FcγRIII). It is hypothesized that immune complex including ACPA activates inflammatory cells via Fcγ receptors and leads to produces inflammatory cytokines in rheumatoid arthritis (RA). It has been reported that the proportion of intermediate monocytes (CD14^{bright}CD16+ monocytes; Int-Mo) increased in patients with RA. However, the pathogenesis of increase of Int-mono is still unclear and the relationship between cytokines and Int-Mo is unknown particularly in RA. The purpose of this study is to investigate influence of anti-cytokine treatment on Int-Mo in RA patients. Methods: 32 RA patients and 14 healthy controls (HC) were enrolled. All patients had never received a treatment with methotrexate (MTX) or any biological agents. Blood samples and clinical records of the patients were sequentially obtained. Monocyte subsets are quantified by flow cytometry. Results: 8 patients received tocilizmab (TCZ) treatment alone, 12 patients received adalimumab (ADA) with MTX treatment and others received only MTX treatment. The proportion of Int-Mo significantly increased in patients at baseline compared with HC. The proportion of Int-Mo significantly decreased after TCZ and ADA treatment. Moreover, the proportion of Int-Mo was significantly and positively correlated with DAS28 score and DAS28 score decreased in accompany with Int-Mon after inhibition of cytokine signal. Conclusion: Int-Mo significantly decreased with the change of disease activity by key cytokines, IL-6 or TNF-α signal blockade. This result indicates that monocyte subsets are controlled by IL-6 and TNF-α axis and reflecting disease activity in RA.

ICW-B5-4

Distribution of peripheral blood Th22 cells and its relevance to the pathogenesis in rheumatoid arthritis

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Conflict of interest: None

Objectives. Although elevated levels of IL-22 in the synovial fluids of rheumatoid arthritis (RA) patients were reported, its pathological roles remain unclear. Th22 cells have been identified as a new subset secreting IL-22. We examined the frequencies of Th22 cells in peripheral blood and synovial tissue in a correlation with clinical findings in patients with RA. ***Methods.*** Circulating Th22 cells in 80 patients with active RA and 14 healthy controls (HC) were analyzed by multi-color flow cytometry. We evaluated the proportion of peripheral T helper subsets including Th22 cells before and after 24weeks treatment with biological DMARDs.

IL-22 producing $CD4^+$ T cells in synovial tissues in patients with RA and osteoarthritis (OA) were evaluated by immunohistochemistry. ***Results.*** The proportion of $CD3^+CD4^+CCR4^+CCR6^+CCR10^+$ Th22 cells was decreased in active RA, compared to HC, while other helper subsets such as Th1, Th17 or Treg cells did not differ between RA and HC. There was a negative correlation between the proportion of circulating Th22 cells and disease activity score in RA patients. According to the reduction of disease activity at week 24 after bDMARD treatment, the proportion of Th22 cells, but not other subsets, was significantly increased. IL-22 producing $CD4^+$ T cells were markedly infiltrated in synovial tissue in patients with active RA, whereas there were few IL-22 producing $CD4^+$ T cells in OA synovial tissues. ***Conclusions.*** The results revealed a decrease of Th22 cells in peripheral blood and an their increase in synovial tissue in patients with highly active RA. Th22 cells, which co-express chemokine receptors CCR4, CCR6 and CCR10, therefore, possess strong potency of tissue migration and accumulate into inflamed synovial tissues where the ligands such as CCL20 are highly expressed. Thus, Th22 cells may play a role in the pathogenesis of RA synovitis.

ICW-B5-5

Evaluation of pathophysiology of rheumatoid arhthritis byT cell repertoire analysis using next generation sequencing

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Conflict of interest: Yes

<Object> The diversity of T cell receptor (TCR) of CD4+ T cells is decreased in rheumatoid arthritis (RA). To investigate the significance of this phenomenon, we analyzed TCR repertoire and its association with disease activity. <Methods> TCR-beta CDR3 regions of peripheral CD4+ memory and naïve T cells from 18 RA patients and 21 age and sex-matched healthy donors were sequenced by next generation sequencer. Renyi entropy was used to comprehensively assess TCR repertoire diversity, and correlations with disease activity, concentrations of serum cytokines and other clinical parameters were examined. <Results> TCR repertoire diversity of both memory and naïve CD4+ T cells was significantly reduced in RA patients with high disease activity compared to healthy donors. The reduction of TCR diversity in memory CD4+ T cells generally suggests the existence of antigen specific immune responses in RA, and it was associated with the possession of HLA risk allele and increase in disease activity but not with serum proinflammatory cytokine concentrations. The reduction of TCR diversity in naïve CD4+ T cells may be a reflection of immune phenomenon related to homeostatic expansion and was associated with high disease activity. <Conclusion> Our data suggested that antigen specific immune responses of CD4+ T cells may contribute to the pathophysiology of rheumatoid arthritis in a different manner from proinflammatory cytokines.

ICW-B5-6

CXCL13-producing $CD4^+$ T cells induced by TGF-beta is similar to that in RA synovium

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Conflict of interest: Yes

【Object】 Ectopic lymphoid like structures (ELSs) are frequently observed in inflammatory sites of chronic diseases such as rheumatoid arthritis (RA). CXCL13, a crucial chemokine for the formation of ELSs, is mainly produced by $CD4^+$ T cells in RA synovium. RA synovial CXCL13-producing $CD4^+$ T cells fail to produce IFN-γ, IL-4 and IL-17, and are strongly affected by proinflammatory environment, implying that these cells are a distinct population involved in RA pathology. However, it is unknown how these cells are generated from $CD4^+$ T cells. 【Method】 Human naïve $CD4^+$ T cells obtained from peripheral blood of healthy donors were cultured with various cytokines, and were analyzed the CXCL13 production and other features. 【Result】 TGF-beta induced the differentiation of CXCL13-producing cells from naïve $CD4^+$ T cells in vitro. Interestingly, despite middle Foxp3 expression in CXCL13-producing cells, overexpression or knockdown of FoxP3 gene revealed that the expression of FoxP3 was not required for the differentiation of these cells. Consistently, neutralization of IL-2 and knockdown of both STAT5A and STAT5B clearly upregulated the CXCL13 production. As was reported in RA synovial $CD4^+$ T cells, TGF-b induced CXCL13-producing cells failed to produce IFN-γ, IL-4 and IL-17, and lacked Tfh signatures. Furthermore, proinflammatory cytokines induced the secondary CXCL13 production from reactivated CXCL13-producing $CD4^+$ T cells. TGF-beta-induced CXCL13-producing cells recruited cells expressing CXCR5, the receptor of CXCL13. 【Conclusion】 CXCL13-producing cells are differentiated via TGF-beta signaling and are regulated by inflammatory cytokines. It seems that the differentiation is favored by an IL-2-limited environment such as RA joints. Moreover, these cells have an ability to recruit cells. These findings imply that CXCL13-producing $CD4^+$ T cells play a role in the formation of ELSs by recruiting cells into inflammatory site.

ICW-B6-1

Association of Killer Cell Immunoglobulin- like Receptor Genes in Iranian Patients with Behcet's disease

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Conflict of interest: None

Background: Behçet's disease (BD) is a multi-organ vasculitis disorder, which is characterized by mucocutaneous and ophthalmological manifestations. It has been postulated that defects in natural killer (NK) cell repertoire may be involved, mainly through Killer cell Immunoglobulin-like Receptors (KIRs). The aim of this study was to genotype 16 KIR genes, 3 pseudo genes, and 6 HLA class I gene ligands in BD patients and control subjects. **Patients and Methods**: In this case-control study, KIR and HLA genes were genotyped by Sequence-Specific Primer Polymerase Chain Reaction (SSP-PCR) on genomic DNA of 397 BD patients (according to International Criteria for BD (ICBD)) and 300 age- and sex- matched healthy controls. Differences in the frequency of genes and haplotypes were determined by χ^2 test. **Results:** KIR-2DL3 showed a significant protection (OR=0.62, *P*=0.04, 95% CI=0.39-0.99) against BD which was operative only in women. A KIR full array genotype (2DL1/3/4/5, 3DL1/2/3, 2DS1/4/5, 3DS1, 2DP1, 3DP1) exerted a protective effect independent of HLA status (OR=0.55, *P*=0.04, 95% CI=0.31-0.97). An inhibitory KIR genotype (KIR2DL1/2/4/5a/5b, KIR3DL1/2/3) was associated with gastrointestinal disorders (OR=9.13, *P*=0.001, 95% CI= 3.02-27.62). **Conclusions:** As far as we know, we have provided the first report on association of full KIR/HLA haplotypes with Behcet's disease. Full KIR and inhibitory KIR genotypes have potential role in susceptibility and pathogenesis of Behçet's disease.

ICW-B6-2

DNA microarray analysis of labial salivary glands in patients with Sjögren's syndrome: comparison with IgG4-related disease

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Conflict of interest: None

Objective: To examine genes expressed specifically in labial salivary glands (LSGs) of patients with Sjögren's syndrome (SS) in comparison with those of patients with IgG4-related disease (IgG4-RD). Methods: 1) Gene expression was analyzed by DNA microarray in LSGs of SS, IgG4-RD and healthy controls (HC). Validation of differentially expressed genes (DEGs) up-regulated in SS was performed by quantitative PCR. 2) The protein production of validated genes in LSGs from SS and IgG4-RD was examined by immunofluorescence assay. 3) Expression and functional analysis of the DEG was performed using peripheral $CD4^+$ T cells of SS. Results: 1) Among 1320 DEGs up-regulated in SS, CXCL9, NR4A2, CD26, SGK1 and PDK1 were selected as candidates for validation. PCR validated significantly higher expression of NR4A2 and CD26 in SS than in IgG4-RD. 2) Immunofluorescence staining in LSGs revealed higher production of NR4A2 and CD26 in SS than in IgG4-RD and localization of NR4A2 in $IL\text{-}17^+$ and $CD4^+$ cells. 3) Higher expression of NR4A2 was observed in peripheral naïve $CD4^+$ T cells of SS and peripheral $CD4^+$ T cells showed increased Th17 polarization in SS compared with HC. Conclusion: NR4A2 and CD26 might be novel molecules involved in the pathogenesis of SS via regulation of T cells in salivary glands.

ICW-B6-3

Mast cells contribute to muscle regeneration, more than inflammation in the C-protein induced myositis model

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Conflict of interest: None

Objective Mast cells (MCs) function as the immune sentinel in tissue. The well-known cellular infiltrate in inflammatory myositis mainly consists of macrophages and lymphocytes that produce numerous inflammatory mediators augmenting inflammatory cell infiltration and myofiber damage. We aimed to study the phenotype and role of MCs in a murine myositis model. **Methods** C-protein induced myositis (CIM) was induced in MC-deficient SASH mice and controls (C57BL/6). Tissue inflammation was evaluated in hematoxylin & eosin (H&E) stained sections via a scoring system of 0-4. Immunohistochemistry (IHC) of mouse MC protease (mMCP) -1, -4, -5, -6, CD8 and measurement of serum cytokines and chemokines were performed. Total MC density and degranulating MCs was enumerated in 5 high power fields in CIM and control tissues stained with toluidine blue. Inflammatory infiltrates and regeneration muscle fibers were counted in CIM tissue stained with H&E. Regeneration muscle marker Mi-2 was assessed in CIM tissue by IHC. **Results** Total MC density was significantly increased in CIM tissues compared with healthy mice (35.2 ± 2.3 versus (vs.) 18.0 ± 2.4, $p = 0.028$), as well as degranulating MCs (17.5 ± 5.0 vs. 3.3 ± 1.9, $p = 0.029$). However, there was no difference in muscle inflammation between CIM induced SASH mice and CIM induced controls. Serum levels of TNF-α, IL-1β, IL-6 and IFN-γ were not significantly different between the 2 groups. Yet, infiltration of CD8 positive cells in inflamed muscle fibers was decreased in SASH compared to controls (6.4 ± 0.8 vs. 2.1 ± 0.5, $p < 0.0001$), where Mi-2 positive fibers were also significantly decreased (SASH CIM, 2.4 ± 0.5 vs. control CIM, 10.58 ± 2.0, $p < 0.0002$). **Conclusion** The connective tissue-type MCs in skeletal muscles are activated upon CIM induction. The MCs do not engage in inducing robust muscle inflammation, but may play a role in muscle regeneration.

ICW-B6-4

Follicular Helper Type 2 T Cells are Highly Activated and Associated with Disease Activity in IgG4-Related Disease

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Conflict of interest: None

Objectives. We have previously reported that follicular helper type 2 T cells (Tfh2) were exclusively increased in IgG4-related disease (IgG4-RD). However, a functional role of Tfh2 is still unclear. The aim of this study is to further elucidate the role of activated Tfh2 in the pathogenesis of IgG4-RD. **Methods.** Active, untreated IgG4-RD (n=16) was included and compared to primary Sjögren syndrome (pSS, n=20), multicentric Castleman's disease (MCD, n=5), and healthy controls (HC, n=12). Proportion of Tfh1, Tfh2, Tfh17 subsets and percentage of activated cells ($CCR7^{lo}PD\text{-}1^{hi}$) in each subset in blood were assessed by flow cytometry. Disease activity was measured by IgG4-RD Responder Index (IgG4-RD RI). **Results.** Percentage of total Tfh2 was higher in IgG4-RD compared to pSS, MCD and HC and correlated with serum IgG4 levels or percentage of plasmablasts. No obvious change was observed in percentage of total Tfh2 along with glucocorticoid (GC) treatment. As for the activation status of Tfh2, percentage of activated Tfh2 was also substantially higher in IgG4-RD (mean±SEM, 8.3±1.7%) compared to pSS (1.4±0.2%, $p<0.0001$), MCD (1.6±0.5%, $p<0.0001$), and HC (1.2±0.2%, $p<0.0001$). Importantly, percentage of activated Tfh2 strongly correlated with IgG4-RD RI ($\rho=0.791$, $p<0.0001$) or the number of affected organs ($\rho=0.808$, $p<0.0001$). Further, percentage of activated Tfh2 decreased by GC, which was paralleled with improvement of the disease. Of note, we experienced the case whose percentage of activated Tfh2 was re-elevated at the disease relapse. **Conclusion.** We demonstrated that percentage of activated Tfh2 was increased and associated with disease activity and also linked to the extent of affected organs, suggesting that activated Tfh2 plays an important role in the pathogenesis of IgG4-RD. Moreover, total Tfh2 count was constantly increased in circulation even after GC treatment, indicating that polarization toward Tfh2 may be underlying immunological abnormality in IgG4-RD.

ICW-B6-5

A20/TNFAIP3 gene mutation reinforces inflammation and causes autosomal dominant Behçet's disease

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Conflict of interest: None

Objective Although Behçet's disease (BD) is a chronic inflammatory disorder of uncertain etiology, the existence of familial BD with autosomal dominant traits suggests that responsibility gene (s) exist. We investigated a Japanese family with a history of BD to identify pathogenic mutation that reveal underling biological mechanisms driving BD. **Methods** Six patients over 4 generations who had suffered from frequent oral ulcers, genital ulcers, and erythema nodosum-like lesions in the skin were assessed. The proband's dermal symptoms responded promptly to low doses of prednisolone in parallel with decreases in serum inflammatory cytokines. Whole-exome sequencing was performed on genomic DNA extracted from mononuclear cells from proband and his mother. Cytokine production was assayed from stimulated mononuclear cells. Inflammatory cytokine secretion and Nod2-mediated NF-kB activation were analyzed by transfection using wild and mutated *A20/TNFAIP3*. **Results** By whole-exome sequencing, we identified a heterozygous missense mutation in *A20/TNFAIP3,* a gene shown to regulate NF-kB signaling. The affected family members, all of which carried a heterozygous C243Y mutation in the ovarian tumor domain of *A20/TNFAIP3*. Mononuclear cells obtained from the proband and his mother produced large amounts of IL-1b, IL-6 and TNF-a upon stimulation with LPS, MDP, and PolyI:C as compared with those from normal controls. Inflammatory cytokine secre-

tion was suppressed by wild type transfection, but suppressed much less by mutated C243Y *A20/TNFAIP3*. Impaired suppression of Nod2-mediated NF-kB activation by C243Y A20/TNFAIP3 was found. **Conclusions** These findings were in agreement with reported *tnfaip3*$^{-/-}$ murine model data. A C243Y mutation in *A20/TNFAIP3* enhances production of human inflammatory cytokines by disorder of suppressing NF-kB activation, and have been responsible for the autosomal dominant Mendelian mode of BD transmission in this family.

ICW-B6-6

Knock Out of Endothelin Type B Receptor Signaling Attenuate Bleomycin-induced Skin Scrolosis in Mice

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Conflict of interest: None

【Background】Endothelin-1 (ET-1) has been reported to play an important role in the pathogenesis of systemic sclerosis (SSc). It has been reported that plasma concentration of ET-1 are higher in SSc patients, and that endothelin receptor expression are also increased in lungs and skins in the patients. ET-1 acts by binding to 2 subtypes of its receptors, endothelin type A (ETA) and type B (ETB) receptors. Dual ETA/B receptors and selective ETA receptor antagonist have been clinically used to SSc patients and the effect of those antagonists on fibroblast activation has been reported. However, ETB receptor signaling in fibrogenesis has been less understood. 【Methods】ETB receptor- knockout (ETBKO) mice, which were genetically rescued from lethal intestinal aganglionosis with ETB receptor transgene driven by the human dopamine b-hydroxylase (DbH) gene promoter, and wild-type mice with DbH-ETB (WT) were administered bleomycin (BLM) or PBS using osmotic pumps implanted subcutaneously to assess skin fibrosis. Then, dermal fibroblasts isolated from ETBKO and WT mice were cultured in vitro to compare profibrotic gene expressions in response to BLM or ET-1 stimulation. 【Results】Epidermal - dermal distance which increased in WT-BLM compared to WT-PBS, did not increase in ETBKO-BLM. Similarly, dermal - subcutaneous fat distance was reduced in WT-BLM compared to WT-PBS, but not in ETBKO-BLM. ETBKO mice were resist to BLM-induced scleroderma via inhibition of fibroblast activation because alpha-smooth muscle actin (aSMA)-expressing myofibroblasts in dermis significantly increased in WT-BLM compared to WT-PBS but not in ETBKO-BLM. *In virto* study, dermal fibroblasts isolated from ETBKO mice showed lower gene expressions of *aSMA* and *collagen 1a1* (*Col1a1*) in response to BLM or ET-1 stimulation than those from WT mice. 【Conclusion】ET-1 - ETB receptor signaling is involved in skin sclerosis and collagen synthesis of dermal fibroblast.

ICW-B6-7

Value of composite assessment of nailfold microvascular changes, phenotype of peripheral lymphocyte and pathology of the skin in systemic sclerosis (SSc)

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Conflict of interest: None

[Objectives] SSc is a complex disease which consists with "autoimmunity", "inflammation", "fibrosis" and "vasculopathy". To evaluate such complicated pathogenic mechanisms, we established composite assessment including the morphological microvascular damage, immunophenotyping of peripheral blood and the pathological findings of the skin in SSc patients. **[Methods]** 32 SSc patients were enrolled. Nailfold videocapillaroscopy (NVC) was performed for qualitative assessment (normal, early, active, late pattern) of morphological microvascular. Circulating lymphocyte subsets were defined based on flow cytometric analysis termed 'the Human Immunology Project' established by NIH/FOCIS. Immunohistochemical staining of the skin and organ involvement score were assessed. **[Results]** Qualitative assessment (normal, early, active, late) on the basis of nailfold capillary abnormalities reflected m-Rodnan skin score (p=0.001) and dysfunctions of digestive organs (p=0.01). The proportion of activated T cells, Th1 and switched memory B cells in peripheral blood correlated with severity of digital ulcer, whereas plasmablast correlated with m-Rodnan skin score (p=0.01), renal (p=0.001) or cardiac dysfunctions (p=0.04) and pulmonary hypertension (p=0.001). On the other hand, there were no correlations between pathological findings of the skin and organ involvement. Of note, the presences of B cells in the skin correlated with the proportion of switched memory B cells in peripheral blood (P=0.02). Likewise, the proportion of plasmablast in peripheral blood was increased in patients with late NVC pattern (p=0.04). **[Conclusion]** Comprehensive assessment reflected the diversity of pathogenesis of SSc. Our data indicated the relationship between abnormal B cell differentiation and organ involvement as well as progress in skin microvascular changes in SSc. The composite assessment is useful in evaluating the pathogenesis and in determining the potential therapeutic target of each patient.

ICW-B7-1

TNFα Induces the Calcified Nodule Formations and Increased Osteoblastic Marker Expression in Human Peripheral Blood Mononuclear Cells on Dentin Slices

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Conflict of interest: None

[Object] Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with an increased risk of the developing cardiovascular diseases. A major risk factor for the cardiovascular diseases is vascular wall calcification, underlying molecular mechanisms of which remain as yet unclear. Recent studies have suggested that circulating osteoblast-lineage cells are associated with a marked induction of vascular wall calcification. Here we investigated the effect of proinflammatory cytokine on vascular wall calcification mechanism in human peripheral blood mononuclear cells (PBMCs). **[Methods]** PBMCs were obtained from in healthy volunteers. PBMCs were cultured on dentine slices for 21 days in the presence of TNFα. After removal of the cells, the mineralized nodules were examined by scanning electron microscope. The structures formed in mineralized nodules were examined by energy-dispersive X-ray spectroscopy. Measured by real-time PCR were expression levels of mRNA in alkaline phosphatase (ALP), osteocalcin, runt-related transcription factor 2 (RUNX2), SP-7, which are osteoblastic markers, and osteoprotegerin (OPG) and RANKL. **[Results]** Stimulation of PBMCs with TNFα formed mineralized nodules on dentin slices in a dose-dependent manner. Energy-dispersive X-ray spectroscopy confirmed that these structures were calcified matrices composed of calcium and phosphate. Expression levels of mRNA on ALP, osteocalcin, RUNX2, SP-7 in PBMCs by stimulation with TNFα was significantly up-regulated compared with unstimulated ones. Ratio of OPG/RANKL mRNA was significantly higher in PBMCs by stimulation with TNFα. **[Conclusions]** Our results demonstrate that the proinflammatory cytokine TNFα can induce the calcified nodule formations and increased osteoblastic marker expression in PBMCs on dentin slices. It indicates that anti-TNF therapy in patients with RA may improve not only the disease activity, but also vascular wall calcification.

ICW-B7-2

Tankyrase Inhibitor Promotes Osteoclastogenesis by Enhancing SH-3BP2 expression

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Conflict of interest: Yes

[Purpose] Tankyrase inhibitor is widely recognized as a Wnt/β-catenin inhibitor and has received the attention in cancer research by its anti-cancer effect. Tankyrase, poly (ADP-ribose) polymerases, has recently been reported to degrade an adaptor protein SH3BP2 (SH3 domain-binding protein 2). In our previous studies, gain-of-function mutations in SH3BP2 enhance RANKL- and TNF-induced osteoclastogenesis. However, it is not fully elucidated whether Tankyrase is involved in osteoclastogenesis. In this study, we investigated the effect of Tankyrase inhibitor on bone metabolism. [Methods] Primary murine bone marrow-derived macrophages were treated with either RANKL or TNF in the presence of Tankyrase inhibitor (IWR1) and Wnt inhibitors (IWP2 and C59). Osteoclast differentiation was evaluated by TRAP-positive multinucleated cells (TRAP+ MNCs) formation and osteoclast-associated genes expression. Osteoclastic function was determined by resorption assay. SH3BP2 and NFATc1 expression levels in the cells were determined by western blotting. [Results] Tankyrase inhibitor IWR1 enhanced both RANKL- and TNF-induced TRAP+ MNCs formation and osteoclast-associated genes expression. Mineral resorbing activity was significantly enhanced in IWR1-treated cells. SH3BP2 protein levels were elevated in IWR1-treated cells but not in Wnt inhibitors-treated cells. NFATc1 nuclear localization was significantly augmented in the IWR1-treated cells. Finally, FK506, an NFATc1 inhibitor, fully abolished the promoting effect of IWR1 in osteoclast formation in a dose dependent manner. [Conclusion] These data suggest that the inhibition of Tankyrase activity enhances osteoclastogenesis via elevated SH3BP2 expression. Our findings highlight the undetermined effect of Tankyrase inhibitor in addition to the Wnt/β-catenin inhibition. A potential risk of osteoporosis should be further assessed before the clinical application of the Tankyrase inhibitors.

ICW-B7-3

The effects of biological agents for inflammatory bone destruction analyzed by intravital two-photon microscopy

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Conflict of interest: None

Object: Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by progressive bone destruction. Recently, the remarkable advances of biological agents have improved the outcomes of RA patients. There have been many studies about the pharmacological properties of biological agents, but most of them were analyzed by conventional methods such as micro-CT and histological analysis. How biological agents can inhibit inflammatory bone destruction *in vivo* remains elusive. This study aimed to investigate the effects of biological agents on the function of mature osteoclasts in inflammatory sites by using intravital two-photon microscopy. **Methods:** We utilized the mice expressing GFP under the promoter of a vacuolar type H^+-ATPase a3 subunit that was abundantly expressed in mature osteoclasts (a3-GFP mice). LPS (20 mg/kg) was subperiosteally injected into the calvariae of a3-GFP mice. Anti-IL-6 receptor antibody (10 mg/kg), anti-TNFα antibody (5mg/kg), or vehicle was administered intraperitoneally. Five days later, by using intravital two-photon microscopy, we observed skull bones and visualized fluorescently labeled mature osteoclasts. **Results:** In control condition, we identified different populations of living mature osteoclasts in terms of their motility and function, i.e., 'static - bone resorptive (R)' and 'moving - non resorptive (N)'. On the other hand, in LPS-induced bone destruction model, the number of mature osteoclasts was increased and most of them were R-type. We also found that treatment with anti-IL-6 receptor and anti-TNFα antibody decreased the proportion of R-type osteoclasts. **Conclusions:** By means of intravital imaging system, we succeeded in visualization of inflammatory bone destruction *in vivo*, and found that biological agents could inhibit osteoclastic bone resorption in living bone tissues. This approach would be quite useful for evaluating novel anti-bone resorptive drugs currently developed in the world.

ICW-B7-4

Human dendritic cell-derived osteoclasts have the ability for potent bone absorption and T cell stimulation in rheumatoid synovium

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Conflict of interest: None

[Objective] It was reported that dendritic cells (DCs) as well as monocytes differentiate into osteoclasts-like cells in murine system. The aim of this study is to evaluate the role of human dendritic cell-derived osteoclast (DCOC) in the pathogenesis of rheumatoid arthritis (RA). **[Methods]** Tartrate-resistant acid phosphatase (TRAP) and immunohistochemistry staining were used to detect osteoclast and DCOCs in RA synovial tissue. DCOCs were differentiated from human monocyte-derived DCs in vitro. The function of DCOCs was compared with human monocyte-derived osteoclasts (MoOCs). **[Results]** TRAP-positive multinucleated cells (osteoclasts) were detected in rheumatoid synovium. Of note, 33 % of these cells had a costimulatory molecule (CD86), which was not expressed in MoOCs. In vitro culture of human DCs with M-CSF and RANKL resulted in the differentiation into DCOCs positive for TRAP staining and cathepsin K. These DCOCs have potent bone absorption capacity by the Pit-formation assay. On the other hand, DCOCs expressed major histocompatibility complex-class II and costimulatory molecules such as CD80 and CD86, which were not accompanied in MoOCs. Finally, co-culturing of DCOCs with $CD4^+$ T cells increased T cell proliferation, whereas MoOCs did not possess these activities. **[Conclusion]** In the RA synovium, there were characteristic osteoclasts with costimulatory molecules which were not expressed in MoOCs. In other words, human DCs can differentiate into DCOCs in the inflammatory lesion without being controlled by osteoblasts/osteocytes. DCOCs have not only the bone resorption ability but also the function of T cell stimulation. These results suggest that DCOC may play an pivotal role in the pathogenesis of RA by the maintenance of inflammation and joint destruction.

ICW-B7-5

Trabecular minimodeling structure of femoral head in rheumatoid arthritis cases

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Conflict of interest: None

[Objectives] Modeling is the biologic mechanism that adapts the skeleton to provide mechanical competence. Frost considered the same modeling process can occur in miniature on trabeculae. Minimodeling was termed on this process for trabecular. We hypothesize that minimodeling can go on throughout life, especially at the weight bearing area, and we have looked for histological finding of minimodeling in trabecular bone from adult human beings. In this study, we address the histological findings using femoral heads taken from patients with rheumatoid arthritis (RA). [Methods] Patients with RA who underwent a hip surgery were obtained. After femoral head was excised, we conducted a bone histomorphometric analysis. Excluding a specimen with severe destruction and difficult to evaluate, we analyzed 14 femoral heads from 13 patients including 12 female specimens. The average age of patients was 65.6 years old (from 27 to 87). A minimodeling structure (MIS) is defined strictly as newly formed bone with an osteoid surface and with a smooth and flat bone surface, not a round, under its structure. We analyzed the histological characteristic findings between groups with MIS or not (control) in the analysis area. [Results] Histologic evidence of MIS was detected in 8 of the entire 14 specimens (57.1%). In comparison with the control group, MIS group significantly elevated osteoid parameters (OV/TV, OV/BV, and OS/BS; $p < 0.01$, respectively) except osteoid thickness (O. Th). There were no significant differences in bone volume (BV/TV, Tb. Th, W. Th), and bone resorption parameters (ES/BS, Oc. S/BS), respectively. In MIS group, the mean MIS-BV/BV, and MIS-OV/OV were 0.08%, and 1.19%, respectively, while the mean MIS-OS/MIS-BS, and MIS-OV/MIS-BV were 44.1%, and 27.7%, respectively.. [Conclusion] These results indicated that the values of MIS-BV and MIS-OV were small, but MIS was recognized in half or more in the adult femoral heads

in RA.

ICW-B7-6

Dysregulated osteoclastogenesis is related to natural killer T cell dysfunction in rheumatoid arthritis

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Conflict of interest: None

Objective. To investigate the role played by NKT cells in osteoclastogenesis and their effects on inflammatory bone destruction. ***Methods.*** Patients with RA (n=25) and healthy controls (n=12) were enrolled in this study. *In vitro* osteoclastogenesis experiments were performed using peripheral blood mononuclear cells (PBMCs) in the presence of M-CSF and receptor activator of nuclear factor kB ligand (RANKL). PBMCs were cultured *in vitro* with a-galactosylceramide (αGalCer), and proliferation indices of NKT cells were estimated by flow cytometry. *In vivo* effects of αGalCer-stimulated NKT cells on inflammation and bone destruction were determined in collagen-induced arthritis (CIA) mice. *Results. In vitro* osteoclastogenesis was found to be significantly inhibited by αGalCer in healthy controls, but not in RA patients. Proliferative responses of NKT cells and STAT-1 phosphorylation in monocytes in response to αGalCer were impaired in RA patients. Notably, αGalCer-stimulated NKT cells inhibited osteoclastogenesis mainly via interferon-g production, in a cytokine-dependent manner (not by cell-cell contact), and down-regulated osteoclast-associated genes. aGalCer-treated mice showed less severe arthritis and reduced bone destruction. Moreover, proinflammatory cytokine expression in arthritic joints was found to be reduced by aGalCer treatment. *Conclusions.* This study primarily demonstrates that aGalCer-stimulated NKT cells have a regulatory effect on osteoclastogenesis and a protective effect on inflammatory bone destruction. However, it also shows that these effects of aGalCer are diminished in RA patients, and that this is related to NKT cell dysfunction. These findings provide important information for those searching for novel therapeutic strategies to prevent bone destruction in RA.

ICW-B8-1

Interleukin-32 exhibited protective effects on osteoporosis

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Conflict of interest: None

Background/Purpose Interleukin-32 (IL-32) has been known to be implicated in the pathogenesis of various inflammatory diseases. Osteoporosis,characterized by low bone density and increases the risk of fracture, was prevalent in systemic inflammatory diseasesmediated through the link between chronic inflammation and bone loss.In this study, we try to investigate the effects of IL-32γ in osteoporosissince the role of IL-32 in bone formation as well as bone resorptionremainslargely unknown. **Methods** To determine whether IL-32γ affects bone formation, we examined bone volume of transgenic (TG) mice overexpressing IL-32*γ* by using micro-CT.Ovariectomized mice were used to know the effects of IL-32*γ* on osteoporosis*in vivo*. In addition, bone formation rate was evaluated by labeling with calcein, a marker of newly formed bone. To elucidate the mechanism of IL-32*γ* effect on bone metabolism, we measured the levels of Dickkopf-1 (DKK-1), is well-known as having an inhibitory effects onosteoblastogenesis. Further, the concentration of IL-32*γ* was measured in the peripheral blood from patients with osteoporosis. **Results** Micro-CT analysis revealed that IL-32*γ* TG mice had an increased bone volume compared with wild-type (WT) mice. Furthermore, bone loss induced by ovariectomy wassubstantiallyattenuated in IL-32*γ*TG mice compared with that in WT mice. Importantly,IL-32*γ* TG mice had higher bone formation rate as assessed by the mineral apposition rate compared with WT mice. In addition, the level of DKK-1 was significantly lower in theIL-32*γ*TG micethan WT mice. Finally,we found that the concentration of IL-32γ wassignificantly lower in the blood of patients with osteoporosis than in those of healthy individuals. **Conclusion** Our present study suggested thatIL-32γenhances bone formation through association with the decrease of DKK-1, which contributes to the protective effects on osteoporosis.

ICW-B8-2

microRNA 27b-3p is modulated by IL-1β in osteoarthritis (OA) synovial fibroblasts: Possible signalling through polo like kinase2 (PLK2) pathway

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Conflict of interest: None

Objectives The aim of this study is to identify the role and regulation of miR-27b-3p in OA synovial fibroblasts. **Methods** Synovial tissues were obtained from OA patients who underwent total knee replacement under informed written consent. Synovial fibroblasts were purified, cultured and stimulated with IL-1β. mirDIP 2.0 was used to predict genes targeted by hsa-miR-27b-3p. The expression of miR-27b-3p and its candidate target genes was assayed by qPCR. **Results** Our laboratory has previously shown that miR-27b-3p is significantly elevated in synovial fluid of late-stage knee OA patients compared to early OA. Synovial explant cultures further revealed that this miRNA responds to IL-1β stimulation. In the present study, synovial fibroblasts -the major cell type in the synovial lining layer- were isolated from OA synoviums, cultured and stimulated with IL-1β. We observed a significant decrease in miR-27b-3p expression levels in IL-1β treated fibroblasts compared to untreated controls. Thus, we searched the genes that could be regulated by miR-27b-3p using computational biology approach. Considering top 1% predictions, 9 genes were listed as potential targets of miR-27b-3p: *CADH11, SPRY, KIAA, NPEPPS, DCUN1D4, RPGRIP, GRB2, LONRF1* and *PLK2*. To identify the potential targets of miR-27b-3 in synovial fibroblasts, all the candidate genes were measured and exhibited substantial expression levels. We observed a remarkable upregulation in *PLK2* mRNA level upon IL-1β stimulation, while *DCUN1D4*, *KIAA* and *NPEPPS* were downregulated. The fibroblasts are now treated with miR-27b-3p mimic to evaluate the effects of miR-27b-3p overexpression on PLK2 mRNA and protein levels, as well as, on the pathways involved in synovial inflammation and fibrosis. **Conclusion** In response to IL-1β stimulation, miR-27b-3p was downregulated in synovial fibroblasts, while *PLK2* was upregulated. Apparently, miR-27b-3p contributes to synovial inflammation partly by regulating PLK2 signaling pathway.

ICW-B8-3

Identification of metabolomic signatures in high-fat diet induced acceleration in age-related and surgically induced osteoarthritis in mice

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Conflict of interest: None

Objectives: We sought to identify the change in metabolomics profile due to distinct diet regimes and their contributions to the pathogenesis of OA. **Methods:** 9 weeks old C57BL6 mice were fed high fat diet -HFD, 60% and lean diet -LD, 10% fat for 18 wk followed by a normal chow diet. Mice were longitudinally evaluated at times 0 (start of diet/baseline), 18 wk of diet (end of diet) and at 9 months of age. At each time point BMI, fasting blood glucose level and body weight were measured. At sacrifice, blood plasma was collected to measure leptin levels, metabolite levels and knee joints were collected for histopathological analysis at 9 months of age. Additional mice on HFD and LD were subjected to experimental OA by DMM surgery at the end of diet regime. Mice were maintained on normal chow and knee joints were collected for histopathological analysis at 10 and 20 wks post surgery. **Results:** We determined that HFD significantly increased fasting blood glucose levels, body

weight, BMI and leptin levels as compared to LD fed mice. Histopathological analysis using OARSI scoring clearly showed that HFD fed mice exhibited accelerated spontaneous OA at 9 months of age as well as acceleration in the surgically induced OA at 10 and 20 wks post surgery in comparison to LD fed mice. Of the 170 metabolites analysed in blood plasma at each time point, lysophosphatidyl choline analogues (lysoPCaC20:4, lysoPCaC17:0, lysoPCaC18:0) and one phosphatidyl choline analogue (PCaaC36:2) were increased longitudinally in the HFD fed mice. Our ongoing studies are now evaluating if these LysoPC metabolomics signatures are responsible for initiating and accelerating cartilage degradative process observed in HFD fed mice. **Conclusion:** We identified that high fat diet induces and maintains selective metabolic changes and increases OA progression in both spontaneous and surgically induced OA. We anticipate that these identified metabolomics signatures are involved in OA pathogenesis during obesity.

ICW-B8-4

Cartilage-specific ablation of Unc-51 like kinase 1 results in an accelerated osteoarthritis phenotype

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Conflict of interest: None

*MAR and JR have equal first author contribution **Objective:** Unc-51 like kinase-1 (ULK1), a serine/threonine protein kinase, is the most upstream inducer of autophagy. We recently showed that ULK1 expression is suppressed in the articular cartilage during Osteoarthritis (OA); however, the role of ULK1 in OA pathogenesis is not known. We sought to determine the contribution of ULK1 to OA pathogenesis. **Methods:** We generated inducible, cartilage-specific ULK1 knockout (KO) mice using Cre-lox technology (ULK1 f/f; Col2-rtTA-cre) and induced experimental OA by surgical destabilization of the medial meniscus (DMM). At 10 weeks post-DMM surgery, the degree of cartilage degeneration, loss of cellularity, and expression of cell death and catabolic markers were determined. *In vitro*, we overexpressed ULK1 in human OA chondrocytes by transfection with a ULK1 expression plasmid to determine the effect of ULK1 on the expression of genes involved in cell death and survival. **Results:** We identified that cartilage-specific ablation of ULK1 resulted in accelerated DMM-induced OA including accelerated cartilage degeneration, proteoglycan loss, chondrocyte cell death, synovial inflammation and increased expression of OA catabolic factors, as compared to control mice. Furthermore, human OA chondrocytes transfected with ULK1 expression plasmid modulated the expression of mTOR, a negative mediator of autophagy, and ADAMTS-5, an OA-associated catabolic factor. **Conclusions:** This study provides the first evidence that ULK1 expression is vital to maintaining articular cartilage homeostasis in surgically-induced OA.

ICW-B8-5

Degenerative lumbar facet cartilage exhibits reduced expression of autophagy and enhanced expression of cell death, inflammatory and catabolic mediators

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Conflict of interest: None

Objectives: Specific mechanisms associated with facet cartilage degeneration during facet joint osteoarthritis (FJ OA) are unknown. We aimed to determine the degree of FJ cartilage degeneration and expression of autophagy, apoptosis, inflammatory, catabolic and cartilage matrix markers in FJ OA cartilage compared to control cartilage. **Methods:**FJ cartilage (L3-S1) was collected from 52 patients (mean age=66.8 years) with lumbar spinal canal stenosis (LSS) (FJ OA group) and 46 young patients (mean age=34.5 years) with lumbar disc herniation (LDH) (control).The severity of FJ degeneration was assessed by the MRI grading scores and further assessed histologically using the Osteoarthritis Research Society International (OARSI) grading system. Protein and RNA extracted from FJ cartilage were subjected to real-time PCR and Western blot analysis. **Results:**MRI showed all patients in control exhibited a degenerative grade of 0 (normal) or 1, whereas all patients with FJ OA exhibited a grade of 2 or 3 for facet joints. Histological analysis further revealed a significant degree of FJ cartilage degeneration in FJ OA patients (OARSI score= 5.5± 0.2) compared to control (OARSI score= 0.9±0.3). Our results further showed FJ OA cartilage exhibited a significant decrease in the expression of chondroprotective autophagy markers (LC3/ULK1), increase in mammalian target of rapamycin (mTOR), apoptosis (PARP-1/caspase-3), inflammatory (IL-1β/TNF-α/IL-6/COX-2/MCP-1), catabolic markers (MMP-3/MMP-13/ADAMTS-5) and decrease in the expression anabolic matrix molecules (aggrecan/type II collagen). **Conclusion:**This study for the first time showed FJ OA cartilage exhibits an enhanced degree of FJ cartilage degeneration associated with reduced expression of autophagy markers and cartilage matrix molecules; and enhanced expression of apoptosis, inflammatory and catabolic markers. These results allow us a better understanding of the endogenous mechanisms associated with FJ cartilage degeneration.

ICW-B8-6

Synovial mesenchymal stem cells (SMSC) from osteoarthritis (OA) and rheumatoid arthritis (RA) patients exhibit good potential for the development of scaffold-free tissue engineering constructs (TEC) for cartilage repair

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Conflict of interest: None

Object: We developed scaffold-free TEC composed of SMSC and its cartilage-repairing efficacy in pig has been demonstrated. In addition, clinical trial of patients with traumatic chondral defect (control group; Ctrl) is on-going. As autogenic TEC have some limitations such as multiple surgeries and prolonged culture period, establishment of allogenic SMSC bank may be promising solution. Synovial tissue can be abundantly obtained in operation of OA and RA, however, high age and inflammation may attenuate its chondrogenic potential. Methods: SMSC was obtained from 25 patients of 4 groups [group; number, age = Ctrl; n=6, 38.6 / OA; n=6, 71.2 / Bio-naive RA; n=6, 67.0, DAS28-CRP 2.4 / Bio RA; n=7, 72.4, DAS28-CRP 2.3]. Following items were evaluated. 1: Proliferative ability of SMSC. 2: Weight and volume of TEC ($1.5*10^6$ cells). 3: Pro-inflammatory cytokine gene expression. 4: Chondrogenesis evaluated by gene expression and glycosaminoglycan (GAG) synthesis. 5: Osteochondral repair of femoral trochlea defect using TEC in F344/NJcl/rnu nude rat [modified O'Driscoll score (0-36) 8weeks after implantation]. Results: In every item, SMSC or TEC from OA and RA groups showed equivalent quality and quantity compared with Ctrl group (mean, Ctrl / OA / Bio-naive RA / Bio RA). 1: Proliferation rate (day3 / day1) 2.0 / 1.8 / 1.7 / 1.7. 2: Weight: Volume (mg: mm^3); 5.9: 5.7 / 6.1: 5.6 / 6.5: 6.3 / 5.7: 5.4. 3: No significant difference in IL1β, IL6 and IL10 gene expression among all groups. 4: GAG component (%); 2.9 / 3.1 / 2.9 / 3.2, No significant difference in SOX9, COL2 and Aggrecan gene expression. 5: All groups showed significantly better repair than only-defect group (defect 13.4 / 21.7** / 21.0* / 21.7** / 22.4**; *$p<0.05$ ** $p<0.01$). Conclusions: Regardless of its high age and inflammatory character, TEC derived from the patients with OA or RA with low-disease activity showed good potential to repair chondral defect, and may be promising source of allogenic SMSC bank.

ICW-B9-1

Canonical TGF-β signaling via Smad3/4 regulates expression and function of SOCS3 to suppress Th17 differentiation

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Conflict of interest: None

We have previously reported that non-canonical transforming growth factor-β(TGF-β) signaling via ERK-linker phosphorylated Smad2-STAT3 cooperates with T cell receptor (TCR) and interleukin (IL)-6 to induce, whereas unphosphorylated Smad3 suppresses differentiation of IL-17-producing $CD4^+$ T helper cells (Th17). However, the roles of canonical TGF-β signaling via C-terminally phosphorylated TGF-β receptor-regulated Smads (R-Smads) and Smad4 in Th17 differentiation remain largely unknown. Here we show that C-terminally phosphorylated Smad3 (pSmad3C) and Smad4 play crucial roles for suppressor of cytokine signaling 3 (SOCS3) to act as a negative regulator of STAT3. T cell-specific Smad4 deletion exacerbates murine collagen-induced arthritis (CIA) with increased Th17 in the arthritic lesions and draining lymph nodes, which phenocopied Smad3 deficient mice. pSmad3C and Smad4 induce transcription of the *Socs3* gene. Moreover, pSmad3C is required for SOCS3 to interact with STAT3 to inhibit its phosphorylation. This work uncovers the novel multi-step roles of canonical TGF-β signaling via pSmad3C and Smad4 in SOCS3-mediated suppression of Th17 differentiation.

ICW-B9-2

The responses of macrophages in interaction with neutrophils that undergo NETosis

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Conflict of interest: None

Objectives: Neutrophil extracellular traps (NETs) are net-like chromatin fibers decorated with antimicrobial proteins, which are released from dying neutrophils. The death of neutrophils with NET formation is called NETosis. Although NETs play important roles in elimination of microorganisms, a persistence of NETs induce autoantibody production against NET components, including DNA and myeloperoxidase, and subsequent development of SLE and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Therefore, NETs are adequately regulated *in vivo*. Currently, DNase I-dependent digestion and phagocytosis by macrophages have been shown as the regulatory mechanisms. In this study, we focused on the interaction of macrophages and neutrophils that underwent NETosis. **Methods:** M1 and M2 macrophages derived from THP-1 cells and human peripheral blood monocytes were co-cultured with neutrophils underwent NETosis. **Results:** Macrophages displayed a phenotype-related response after degradation of NETs. Several hours after the interaction, M2 macrophages induced a pro-inflammatory response, while M1 macrophages underwent cell death with nuclear decondensation in a peptidylarginine deiminase 4-dependent manner resulting in a local release of extracellular DNA. Thereafter, M1 macrophages degraded DNA derived from themselves in a caspase-activated DNase-dependent manner resulting in a clearance of the extracellular DNA within 24 hours. **Conclusion:** This transient increase and subsequent clearance mechanism of extracellular DNA seems reasonable in terms of the double-edged sword-like property of NETs. Since disorder of NET regulation is involved in the production of anti-DNA antibody and ANCA, function of macrophages in patients with SLE and AAV deserves attention.

ICW-B9-3

Involvement of IGF and IGFBP-4 in the induction of regulatory T cells by human mesenchymal stem cells

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Conflict of interest: None

【Background】Although human MSCs (hMSCs) possess the multipotency and immunomodulatory function, the mechanisms remain unclear. We assessed the immune-regulatory mechanisms of hMSCs, shedding light upon Treg. 【Method】Human naïve $CD4^+$ T cells were stimulated with anti CD3/28 antibody and cultured with or without culture supernatant of hMSCs. After 48 hours culture, proliferation, cytokine production, and surface molecules of $CD4^+$ T cells were assessed. 【Result】The hMSCs and their culture supernatant markedly suppressed cell proliferation of $CD4^+$ T cells and enhanced IL-4, IL-10 production of human $CD4^+$ T cells. The hMSC supernatant induced $CD4^+FoxP3^+$ Treg which expressed CD25, CTLA-4, GITR, PD-1/PD-L1 and IGF receptors. The Treg induced by hMSC supernatant efficiently suppressed proliferation of $CD4^+$ T cells. The induction of Treg by hMSC supernatant was further enhanced by the addition of IGFs, but was suppressed by anti-IGF1R Ab. In addition, hMSC supernatant contained a large amount of IGF-binding protein (IGFBP)-4 which inhibited IGF-mediated signaling. Inhibitory effects of IGFBP-4 in hMSC supernatant on the induction of $CD4^+FoxP3^+$ Treg were significantly abrogated by the addition of anti-IGFBP-4 antibody to the culture. 【Conclusion】The data indicated that hMSCs possess passive regulatory action of functional Treg cells through the production of IGF. However, hMSCs also produced IGFBP-4 in a large amount, which abrogated induction of Treg by IGF, suggesting that the hMSC could regulate immunity and inflammation such as RA through balance between IGF and IGFBP-4. Also, the inhibition of IGFBP-4 may be necessary for the efficient application of MSC therapy in the context of joint repair in RA.

ICW-B9-4

Synergistic immunoregulatory roles and mechanisms of TGF-β3 with IL-10 in systemic autoimmunity

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Conflict of interest: None

Backgrounds: We previously identified $CD4^+CD25^-LAG3^+$ regulatory T cells produce both IL-10 and TGF-β3 and regulate humoral immunity. However, the physiological roles of the coexistence of IL-10 and TGF-β3 have not been clarified. **Methods:** pCAGGS-Mock, pCAGGS-Il10, or pCAGGS-Tgfb3 vectors were administered to NP-KLH immunized C57BL/6 mice, and NP-specific antibody levels were quantified by ELISA. Further, the effects of each vector on lupus pathogenesis of MRL/*lpr* mice were assessed. B cells were stimulated with Toll-like receptor (TLR) agonists in the presence or absence of TGF-β3 and IL-10, and the gene expression profiles were determined by next generation sequencing (NGS) and qRT-PCR. The antibody productions were measured by ELISA. **Results:** NP-specific IgG was suppressed only when pCAGGS-Il10 and pCAGGS-Tgfb3 was co-administered. In MRL/*lpr* mice, which displayed higher serum IL-10 levels compared with MRL/+ mice, pCAGGS-Tgfb3 ameliorated splenomegaly, glomerulonephritis, and elevated anti-dsDNA antibody along with suppressing follicular helper T cells and plasmablasts. Hierarchical clustering of NGS data revealed "B cells without stimulation" and "stimulated-B cells with TGF-β3/IL-10" placed in the same cluster. Pathway analyses indicated endoplasmic reticulum (ER) stress response related genes was characteristically suppressed in "stimulated-B cells with TGF-β3/IL-10". Stimulated-B cells either with TGF-β3 or IL-10 enhanced antibody production

with up-regulation of ER stress response related genes, but the coexistence of two cytokines converted to suppress these genes and antibody production. In human, the synergistic suppression on IgG2 production was verified. **Conclusion:** These results indicated that TGF-β3 and IL-10 synergistically suppressed antigen-specific antibody responses and lupus pathogenesis via regulating ER stress responses. The combination of TGF-β3 and IL-10 might provide a novel therapeutic strategy for systemic autoimmune diseases.

ICW-B9-5

Targeted clonal expansion of autoimmune uveitis patient-derived regulatory T cells yields functionally stable cellular product for adoptive transfer-based immunotherapy development

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Conflict of interest: None

Objectives: The *in vitro* expansion of patient-derived regulatory T cells (Treg) for adoptive transfer is a promising therapeutic strategy for the treatment of autoimmune uveitis and other autoimmune diseases. Most of the currently tested approaches to therapeutic adoptive Treg transfer rely on the enrichment and *in vitro* expansion of polyclonal, presumably thymic Treg cells. A major limitation of these approaches is the unintentional co-expansion of potentially harmful contaminating effector T cells which may compromise purity and suppressor function stability. Here, we hypothesized that cloning of human $CD4^{+}CD127^{low}CD25^{high}FoxP3^{+}HELIOS^{+}$ Treg yields a highly pure cellular product with stable suppressor function throughout repeated re-expansion cycles. **Methods:** Cloning of autoimmune uveitis patient-derived Treg was performed through selection for $CD4^{+}CD127^{low}CD25^{high}$ cells by magnetic bead isolation and expansion in limiting dilution conditions. Suppressor function was tested in suppression assays of CD3/CD28-stimulated effector T cells. Clonality was assessed by Vbeta staining. **Results:** Cloning efficiency was 2-5/100 seeded cells. Treg clones were homogenously $CD4^{+}CD25^{high}FoxP3^{+}HELIOS^{+}$, and clonality was confirmed by staining for a unique TCR Vbeta chain. Clones maintained around 80% suppression at a 1:4 Treg:Teff ratio over more than 10 weeks throughout several expansion cycles. Expansion rates were in the billion-fold range by 8 weeks. Suppressive function was maintained after thawing following cryopreservation for more than 6 months. **Conclusions:** Our results indicate that the massive expansion of human regulatory T cell clones and their cryopreservation from patients with autoimmune uveitis is a feasible approach for the generation of a functionally stable regulatory T cell product for preclinical and clinical testing.

ICW-B9-6

Nardilysin is involved in the pathogenesis of autoimmune arthritis via antibody pruduction

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Conflict of interest: None

OBJECTIVES: Several immunological mechanisms are involved in the pathogenesis of autoimmune arthritis. Nardilysin or N-arginine dibasic convertase (NRDc) exists in nucleus, cytosol and cell surface with broad spectrum of functions, but the function in immune system is still unclear. The purpose of this study is to elucidate the role of NRDc in immune system and autoimmune arthritis. METHODS: SKG mice, a well-established mouse model of autoimmune arthritis, were crossed with NRDc deficient (Nrd1-/-) mice. The incidence and severity of arthritis in SKG:Nrd1+/+ and SKG:Nrd1-/- mice were scored. Arthritis score was also evaluated in nude mice in which naive T cells, isolated from SKG:Nrd1+/+ and SKG:Nrd1-/- mice, were adoptively transferred. To assess the capacity of antibody production, Nrd1+/+ and Nrd1-/- mice were immunized with ovalbumin (OVA), keyhole limpet heamocyanin (KLH), hen egg lysozyme (HEL), and 4-Hydroxy-3-nitrophenyl-chiken gamma globulin (NP-CGG). The titers of antigen-specific antibodies were measured by ELISA. B cell subsets in spleen and bone marrow of Nrd1+/+ and Nrd1-/- mice were analyzed by flow cytometry. RESULTS: Mean arthritis score in SKG:Nrd1-/- mice (0.04) was significantly lower compared with that in SKG:Nrd1+/+ mice (5.05). SKG:Nrd1+/+ and SKG:Nrd1-/- naive T cells similarly induced arthritis in nude mice. The titers of antigen-specific IgM and IgG to OVA, KLH, HEL, and NP-CGG were lower ($p<0.05$) and the population of plasma cells in spleen and bone marrow was decreased in Nrd1-/- mice ($p<0.05$). CONCLUSION: These results indicated that NRDc is critically involved in the pathogenesis of autoimmune arthritis via B cell modulation, but not T cell function. NRDc could be a novel and unique therapeutic target for autoimmune arthritis.

Workshop

W1-1

Estimation of the change of the joint ultrasound (US) and MMP-3 in polymyalgia rheumatica (PMR)

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Conflict of interest: None

[Objectives] The correlation of US and clinical and laboratory in patient with PMR were evaluated. [Method] 43 patients (Male 17, Female 26) were diagnosed at PMR from October 2011 to 2015. The patients are satisfied with criteria in ACR/EULAR. The correlation of US with clinical symptoms (VAS, morning stiffness, HAQ) and laboratory test (MMP-3, CRP, ESR). We observed shoulder (subdeltoidbursitis, long head biceps (LHB), subacrominal bursitis) of those thickness and power doppller of Grade 0-3 by US. We evaluated the relationship of US with the clinical and laboratory at baseline and 24 and 56 weeks. All patients were treated with PSL15mg/day. [Result]The difference of thickness of the LHB (ΔLHB) and the difference of MMP-3 (ΔMMP-3) between at baseline and 56 weeks have a positive correlation tendency. (r^2=0.5,P<0.006) [Conclusion] The between ΔLHB and ΔMMP-3 have a positive correlation tendency. US might be a useful tool in addition to the clinical symptoms and laboratory findings in PMR.

W1-2

The efficacy of 2015 EULAR/ACR Recommendations for the Management of Polymyalgia Rheumatica in Japanese patients

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Conflict of interest: None

Objectives: To examine the efficacy of 2015 EULAR/ACR management recommendations for Japanese patients with polymyalgia rheumatic (PMR). **Methods:** PMR were diagnosed by 2012 EULAR/ACR Provisional Classification Criteria for PMR. 35 patients were male/female=1:1.7, age 69.2 ± 9.4 years old. **Results:**. PMR are proved to be active by high levels of CRP, ESR, and MMP-3. Treatment was started with corticosteroids (GC); 10-60mg/day PSL (mean 15mg/day). During GC tapering, the disease recurred in 19 patients, when 7.2 ± 3.9 mg/day was used after 8.3 ± 6.0 months. MTX was added in 18 patients and PSL was increased in a patient. In addition, AZA in 1 case and TCZ in 6 cases were required for further relapse during MTX. ADA was added for TCR-resistant patient. GC could be withdrawed in 9 patients after 17.8 ± 4.8 months treatment. Adverse effects included diabetes, metabolic syndrome, and osteoporosis. **Conclusions:** 2015 EULAR/ACR recommendations are useful for Japanese patients with polymyalgia rheumatic (PMR).

W1-3

Use of serum ferritin and heme oxygenase 1 for the diagnosis of adult-onset Still's disease: 2nd report of multicenter study

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Conflict of interest: None

[Object] To evaluate the use of measuring serum ferritin and heme oxygenase (HO)-1 levels for the diagnosis of adult-onset Still's disease (AOSD). **[Methods]** A total of 106 AOSD cases and 26 disease controls were enrolled. Serum ferritin and HO-1 levels were measured in all of the collected samples by means of ELISA. An association among clinical symptoms, serum ferritin, and HO-1 was explored. **[Results]** Serum ferritin and HO-1 levels were significantly higher in active and relapsed AOSD cases. In remission patients, whose serum ferritin were normal, 20.6% exhibited high HO-1 levels. Remission-induction therapy normalized serum ferritin levels in most of the cases, but more than half of them had high HO-1 levels. ROC analysis revealed cutoff values of serum ferritin >830 ng/ml (sensitivity 85.7%, specificity 82.5%) and HO-1>21.1 ng/ml (sensitivity 94.4%, specificity 87.8%), for the diagnosis of AOSD. Multivariate analysis showed typical rash, lymphadenopathy/splenomegaly, RF/ANA negative, and either ferritin/ HO-1 high, were factors independently associated with the diagnosis. **[Conclusions]**We confirmed that serum ferritin and HO-1 serve as a biomarker for AOSD. We plan to propose a new set of criteria for the diagnosis of AOSD by enrolling more patients (UMIN000012912).

W1-4

Persistent pruritic eruptions associated with adult-onset Still's disease ~the study of dermatologic pathology from 3 cases~

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Conflict of interest: None

【Case 1】A 77-year-old woman presented with fever, arthritis, hepatosplenomegaly, elevated CRP and hyperferritinemia. Skin biopsy from precordial persistent urticarial erythema was performed. IL-18 was significantly elevated, and she was finally diagnosed as adult-onset Still's disease (AOSD).【Case 2】A 76-year-old woman developed fever, arthritis, eruptions, interstitial pneumonia and hyperferritinemia. Skin biopsy from precordial persistent erythematous papules was performed, and she was finally diagnosed as AOSD.【Case 3】A 64-year-old man presented with high fever, arthritis, hyperferritinemia and papules on the trunk to extremities. Skin biopsy from precordial persistent erythema was performed, and she was finally diagnosed as AOSD with high IL-18 levels. 【Outcome】All cases were treated with PSL,Tac,MTX,TCZ or RTX. 【Conclusion】Typical skin rash, which appears and disappears along with respective rise and fall of fever, is well-known in AOSD. Recent reports showed histological features of persistent pruritic eruptions in AOSD were characteristic, and dyskeratotic cells were found in the horny layers as well as in the upper layers of the epidermis. Our 3 cases of AOSD also presented similar eruptions and histological features, and we report with literature.

W1-5

Clinical characteristics of interstitial lung disease associated with adult Still's disease

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Conflict of interest: None

[Objectives] Some patients with Adult Still's disease-associated interstitial lung disease (ASD-ILD) have a poor prognosis. To clarify the clinical characteristic of ASD-ILD which is not yet established. [Methods] We retrospectively investigated 78 patients who were diagnosed for ASD. ILD was diagnosed based on HRCT. We extracted the patients with ILD in ASD and reviewed the clinical and imaging characteristics of the ASD-ILD. [Results] ASD-ILD was identified in 9 (11.5%) out of 78 cases and tended to occur in older female. HRCT showed marked interstitial thickening in all cases. There were neither honeycomb formation nor lung volume loss. Remarkable thickening of the visceral pleura and thickening of the interlobular septa were detected, in the pulmonary histopathology. ASD-ILD showed two clinical subtypes. Four cases had a shorter time from ASD onset to the detection of ILD, higher levels of serum ferritin and rapidly progressive ILD. The other 5 cases had a long time to the detection of ILD and stayed asymptomatic. ASD-ILD cases had a higher relapse rate of ASD. [Discussion] We thought that the cause of the interstitial thickening is more likely to be lymphedema in the acute phase of ASD, and that tissue remodeling and dense fibrosis are not involved in ASD-ILD.

W1-6

The analysis of prognostic factors for corticosteroids resistance in patients with adult-onset Still's disease

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Conflict of interest: None

[Objective] The aim of this study is to investigate prognostic factors for resistance to corticosteroids during remission induction and usefulness the clinical stratification of AOSD by Health, Labour and Welfare Ministry. [Method] We retrospectively analyzed in 30 patients fulfilling the Yamaguchi's criteria who have been followed up in our department between 2007 and 2015. [Result] Of 30 patients, 11 were male and 19 were female. An average age at diagnosis was 47.3 ± 16.6 years old. The clinical coarse was 13 corticosteroids responder and 17 resistance. In univariable and multivariavle analysis, the prognotic factors for corticosteroids resistance were the clinical stratification and low levels of serum IgG (odds ratio; 10.6, 0.99, 95% CI; 22.25-227.3, 0.98-1.00, respectively). In ROC curve analysis, the optimal the clinical stratification cut-off point for corticosteroids resistance was 2 (AUC=0.843, sensitivity 100.0% and specificity 50.0%). The clinical stratification together with low levels of serum IgG was highly predictive of corticosteroids resistance (AUC=0.935) [Conclusion] The clinical stratification of AOSD and low levels of serum IgG were useful prognostic factors for corticosteroids resistance.

W2-1

Monitoring of serum levels of interleukin-18 to predict effectiveness in adult onset Still's disease

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Conflict of interest: None

[Objective] The serum levels of interleukin (IL)-18 was associated with the disease activity in AOSD, so we discussed that monitoring of serum levels of IL-18 was suggestive of drug discontinuation. [Methods] Eight patients with AOSD diagnosed according to Yamaguchi criteria were lowered disease activity at initial treatment with corticosteroids or immunosuppressant, which we divided into high levels IL-18 or low IL-18 in comparison. [Results] After the disease activity lowered with initial treatment in AOSD, four patients with low levels IL-18 (182±27.5 pg/ml) were sparing corticosteroids and three patients drug-free over six months. But four patients with high levels IL-18 (14755±10596 pg/ml) were difficult corticosteroid sparing and kept on some immunosuppressant or biologics.[Discussion] The case of high levels IL-18 was reported multiple drug resistance in AOSD, following anti-cytokine therapy so that tocilizumab need to be continued as long as the level of serum IL-18 remains high. We need to keep corticosteroids and switch immunosuppressant in the patients of high levels IL-18, so that we suggested monitoring IL-18 was the predictive factor of treatment effectiveness. Corticosteroids and immunosuppressant could be discontinued below the serum levels of IL-18: 200 pg/ml.

W2-2

Evaluation of monitoring measures for adult-onset Still's disease (AOSD) activity during induction therapy

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Conflict of interest: None

Objective: To evaluate measures for monitoring AOSD activity during induction therapy after tocilizumab (TCZ) therapy has normalized the serum C-reactive protein levels. *Methods*: A chart review examined the serial serum IL-18 and ferritin levels of seven AOSD patients treated with a combination of TCZ and steroids in the past 2 years. *Results*: There was a positive correlation between the IL-18 and ferritin levels (rs=0.50, P<0.001). The median IL-18 level was 80,654 (746-231,705) pg/mL in the active phase and 1142 (429-2,368) pg/mL in the remission phase. Rapid reductions in the high-dose steroid were achieved after the ferritin levels decreased. Patients who improved and had mild AOSD symptoms had low serum ferritin levels and high IL-18 levels, and low-dose steroids could not be withdrawn in these patients. One patient had high serum ferritin levels and low IL-18 levels during an active infection after the AOSD improved. During AOSD exacerbations due to drug allergies in four patients, the IL18 levels increased from a median 31,417 (19,341-84,175) to 121,780 (92,201-171,982) pg/mL. *Conclusion*: A rapid reduction in high-dose steroid can be achieved when the serum ferritin levels decrease and steroid therapy withdrawal may be considered with low serum IL-18 levels.

W2-3

Study of procalcitonin in connective tissue disease patients including 10 case of adult onset Still's disease

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Conflict of interest: None

[Objectives] Significance of blood procalcitonin (PCT) level in the patient with connective tissue disease (CTD) accompanied by systemic inflammatory response syndrome (SIRS), and PCT in adult onset Still's disease (AOSD) was also studied. [Methods] We analyzed 58 patients with CTD who became hospitalized due to SIRS. Patients who were suspected to have bacterial infections judged from various culture tests and improvement by antibiotics were classified into bacterial infection group (A), and others were classified into non-bacterial infection group (B). [Results] 22 patients belonged to group A and 36 patients to group B. PCT showed a significant difference in A and B (41.73±21.97 vs 0.16±0.02: p=0.018). AOSD 10 patients and other disease 26 patients in non-bacterial infection group showed a significant difference (0.33±0.07 vs 0.09±0.01: p<0.0001). There was no correlation between PCT and ferritin observed in AOSD. [Conclusion] PCT in bacterial infection group and non-bacterial infection group was obvious differed. In AOSD patients in non-bacterial infection group PCT level was mildly elevated, and the

relationship with the pathology was discussed.

W2-4

Tocilizumab as an initial remission induction therapy for adult Still's disease

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Conflict of interest: None

Recently, it has been reported that quite a few cases of refractory AOSD were successfully treated with tocilizumab (TCZ). Here, we reported our experience evaluating both the safety and the efficacy of with TCZ as initial remission induction therapy in 4 patients with AOSD. 【Cases】 We assessed retrospectively a series of 4 patients with new-onset AOSD who were given TCZ. All patients met the classification criteria of AOSD proposed by Yamaguchi et al. One of the patients was male, and the mean age of onset was 32.5 years. The clinical manifestations included fever, arthralgia, skin rush and lymphadenopathy in all patients. DIC was the major complication in one patient, hemophagocytic syndrome in one, pleurisy in one. Two patients were treated with TCZ monotherapy, and last two received TCZ, cyclosporine and oral prednisolone (PSL). TCZ was started at 8mg/kg biweekly or monthly. All patients responded well to TCZ. In one patient, arthritis turned worse after 4 months. Remission was maintained in three patients during the 2 to 12-month follow-up period, and the PSL treatment was withdrawn. Adverse events were not seen in all patients. 【Conclusion】 TCZ therapy was extremely efficacious in treating AOSD, which shows a tendency toward a corticosteroid-sparing effect.

W2-5

Clinical significance of serum interleukin-18 level in adult onset Still`s disease

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Conflict of interest: None

【Purpose】Adult-onset Still`s disease (AOSD) could be divided into 'Systemic AOSD (S-AOSD)' with severe visceral and hemotological complications, and 'Rheumatic AOSD (R-AOSD) 'with more frequent joint damages. AOSD shares several clinical and laboratory variables with hemophagocytic syndrome (HPS). We examine the clinical significance of serum cytokine levels to evaluate the differences S-AOSD and R-AOSD, and to differentiate S-AOSD and HPS. 【Methods】Twenty-two patients with AOSD, who were admitted to our hospital between November 2011 and October 2015, were enrolled. Serum concentration of IL-18, IL-6, sIL-2R, ferritin, CRP and LDH was determined in both AOSD (S-AOSD:16 and R-AOSD:6) and HPS. 【Results】The serum IL-18 and ferritin level in S-AOSD patients was significantly higher than that in R-AOSD patients. On the other hand, IL-6 was higher in R-AOSD patients. IL-18 in S-AOSD patients was significantly higher than that in HPS patients. We determined that a cut-off of 9650pg/ml could distinguish S-AOSD from HPS with a sensitivity of 91.67% and a specificity of 87.50%. 【Conclusion】In AOSD, the cytokines of S-AOSD could be different from that of R=AOSD. We argue that IL-18 can be a biomarker for differential diagnosis between AOSD and HPS.

W2-6

The expression of Toll-like receptors in the peripheral blood of active adult-onset Still's disease

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Conflict of interest: None

Objective. The pathogenesis of adult-onset Still's disease (AOSD) is less understood, but it is suggested that infectious or other environmental factors trigger activation of T cells and macrophages, which results in hyperproduction of inflammatory cytokines. We investigated the expression of Toll-like receptors (TLR), an important receptor family of infectious and endogenous damage-induced materials, in the peripheral blood of patients with AOSD. Methods. RNA was extracted from peripheral blood of active AOSD patients. The expression levels of TLR2, TLR3, TLR4, TLR5, TLR7, and TLR9 were measured by real-time PCR. Results. Seven active AOSD patients (2 men and 5 women, mean age of 48 years) and four controls were enrolled. The expression levels of TLR5 were relatively higher than those in controls. TLR2, TLR4, and TLR9 showed similar levels of expression; TLR3 and TLR7 showed lower levels as compared to those in controls. Positive correlations were found among TLR2, TLR4, and TLR5 expression. The expression levels of TLR5 were correlated to soluble IL-2 receptor concentrations. Conclusion. The expression levels of TLR5 tended to be higher in the peripheral blood of active AOSD patients.

W3-1

Risk factors for malignancy in patients with rheumatoid arthritis based on the IORRA cohort during a 14-year observation period (2000 to 2013)

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Conflict of interest: None

[Object] To examine the risk factors for malignancy in patients with rheumatoid arthritis (RA). [Methods] Among patients with RA enrolled in the IORRA cohort from April 2000 to September 2013, all malignancies were extracted from patients' self-reporting and confirmed by medical records. With regard to overall malignancies and malignancies at frequently involved sites, risk factors were analyzed using Cox regression adjusted by age, gender, smoking history and BMI. [Results] Among 11,106 patients with RA representing 122,706 person-years, 114 lung cancers, 114 malignant lymphomas, 105 breast cancers, 95 stomach cancers and 90 colon cancers were confirmed. RA disease duration was a significant risk factor for lung cancer (HR 0.95, $P = 0.001$) and malignant lymphoma (HR 0.95, $P = 0.004$). RF positivity was a significant risk factor for lung cancer (HR 2.26, $P = 0.018$). DAS28 was a significant risk factor for overall malignancies (HR 1.10, $P = 0.008$), lung cancer (HR 1.25, $P = 0.012$) and malignant lymphoma (HR 1.22, $P = 0.049$). Neither MTX nor biological agent use was a significant risk factor for overall malignancies or malignancies at specific sites. [Conclusions] Shorter disease duration, RF positivity and higher disease activity were risk factors for malignancy in patients with RA.

W3-2

Clinical features of rheumatoid arthritis complicating lymphoma

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Conflict of interest: None

Objective: Lymphoma frequently develops in patients with RA. Importantly. It remains unknown what therapies for RA we select for patients with a history of lymphoma. **Methods:**We extracted RA patients with a history of lymphoma from RA patients who visited our hospital in October 2015. Clinical features were examined by reviewing their medical records. **Results:** Subjects were 12 cases which included 4 males and

8 females, a mean age of the onset of RA and lymphoma were 55 years (± 6.6) and 64.8 years (± 7.6), respectively. Lymphoma was developed after the onset of 11 cases in which before the onset of lymphoma all patients were treated with MTX and 3 were given bilogics. Histopathpological types of lymphoma were diffuse large B-cell in 5 cases, MALT in 3 and Hodgkin's disease in 2 cases. The sites of lymphoma were lymph nodes in 5 cases, salivary glands in 3, and intraocular, intramuscular in 1, mammary gland in 1 and colon in 1. Remission was induced in 9 cases. After remission of lymphoma, therapies for RA were PSL of 6 cases. MTX of 4, tacrolimus of 1, and rituximab of 2. By these therapies, 6 of them were in below low-disease activity. **Conclusion:** To establish the treatment, collection of a large number of cases of RA with lymphoma is required.

W3-3

Characterization of lymphoproliferative disorders occurring in 15 rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) represents a risk factor for having malignant lymphoma. Certain RA patients (pts) treated with methotrexate (MTX) develop lymphoproliferative disorders (LPD). [Methods] We analyzed 15 pts with RA who developed LPD from January 2010 to October 2015. [Results] Fourteen pts had been administered with MTX and 5 pts had received biological DMARDs. The mean age was 66±8, mean disease duration of RA 16±10 years, and mean duration of MTX treatment 4.9±2.3 years. Seven pts were diagnosed to have diffuse large B cell lymphomas, one had Follicular lymphoma, one Hodgkin lymphoma, one T cell-rich large B-cell lymphoma and one plasmablastic lymphoma. EB virus infection was detected in tumor tissues from 4 of 12 pts analyzed. Ten pts received chemotherapy, while 5 discontinued MTX. In 9 pts, RA recurred within mean 13±8 months after the treatment of LPD. LPD did not recur in all pts during observation period. [Conclusion] RA recurred after treatment of LPD was safely treated with DMARDs excluding MTX without recurrence of LPD.

W3-4

Abatacept therapy in 4 rhematoid arthritis with interstitional lung disease

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Conflict of interest: None

Deciding on biologic therapy in RA patients with preexisting Interstitial lung disease (ILD) is not easy. 4 patients who developed ILD or whose ILD deteriorated while MTX or anti-TNFα therapy were treated with abatacept. When the patients have acute symptoms, they initiated high-dose corticosteroids and antimicrobials. After the acute symptoms resolved, although radiography showed persistence of ILD, they initiated therapy with abatacept. 2 patients get remissions, 4 patients have had no further episode of respiratory insufficiency. The effect of abatacept on lung disease is controversial. But our experiences show that we can choose abatacept to control RA disease activity and prevent deterioration of ILD.

W3-5

Relation of serum rheumatoid factor (RF) level with extra-articular involvements in rheumatoid arthritis (RA) patients

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Conflict of interest: None

[Objective] Whether serum RF level indicates difference in disease state of RA is studied. [Patients & Methods] Patients who were examined for RF level (turbidimetric immunoassay, normal range: <15 U/mL) in our hospital from Jan. 2012 to Oct. 2015 were included. Patients showing an RF level of > mean +1SD were checked for extra-articular involvements from their medical records. [Result] A total of 4162 samples from a total of 1114 patients (M: 400, 65±15 y; F: 714, 64±16 y) were measured for RF. The mean +1SD was 109+447. All 24 patients (M: 11, F: 13) with an RF ≧556 had RA. Half of them (M: 7, F: 5) had an extra-articular involvement; 6: pneumonitis, 3: Sjögren's syndrome, 2: serositis, and 1: vasculitis. The ratio of patients with both a high RF level and an extra-articular involvement was 1.75 % in male, and 0.70 % in female. [Conclusion] Only a small number (2.15 %) of patients showed a high RF level; among them, male predominated. Half of them had any extra-articular involvement. The male predominance was quite different from it in usual RA. RA patients with a high RF level, especially male, would be better paid attention to their extra-articular involvement. Relationships among RF level, sex and extra-articular involvement remain to be elucidated.

W3-6

Study of rheumatoid arthritis with malignant tumor

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Conflict of interest: None

Purpose: To examine the risk of malignant tumor in rheumatoid arthritis (RA). Subjects and Methods: The clinical features and the therapeutic agents were investigated in 200 cases with RA who had been treated until October 31, 2015 from April 1, 2013. Results: There were 11 cases with malignant tumor (1 stomach cancer, 1 lung cancer, 1 duodenal cancer, 1 colon cancer, 2 hepatocellular carcinoma, 1 renal pelvis cancer, 1 breast cancer, 1 thyroid cancer, 2 malignant lymphoma, 1 MTX-related lymphoproliferative disorder). The age at the time of the malignant tumor diagnosis was 65.5 ± 10.9 years old. Disease duration of up to malignant tumor diagnosis was 166.6 ± 126.7 months. Five cases had family history of cancer. MTX had been prescribed to nine cases (an average of 6.7 mg/week), biological agents had been prescribed to five cases, DMARDs had been prescribed to two cases, immunosuppressive drugs had been prescribed to three cases, prednisolone had been prescribed to six cases (an average of 4.5 mg/day). The death due to cancer was one case. Conclusion: The proportion of blood malignancies in RA with malignant tumor was high. There was no obvious relationship between malignancies and the therapeutic agents.

W4-1

Prevalence and risk of interstitial pneumonia in patients with rheumatoid arthritis

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Conflict of interest: None

OBJECTIVE To reveal risk of acute interstitial pneumonia in patients with rheumatoid arthritis (RA). **METHOD** Subjects were RA patients who attended our hospital from 2009 to 2013. In those, the background factors of patients who developed non-infectious acute interstitial

pneumonia (IP) were retrospectively analyzed. Factors addressed in multivariate logistic regression included age, sex, disease duration and activity of RA, medication and underlying chronic IP found with CT. **RESULTS** Total subjects were 9210 patient-yrs consisted of 2688 patients (female 82.3%). Their median age was 66.0 yrs and disease duration was 12 yrs. Receivers of corticosteroids, methotrexate (MTX) or biologics was 53.0%, 58.9% or 13.2%, respectively. Underlying chronic IP was found in 281 patients (10.5%), which increased after the first 2 yrs of occurrence of RA. In 30 patients with acute IP, 20 had underlying chronic IP ($p<0.0001$) and 20 had received MTX ($p=0.4596$). Significant risk factors detected by multivariate analysis for acute IP were higher age (odds ratio (OR) 2.1 per 10 additional yrs of age), underlying chronic IP (OR 18.4), use of MTX (OR 4.0). There was no dose dependency in MTX. **CONCLUSIONS** MTX for patients with higher age and/or chronic IP can be a risk for acute IP.

W4-2

Comparison of the two year change of disease activity between rheumatoid arthritis patients with or without interstitial pneumonitis

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Conflict of interest: None

[Background]Rheumatoid arthritis (RA) often complicates with interstitial pneumonia (IP). Because of these risks, it is assumed that therapeutic strategy be looser and disease activity be worse in RA patient with IP. [Methods]267 RA patients registered in KURAMA cohort from 2012 to 2014 were enrolled retrospectively. We checked all patients' chest X-ray, and if abnormality was pointed out, IP was confirmed by chest CT. [Results]The number of RA patients with or without IP were 21 and 246, respectively. Baseline median age of RA patients with IP was elder than group without IP (70 vs. 64;$p=0.0058$), but disease duration, usage rate of methotrexate (MTX), corticosteroids, biologic DMARDs and DAS28-ESR were not different. In RA patients with IP, two-year changes of DAS28-ESR were significantly higher (0.139 vs. -0.241; $p=0.0017$) and the number of the patients of low disease activity (LDA) decreased (11 to 9 vs. 130 to 159). The usage rate of MTX and biologic DMARDs and median amount of MTX were declined in the patients with IP. [Conclusion]Our Study showed disease activity of arthritis tends to be getting higher in RA patients with IP, which might be resulted from the limitation and inadequate use of DMARDs.

W4-3

Biological treatment with respiratory tract disease recognized an extara-articular manifestation of rheumatoid arthritis, in particularly complicated with pulmonary nontuberculous mycobacteriosis

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Conflict of interest: None

The respiratory tract disease with RA is thought to be extra-articular manifestation and the evaluation of the risk of biological treatment is important. We retrospectively analyzed 25 RA patients (mean age 69, M/F 3:22) complicated with bronchial and bronchiolitis including 7 patients with nontuberculous mycobacteriosis (NTM). These patients were seen high titer of ACAP (466 IU/ml) and RF (441 IU/ml) and long standing RA (12.5 years). Biological treatment discontinued by adverse event was seen in 5 patients (2 pneumonia, 1 exacerbation of MAC, 1 pyelonephritis). Seven were diagnosed bacteriologically with pulmonary MAC (6 nodular bronchiectatic, 1 fibrocavitary disease). Positive serum MAC antibody were detected in 6 patients. Four were administered biologics before treatment of MAC and these patients were reached low disease activity or remission without flare of pulmonary MAC. One patients preceding biological treatment was discontinued biologics caused by exacerbation pulmonary MAC. Six patients complicated MAC were continued biologics with recent administration of abatacept. Although RA patients was complicated with respiratory tract disease including pulmonary MAC, careful administration of biologics was possible.

W4-4

Clinical characteristics of interstitial pneumonia with rheumatoid arthritis in *NinJa* 2014 database

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Conflict of interest: None

【Objectives】To evaluate the clinical characteristics of interstitial pneumonia (IP) associated with rheumatoid arthritis (RA) patients registered with *NinJa* 2014 database. 【Methods】The RA patients of 15032 persons registered with *NinJa* 2014 were subjected. Seventy-four patients hospitalized for IP (IP group) were compared with the others (non-IP group). 【Results】The ratio of male patients was 0.38 in IP group, whereas 0.20 in non-IP group. The average age was 68.7 in IP group, and 64.3 in non-IP group, and disease duration was 11.8 years, and 12.9, respectively. The smoking history was 42.5% in IP group, and 27.7% in non-IP group. The titers of rheumatoid factor and anti-CCP antibody were higher in IP group (431 IU/ml and 476 U/ml) than in non-IP group (124 IU/ml and 243 U/ml), respectively. Glucocorticoids was medicated in 75.4% of the patients in IP group, and 40.2% in non-IP group, DMARDs was 75.4% and 92.8%, MTX was 30.4% and 64.2%, and biologic DMARDs was 21.6% and 26.9%, respectively. 【Conclusion】The patients of IP associated with RA were more in men, were elder age, and had more frequent smoking history than that of non-IP group. Medication for RA in IP group was differed from that in non-IP group. Father study for prognosis of RA patients with IP was desired.

W4-5

Airway diseases on high-resolution computed tomography in patients with rheumatoid arthritis

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Conflict of interest: None

[Object] To determine the association between airway disease detected by high-resolution computed tomography (HRCT) and characteristics in patients with rheumatoid arthritis (RA). [Methods] HRCT was performed to evaluate or to screen lung diseases in patients with RA who visited our clinic for regular visits. Presence of airway and interstitial diseases was assessed, and association was analyzed among the airway involvement and clinical backgrounds including age, disease duration, disease activity, physical function, serology, inflammatory markers, and pulmonary symptoms. [Results] Total of 109 patients were evaluated. Presence of airway involvement was found in 46 patients (42.2%), and was significantly associated with disease duration. There were no significant association with concomitant interstitial lung involvement or other patient characteristics previously reported to be associated with interstitial lung diseases in RA. [Conclusion] There may be different background characteristics between airway diseases and interstitial lung diseases in patients with RA.

W4-6

Clinical Characterization of Interstitial Lung Disease in Rheumatoid Arthritis Patients in High Resolutional CT and Titer of Anti Citrullinated Peptide Antibodies

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Conflict of interest: None

Background/Purpose: To investigate clinical characteristics of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients. Methods:472 patients with RA were treated at our hospital and followed up at least one year as newly onset RA. Results:101 out of 472 patients showed ILD at initial presentation (21.4%). In HRCT findings, ILD in these 6 cases were widely spread at the initial presentation. The rest of 95 patients showed no progression of ILD and asymptomatic. However there were no difference in the HRCT findings which include nonseptal linear attenuation, ground-glass attenuation and air space consolidation between rapidly progressive ILD group and asymptomatic group, rapidly progressive ILD group showed more higher degree in honeycombing ($p<0.0001$) and extensive ILD ($p=0.0012$). Higher anti-CCP2 titers were found in higher extensive score of ILD ($p<0.0001$). Conclusion: HRCT findings focused on the extension score at the initial presentation is a useful predictor of the outcome of ILD in RA. Anti-CCP2 is one of the related factor of the extension score.

W5-1

ANCA-associated vasculitis with joint symptoms at presentation

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Conflict of interest: None

【Objectives】Patients with ANCA-associated vasculitis (AAV) often suffer from arthralgia, which resembles rheumatoid arthritis (RA) or polymyalgia rheumatica (PMR). We investigated the patients with AAV who showed joint symptoms at the onset. 【Method】AAV patients who complained joint symptoms at their first visit were reviewed retrospectively.【Results】Ten patients (MPA 7, GPA 1, unclassified 2) with the average age of 69.6 were enrolled. Eight patients were MPO-ANCA positive, 2 were PR3-ANCA positive (including one with double-positive), and one case was ANCA-negative. RF was positive in 7 patients, whereas none was positive for ACPA. Among 9 patients, no bone erosion was noted in X-Rays. Synovitis was detected by US or MRI in 3 cases. In one case, the patient developed alveolar hemorrhage after 2 months' treatment with PSL and DMARDs for RA. Another patient, who had been treated with PSL for PMR, showed fever and positive PR3-ANCA, and she was diagnosed as GPA after 2.5 years. All had organ injuries, and 4 cases were severe; 2 with alveolar hemorrhage and 2 RPGN. 【Conclusions】 Compared with RA or PMR, AAV can cause more severe organ damage, some of which lead to permanent sequelae. AAV is an important differential diagnosis of arthritis, especially in elderly patients.

W5-2

A clinical Study of ANCA-associated vasculitis (AAV) complicated with malignant tumor

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Conflict of interest: None

Background: Although it has been reported that the AAV complicated with the malignant tumor, majority of the reports are concerned about *de novo* tumor, which occurred after treatment using immunosuppressive agents. Reports about the malignant tumor and simultaneous AAV rarely existed. **Object:** To estimate clinical features and prognosis of ANCA (+) patients with malignancy. **Methods:** In order to clarify the clinical findings, course and laboratory data in the patients, who has *underlining tumor* with ANCA retrospectively, we attempted to make a list for about seven-years (from January 2008 to October 2015) using our hospital database. The definition of "*underlining tumor* " in this study was the patients found the malignancy somewhere within 6 months period before and after diagnose of ANCA (+), to eliminate *de novo* tumor, which was caused by immunosuppressive agents. **Results:** The total number of patients were 11, 5 males and 6 females, average age of these patients was about 71.8 years old (56-84). The c-reactive protein levels were lower in the ANCA positive patients without the evidence of systemic vasculitis than in the patients with overt vasculitis. **Conclusion:** The careful observation for eliminating malignancy could be important when the ANCA positive patients diagnose as AAV.

W5-3

Malignancies of Anti-neutrophil cytoplasmic antibody-associated vasculitis

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Conflict of interest: None

[Objective] To examine malignancy incidence and clinical features in patients with Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV). [Methods] Retrospective review of the records of 106 patients diagnosed with AAV observed from 2005 to 2015 in our hospital was performed. [Results] Mean age was 68.8 years. There was no gender preference (male/female: 56/53). Of 106 patients, 82 patients were diagnosed with microscopic polyangiitis (MPA), 21 patients with eosinophilic granulomatosis (EGPA), and 3 patients with granulomatosis with polyangiitis (GPA). Malignancy was found in 25 patients, and all malignancies were solid tumor. In six cases, malignancy was diagnosed at the same time. Three of 6 patients had gastric cancer, 1 had colon cancer, and 2 had breast cancer. All 6 patients were early cancer. Eight cases were diagnosed after the diagnosis of AAV. [Conclusion] Incidence for malignancies in AAV was 23.6%(25/106), that were higher than European and American studies. The search for malignancies, particularly endoscopy are recommended in Japan.

W5-4

A cross-sectional study of health-related quality of life (HRQoL) in patients with ANCA-associated vasculitis (AAV)

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Conflict of interest: None

[Object] We aimed to cross-sectionally investigate the relationship between HRQoL assessed by the SF-36 and the EQ-5D, and clinical background and indices among AAV patients. **[Methods]** AAV patients who visited our clinics and those who were hospitalized in our hospital from July through September 2015 were eligible. The patients were asked to complete the SF-36, the EQ-5D, and other related demographic questionnaires. Clinical information was collected simultaneously. **[Results]** A total of 28 patients with AAV (MPA 19, GPA 6, and EGPA 3) participated. In the study population, the mean age was 66, 23 were woman, the mean disease duration was 6 years, the mean prednisolone dosage was 11.8 mg/day, the mean BVAS was 5.9, and the mean VDI was 2.9. The mean physical (PCS) and mental component summary (MCS) scores of the SF-36 were 28.3 and 46.3, respectively and were significantly lower than the Japanese norms. The mean EQ-5D score was 0.72. In univariate analyses, the PCS and the EQ-5D score had moderate inverse correlation with age, the prednisolone dosage, the BVAS, and the VDI, whereas the MCS did not. **[Conclusions]** In the study population,

HRQoL of AAV patients was poorer than the norm. The PCS was inversely correlated with age, the prednisolone dosage, the BVAS, and the VDI.

W5-5

Clinical features in patients with elderly onset microscopic polyangiitis

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Conflict of interest: None

Objectives: To clarify the clinical features in elderly microscopic polyangiitis (MPA) patients. Methods: MPA patients who initially treated in our department from April 2004 to June 2015 were included in this study. The patients were divided into 2 groups (elderly: 75 years old or older, younger: below 75 years old) and clinical features were analyzed by retrospective review. Results: Nineteen patients (elderly: 6, younger: 13) were included in our study. Elderly patients showed significantly shorter hospitalization days (elderly: 38 days, younger: 61 days, $p = 0.035$) and decreased AST levels. Cutaneous symptom was significantly decreased in elderly group. One year survival rate was significantly lower in elderly patients (elderly: 50%, younger: 92.3%, $p = 0.02$). The main cause of death was pulmonary hemorrhage and infection. Significant negative correlation was detected between age at diagnosis and hospitalization days. Conclusion: Elderly MPA patients may show shorter hospitalization, whereas elderly patients may have elevated mortality rates due in part to disease itself or adverse events.

W5-6

Clinical characteristics of Giant cell arteritis (GCA) associated with polymyalgia rheumatica (PMR)

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Conflict of interest: None

[Background] Giant cell arteritis (GCA) is a relatively rare disease in Japan, and it is common in the elderly and often associated with polymyalgia rheumatica (PMR). There have been few reports regarding GCA with PMR. [Purpose and Method] To analyze the clinical characteristics of GCA patients, we examined clinical parameters including the incidence of association with PMR. 19 cases of GCA, which were newly diagnosed or flared in our hospital were examined retrospectively. We diagnosed GCA by the criteria of the American College of Rheumatology. [Results] The total number of 19 patients consisted of 6 (31.6%) males and 13 (68.4%) females, and average age was 74.6±10.0 (53-89). Six (31.6%) patients (male: female 1:5) were associated with PMR (average ages of the onset was 74.3±9.30). In the context of the onset of PMR and GCA in these patients, they were simultaneous in 3 cases, PMR preceded GCA in 3 cases, and GCA never preceded PMR. Five cases of the 6 GCA with PMR had symptoms of PMR at the onset of GCA. [Discussion and Conclusion] PMR often preceded GCA in the cases of GCA associated with PMR, suggesting the possibility that PMR is involved in the pathogenesis of GCA. We present the clinical characteristics of GCA in our hospital, along with some literature reviews.

W6-1

Three cases of hypersensitive vasculitis due to acetaminophen

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Conflict of interest: None

Case 1: 59-year-old male noticed fever, erythematous rush and polyarthritis. He had palpable purpura on both of legs and its biopsy specimens showed leukocytoclastic vasculitis. As high fever appeared after acetaminophen intake, we discontinued acetaminophen. We diagnosed as hypersensitive vasculitis (HSV) and 30mg daily dose of prednisolone was initiated and his symptoms were improved swiftly. Drug lymphocyte stimulation test (DLST) was positive for acetaminophen. **Case 2:** 43-year-old female visited our patient clinic for fever and erythematous rush on both of legs. Biopsy at left leg was performed and vasculitis was suspected by the pathological findings. Similar to Case 1, she noticed high fever repeatedly after acetaminophen intake. We discontinued acetaminophen resulting improvement of symptoms. Afterwards, DLST was positive for acetaminophen. **Case 3:** 74-year-old female presented fever, edema both of legs with rose-pink purpura, polyarthralgia and glomerular hematuria. As a recurrent fever after intake of acetaminophen was observed, we suspected HSV due to acetaminophen. Although skin biopsy was not available, clinical course strongly suggested the existence of HSV. **Conclusion:** An attention needs to be paid to the risk of HSV in using acetaminophen.

W6-2

A refractory case of vasculitis whose phenotype suddenly changed from cutaneous polyarteritis nodosa to IgA vasculitis (Henoch-Schönlein purpura) after 13 years

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Conflict of interest: None

[Case] A woman in her 40s was diagnosed with cutaneous polyarteritis nodosa 13 years ago.6 months before the admission to hospital, skin biopsy of livedo reticularis was performed and neutrophils, nuclear dust and fibrin were seen within the wall of medium-size vessels in the deepest layer of subcutaneous tissue. She presented with palpable purpura of all extremities, upper quadrant pain, paralysis of upper and lower limbs and arthralgia of both elbows and knees 10 days before the admission. She also had a fever over 38 degrees. Skin biopsy was performed again. Neutrophils, nuclear dust and fibrin were seen in dermis but no vasculitis was observed within the wall of medium-size vessels. All symptons was reliefed with using high-dose steroid, however proteinuria, microhematuria and granular cast appeared 2 weeks after the admission. Renal biopsy revealed IgA nephritis, and she was diagnosed with IgA vasculitis.**[Clinical Significance]** It is difficult to judge whether clinical phenotype would change in the same pathophysiology or cutaneous polyarteritis nodosa and IgA vasculitis would be concurrent. So it is an interesting case when we discuss the pathophysiology and classification of vasculitis on the whole.

W6-3

Significance of temporal artery ultrasonography in the diagnosis of giant cell arteritis

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Conflict of interest: Yes

[Objectives] To investigate whether temporal artery ultrasonography (US) assists the diagnostic performance of giant cell arteritis (GCA) in 1990 ACR classification criteria. [Methods] Fourteen patients who was suspected to have a GCA and received temporal artery US and temporal artery biopsy from April 2014 to August 2015 were enrolled in this study. Clinical course and laboratory data of all cases were retrospectively evaluated, and each case was respectively defined as "biopsy-proven GCA", "clinical GCA", and "non-GCA". Diagnostic significance of "halo sign" in US was evaluated. [Results] Seven of fourteen patients were diagnosed as GCA (5 biopsy-proven GCA and 2 clinical GCA), and the remaining seven cases were regarded as non-GCA. The 1990 ACR criteria classified GCA at a sensitivity of 85.7%, a specificity of 71.4%, and a positive pre-

dictive value (PPV) of 75.0%. When we substituted “tenderness, pulse decrease or US halo-sign” for the item 3 in the ACR criteria, and classified GCA in case of fulfillment of 4 or more items in the revised criteria, the diagnostic sensitivity was found to be 85.7%, the specificity 100%, and the PPV 100%. [Conclusion] Temporal artery US may be useful to assist diagnostic performance of the 1990 GCA criteria.

W6-4

Clinical features and radiographic findings of 3 cases of giant cell arteritis diagnosed by FDG-PET

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Conflict of interest: None

【Objective】To investigate clinical features and radiographic findings in patients with giant cell arthritis (GCA) in our institution. 【Method】 Patients who were diagnosed GCA by using FDG-PET between April 2015 and October 2015 were retrospectively reviewed. 【Result】Three patients were reviewed. The mean age was 73.3yrs (range 67-75yrs). All of them were female. Clinical symptoms are the followings: systemic symptoms (pyrexia and general fatigue) in two; jaw claudication in one. No patient had headaches or visual symptoms. No case had concomitant polymyalgia rheumatica. Their blood tests showed elevation of CRP (2.85-8.53mg/dl) and erythrocyte sedimentation rates (above 50mm/hr). They underwent FDG-PET and FDG uptake was found in aorta and large vessels. We diagnosed large-vessel GCA. But in some cases, distinguishing between atherosclerosis and GCA by patterns of FDG uptake was difficult. All patients were treated with oral prednisolone (PSL). They required moderate-dose PSL (0.5-0.6 mg/kg/day), and all of them achieved good responses. 【Conclusion】FDG-PET visualizes inflammation. Both atherosclerosis and GCA cause vascular inflammation, but distinguishing the two may be difficult.

W6-5

Outcome of induction therapy for giant cell arteritis and clinical features of the resistant cases

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Conflict of interest: None

[Objectives] To investigate outcome of induction therapy for giant cell arteritis (GCA) and clinical features of the resistant cases [Methods] All GCA cases referred to Rheumatology service at Keio University Hospital from April 2008 until October 2015 were enrolled. Clinical information was collected from medical chart and statistically analyzed. [Results] 20 GCA patients including 11 females were involved. The average age at the time of diagnosis was 72.6 years old. Glucocorticoids (GCs) were administrated in all patients. Average dose was 42.8 mg/day as PSL. GC pulse therapy was introduced for five cases including three eye involvements. In 12 cases, which were started and followed up over 6 months at our division, 5 cases were induction failure (42%). Average period from diagnosis was 4 months, and PSL amount was 11.2 mg/day. Increase of PSL (3), increase or add of immunosuppressants (IS) (3) and tocilizumab (TCZ) (2) successfully made all cases to stable state at final observation point. Remarkably, all 3 TCZ received cases were effective. [Conclusions] Induction therapy for GCA by GCs was initially effective, but often resistant in the reduction phase. Application of IS and/or TCZ in addition to GCs can make re-induction and subsequent maintenance possible.

W6-6

The efficacy and safety of tocilizumab monotherapy in Takayasu arteritis

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Conflict of interest: None

[Objectives]To evaluate the efficacy and safety of tocilizumab (TCZ) monotherapy in Takayasu arteritis (TAK). [Methods]We investigated 4 patients with TAK who had been diagnosed at our hospital from January 2013 to December 2014,and were enrolled in open-label prospective trial of TCZ monotherapy for TAK. TCZ (8mg/kg) was given every 2 weeks for the first 2 months and every 4 weeks for the next 10 month (total 15 times).The efficacy was assessed as symptoms,CRP/ESR,CT findings at week 12 and 48.The ”complete remission” was defined as normalization or disappearance of all findings. [Results] Baseline mean age was 43±18.8,mean disease duration was 39.7±42.6 months,mean CRP was 10.4±4.7mg/dL.All patients had artery wall thickening by CT. At week 12,all patients could achieve clinical remission. At week 48, CT findings disappeared in three cases (complete remission).One case who was pregnant at entry had normal delivery at week 12.There were no significant adverse events. [Conclusion]TCZ monotherapy may be a good alterative remission induction therapy for TAK patients who are reluctant to take glucocorticoids.

W7-1

The clinical utility of serum interleukin-17A in the diagnosis of early rheumatoid arthritis

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Conflict of interest: None

[Objective] IL-17 is a key cytokine in autoimmune disease such as RA. We considered the serum levels of IL-17A as the useful biomarker of diagnosed with early RA.[Methods] We measured the serum levels of IL-17A by enzyme-linked immunosorbent assay kit in twenty-six RA patients and thirty-five non RA with arthralgia patients. In the non-RA patients, adult onset Still’s disease was 8 patients, Reactive arthritis 4, vasculitis 4, inflammatory myositis 3, SLE 3, Sjogren’s syndrome 2, PMR/MCTD/SSc/Bechet/PsA 1, Pneumonia 2, FUO 3 and other 1.[Results] The serum levels of IL-17A in all patients were 56.5±183.7 pg/ml, in RA patients 117.7±265.7 pg/ml and non-RA patients 11.0±51.5 pg/ml, which were higher in the RA patients (p=0.04). We measured ACPA at forty-seven out of a population of all sixty-one patients, ACPA-positive RA patients were sixteen out of a population of seventeen measured ACPA in RA. The serum levels of IL-17A was higher in sixteen ACPA-positive RA patients than in twenty-eight ACPA-negative non-RA patients (P=0.0001).[Discussion] We measured serum IL-17A in patients accompanied by arthralgia, which was higher in ACPA-positive RA patients. It is supposed that serum IL-17A is useful in diagnosis with early RA involved in the pathology.

W7-2

Shared epitope positivity is related to efficacy of Abatacept in Rheumatoid Arthritis

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Conflict of interest: Yes

[Object]To identify the relation between the efficacy of abatacept on patients with rheumatoid arthritis (RA) and their HLA-DRB1 phenotype including whether having shared epitope (SE).[Methods]HLA-DRB1 phenotype of 46 patients treated with abatacept was identified, and divided into 2 group, SE (HLA-DRB1 0101, 0401, 0404, 0405, 1001) positive and SE negative. To overcome potential bias, multivariate logistic regression using the propensity score was done in this retrospective cohort. [Results]They were divided into 27 SE positive patients (59%) and 19 SE negative patients (41%). The retention rate of abatacept treatment at week 52 were 92.6%/52.6%(SE positive/SE negative, p=0.0001, log-rank

test), respectively. The EULAR good response rate at week 24 were 81.5%/15.8%(SE positive/SE negative, p<0.0001, Fisher's exact test), respectively. Multivariate logistic regression revealed the odds ratio of EULAR good response and SDAI remission achievement in SE positive patients was 25.1 and 5.47 (p<0.0001 and p=0.027), respectively. [Conclusions]Abatacept is strictly effective to SE positive RA patients.

W7-3

The effect of Abatacept for the clinical evaluation in patients with rheumatoid arthritis using the change of bone metabolic markers

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Conflict of interest: None

【Purpose】We studied the short to moderate term effect of ABT for the bone resorption in patients with RA by analyzing the changes in bone metabolic markers. 【Methods】Sixty three patients with RA (mean age:62.0 y.o.) were studied. We measured CRP and DAS28-CRP as the index of inflammation of RA, pyridinoline (PYD) and deoxypyrudinoline (DPD) as markers of bone resorption proper to treatment, 3, 6,12,18 and 24M after ABT therapy. We check the modified total Sharp Score (mTSS) at baseline, 12M and 24M. 【Results】PYD and DPD reflected the disease activity of RA from 6M to 24M. PYD and DPD reflected the mTSS of baseline but did not reflect the change of mTSS. The subgroup with decline of CRP more than 20% of baseline at 3M show the decline of PYD in 41% case and the decline of DPD in 32% case. On the other hand, subgroup with failure to decrease CRP at 3M showed the decline of PYD in 21% case and the decline of DPD in 37% case. PYD reflected the disease activity of RA at 3M, but DPD did not reflect the disease activity at 3M. 【Conclusion】The change of PYD and DPD reflect the disease activity of RA from 6M to 24M. The change of DPD at 3M after ABT therapy suggests the possibility of the direct effect of ABT for the suppression of bone resorption in RA.

W7-4

IL-6 blockade increases the proportion of CD25+CD4+ T Cells in rheumatoid arthritis patients

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Conflict of interest: None

[Objective] The proportion of CD25+CD4+ T cells is increased in ACPA (+) rheumatoid arthritis (RA) patients compared with ACPA (-) RA patients. Abatacept (ABA), a biologic blocking T cell co-stimulation, decreased the proportion of CD25+CD4+ T cells and IL-6 levels in ACPA (+) RA patients. It has been reported that CD25 expressions are increased by IL-6. Thus, we aimed to investigate whether IL-6 blockade with tocilizumab (TCZ) decreases the proportion of CD25+CD4+ T cells. **[Methods]** PBMCs were isolated from 12 ACPA (+) RA patients at baseline, 24 and 48 weeks of TCZ treatment. The proportion of CD25+CD4+ T cells was analyzed with FACS. **[Results]** The proportion of CD4+ T cells were significantly increased at 24 and 48 weeks compared with that at baseline (30.5±18.7% at baseline; 38.5±12.8%, *p=0.0123* at 24 weeks; 39.1±13.7%, *p=0.0247* at 48 weeks). The proportion of CD25+CD4+ T cells were significantly increased at 48 weeks compared with those at baseline (4.6±1.4% at baseline; 5.9±3.4%, *p=0.30* at 24 weeks; 7.1±2.2%, *p=0.039* at 48 weeks). **[Conclusion]** IL-6 blockade increased the proportion of CD4+ T cells as well as that of CD25 in CD4+ T cells. An increase in CD25+CD4+ T cells may result in an increase in regulatory T cells contributing to the therapeutic effect.

W7-5

Differential effects of certolizumab pegol and infliximab on human monocytes

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Conflict of interest: None

[Object] Certolizumab pegol (CZP) is an agent which comprises humanized anti-TNF-α monoclonal antibody Fab' fragment linked to polyethylene glycol (PEG). The current study was undertaken to compare the effects of CZP and infliximab (IFX) on human monocytes. [Methods] Monocytes were purified from peripheral blood mononuclear cells obtained from healthy donors using magnetic beads. Purified monocytes were cultured in 24-well microtiter plates with CZP, IFX, control IgG, or PEG at pharmacological attainable concentration. RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) or 10% autologous normal human serum (NHS), were used for cultures. After 24 hours, the supernatants were replaced with fresh culture medium, followed by the addition of LPS. After additional 24 hours of incubation, the supernatants were assayed for TNF-α. [Results] The suppressive effects of IFX on the TNF-α production were significantly diminished, whereas those of CZP were rather enhanced, in cultures with NHS compared with in cultures with FBS. [Conclusions] These results indicate that CZP suppresses the production of TNF-α by human monocytes in a different mechanism from IFX.

W7-6

Pathological changes in rheumatoid arthritis synovial tissues before and after the use of biological drug

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Conflict of interest: None

[Purpose] We examined the impact that Bio has on RA synovial tissues, using the pathological findings of a RA patient who underwent surgery and synovial tissues were collected before and after the use of Bio. [Methods] We targeted 22 joints of RA patients. We assessed pathological findings before and after the use of Bio by identifying the presence or absence of fibrinoid necrosis and plasma cells and using the Rooney score. We discussed the association with the synovial pathological findings, disease activity (CDAI) and blood biochemical findings. We used ETN11, IFX5, TCZ2, ADA2 and ABT2. [Results] Fibrinoid necrosis was identified in 4 joints (18.2%) and plasma cells were identified in 13 joints (59.1%) after the use of Bio, which showed significant improvement. The Rooney score also improved significantly, from 30.6 to 12.6. The perivascular lymphocytic infiltrate, lymphoid follicles and lymphocyte infiltration decreased significantly. There was a correlation between the Rooney scores and MMP3 after the use of Bio.[Conclusions] The improvement of inflammatory in the synovial membrane was observed by the use of Bio. Furthermore, pathological findings in synovial tissues have been suggested to reflect the disease activity.

W8-1

TCZ modulates the production of ccfDNA derived from RA synovial cells

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Conflict of interest: None

Objective: Circulating cell-free DNA (ccfDNA) is detected in sera of patients with rheumatoid arthritis (RA) and various cancer as well. We have shown the relation between ccfDNA in sera and disease activities of RA patients. In this study, we investigated the mechanism of ccfDNA production and the modulation of those by biological DMARDs. **Methods:** We collected the supernatant of RA synovial cells for each step of cellular-confluency; 40% to 120%. After stimulated with IL6/IL6R or TNFα, we collected the supernatant additionally incubated with and without tocilizumab (TCZ: 100μg/mL) or etanercept (ETN: 10μg/mL). Then, we analyzed ccfDNA by qPCR, and cell viability by WST-8. **Results:** Before and after 100% confluency state, the amount of ccfDNA in the supernatant increased first and decreased thereafter. The amount of ccfDNA incubated with TCZ was significantly suppressed, while those with ETN were not. There is no significant difference in cellular viabilities between non-treated and biological DMARDs-treated groups. **Conclusions:** Since the amount of ccfDNA was increased by cell proliferation and decreased in the growth inhibition by cell-to-cell contact. Results suggested that ccfDNA was released along with the physiological cell division, and TCZ could inhibit this.

W8-2

Development of the new rheumatoid arthritis disease activity marker using glycosylation change of MMP-3

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Conflict of interest: None

[Objectives] In rheumatoid arthritis (RA), MMP-3, CRP, and ESR are commonly used as a serologic disease activity marker, but they have a problem at points such as sharpness and specificity. Therefore, we analyzed glycosylation change of MMP-3 to find RA specific disease activity index which reflects disease activity well. [Methods] MMP-3 was collected by immunoprecipitation from the serum of 24 RA patients, and their glycosylation patterns were analyzed using lectin microarray. We made disease activity index using lectin signals. It was validated by 2nd cohort, which included 60 serum from 30 RA patients. We also checked it in synovial fluids MMP-3 of RA and osteoarthritis (OA). [Results] Lectin such as ACG, ABA, ACA, and Jacalin reacted well with MMP-3. It meant that MMP-3 had O-glycan. We made an index, ACG/Jacalin, which correlated with DAS28-ESR (r^2=0.27, p<0.01). This index was validated by 2nd cohort; ACG/Jacalin was correlated with DAS28-ESR (r^2=0.34, p<0.01), and the change of ACG/Jacalin was correlated with the change of DAS28-ESR (r^2=0.32, p<0.01). The ACG/Jacalin of MMP-3 in synovial fluid was also higher in RA than OA. [Conclusion] We succeeded in development the new RA specific disease activity index using glycosylation change of MMP-3.

W8-3

Serum gliostatin can be a clinical marker of rheumatoid arthritis patients treated with Tofacitinib

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Conflict of interest: None

[Objective] Gliostatin (GLS) is known to have angiogenic and arthritogenic activities. We previously demonstrated significantly higher concentrations of GLS in the sera and synovial fluids of patients with rheumatoid arthritis (RA) compared to those with osteoarthritis or normal controls. The expression of GLS in serum from RA patients was significantly correlated with disease activity. Tofacitinib (TOF) is a novel oral Janus kinase inhibitor. In this study we examine serum GLS concentrations of RA patients treated with TOF. [Patients and methods] Three RA patients (two females and one male) who had a history of failed therapy with at least one biological DMARD, have received TOF therapy (10mg/day) for more than 12 weeks. The mean age and the average disease duration of RA were 59 years old and 22 years, respectively. Serum samples were collected for measurement of CRP, MMP-3 and GLS. GLS were measured by enzyme immunoassay. [Result] The mean CRP (6.9mg/dl) improved to 0.5 at Week 12, mean MMP-3 (418.7ng/ml) improved to 98.1 at Week 12, the mean DAS28-ESR (4.0) improved to 3.4 at Week 12. Serum GLS levels decreased from 4.9 to 1.8 ng/ml. [Conclusion] Serum GLS was reduced by TOF treatment, and correspond with clinical outcomes in RA.

W8-4

Serum 14-3-3 η reflects therapeutic response in patients with rheumatoid arthritis

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Conflict of interest: None

[Purpose] 14-3-3η is a new biomarker suggesting relevance to joint damage in rheumatoid arthritis (RA). We assessed relationship between serum 14-3-3η and therapeutic response to tocilizumab (TCZ). [Methods] Serum 14-3-3η was measured by ELISA before and after 1 year of treatment with TCZ in 156 RA patients. [Results] Baseline (BL) (median) age was 62.0 year and disease duration was 72 months. BL characteristics of 14-3-3η-positive (≥0.19 ng/ml) patients (N=110, 74%) and negative-patients were DAS28ESR [5.7 vs. 5.7, p=0.62], CDAI [34.6 vs. 24.8, p=0.54], ESR [48 vs. 35, p=0.53], RF [118.9 vs. 15, p<0.0001], CCP [92.5 vs. 28.8, p=0.028]. BL_14-3-3η had a significant correlation with DAS28-ESR 1 year after TCZ treatment (p=0.0088) in 127 RF-positive patients, whereas BL-ESR, CRP, RF, CCP did not. BL-14-3-3η low patients (<3.43ng/ml) had lower DAS28 1 year after TCZ than BL-14-3-3η high ones (2.18 vs. 2.78, p=0.0024). [Conclusion] Serum 14-3-3η correlated with RF and CCP and may be a prognostic marker for therapeutic response to TCZ in RA.

W8-5

Serum soluble folate receptor beta is a marker of responsiveness to anti-TNF biologics in RA

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Conflict of interest: None

Purpose. Folate receptor beta (FRB) is expressed on most synovial infiltrated macrophages from rheumatoid arthritis patients (RA). Previously, we established the assay system of serum soluble FRB using the sandwitch ELISA and showed elevated levels of soluble FRB in RA sera. The purpose of this study is to define whether serum soluble FRB in RA is a predictive marker of responsiveness to anti-TNF biologic agents. Methods. Serum soluble FRB was measured by using F $(ab')_2$ anti-FRab antibody as captured antibody and biotinylated anti-FRB antibody as detection antibody. Recombinant soluble FRB was used as standard protein. Serum soluble FRB values and DAS28CRP scores in 24 RA patients were measured before and 3 month after the treatment. Results.

Most RA patients with high values of soluble FRB was responsive to the treatment. These patients had high disease activity. Conclusion. The results show that high values of serum soluble FRB is a predictive marker of responsiveness to anti-biologic agents in RA.

W8-6

CXCR3-positive Th17 cells (Th17.1) and Abatacept effect in RA patients

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Conflict of interest: None

[Object] We analyzed association with Abatacept (ABT) effect and CXCR3+CCR4low Th17cells (Th17.1), the most pathologic Th17cells, in rheumatoid arthriti (RA). **[Methods]** We obtained peripheral blood in 40 RA patients, before and after ABTtherapy (0, 4, 24wks), and analyzed ratio of Th17.1 in CD4+ lymphocytes using multi-color flow cytometry. **[Results]** We analyzed the change of the ratio of Th17.1. Although classical Th17 significantly decreased (p=0.0031), the change of Th17.1 was slight (p=0.18). In the association with the clinical course, there was significantly little Th17.1 (0.78%(p=0.021)) in the GOOD RESPONSE (GR,EULAR response criteria) group, in comparison with the non-GR group (1.7%). Furthermore, there was a significant association between the change of DAS28-CRP (ΔDAS28CRP, 0-24wks) and Th17.1 (0wks) (p=0.017). In,multivariable analysis (logistic-regression analysis), we analyzed effect on ABT response (GR) by Th17.1 (0wks) and the clinical parameter (age, gender, DAS28, SDAI, disease duration, ACPA, past BIO history, drug). As a result, a medical history of BIO (p=0.04) and Th17.1 (p=0.03) showed a significant difference. **[Conclusions]**These data suggested that Th17.1 becomes the independent predictive factor of the effect of ABT treatment.

W10-1

Investigation and comparison of pre-surgical status and condition among the different surgical groups of rheumatoid arthritis using the NinJa database

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Conflict of interest: None

[Objectives] NinJa 2013 was used to investigate pre-surgical status of rheumatoid arthritis patients among the different surgical groups. [Methods] We identified 325 patients (290 women, 35 men) in NinJa 2013 who underwent the extremity surgery in 2014. 37, 38, 25, 55, 84, 26 and 60 patients had surgery on the finger (Fi), wrist (W), elbow (E), hip (H), knee (K), ankle (A), and feet (Fo). Examined items included age, onset age, disease duration, BMI, stage, class, mHAQ, CRP, ESR, RF, arthroplasty count, swollen/tender joints, PtPain/Pt/Dr VAS, DAS28, CDAI, SDAI, HAQ-DI, mHAQ, EQ-5D, and HADS. [Results] In most of the items, there were no significant differences among the surgeries except for age (mean: Fi 58.7yo vs E 68.0, H 66.8, K 65.8, Fo 66.9), onset age (Fi 46.3yo vs E 55.0, K 53.2), disease duration (Fi 12.4y vs Fo 16.9), arthroplasty count (Fi 0.22 vs H 0.75), HAQ-DI (Fi 0.72 vs. E 1.57, H 1.24), and mHAQ (Fi 0.22 vs E 1.07, H 0.95). [Conclusion] The patients who undergo finger surgery are suggested to be relatively young, have less physical function deterioration compared with other surgery groups. On the other hand, it was assumed that there are not differences in disease activity, quality of live, status of anxiety and depression among the different surgery groups.

W10-2

Changes in the number of rheumatoid arthritis-related surgeries performed by the Akita Orthopedic Group on Rheumatoid Arthritis

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Conflict of interest: None

[Object] To analyze the changes in the number of RA surgeries performed by the Akita Orthopedic Group on Rheumatoid Arthritis (AORA). [Methods]RA surgeries performed between 2010 and 2014 for patients treated at one of the 28 facilities belonging to AORA were investigated. [Results] The annual number of surgeries was approximately 60-70 throughout, showing no major changes. Regarding the proportion of surgeries performed on the upper limbs, lower limbs, and spine among the total number of surgeries performed each year, surgeries on the upper limbs decreased, while surgeries on the lower limbs increased. Regarding the specific types of lower limbs surgery, total joint arthroplasty accounted for approximately 30-40% of lower limbs surgeries throughout, showing no major changes, but foot surgeries showed a tendency to increase. The proportion of patients using biologics among patients undergoing surgery was approximately 20-30% throughout. Regarding the foot surgery, the proportion of patients using biologics increased. [Conclusions] The annual number of surgeries and the proportion of patients using biologics among patients undergoing surgery showed no major changes. Regarding the foot surgery, the proportion of patients using biologics increased.

W10-3

Report of the rheumatoid arthritis cases with fragility fractures caused after lower limbs arthroplasty (TKA, THA)

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Conflict of interest: None

(Objective) We performed 257 lower limb arthroplasty (TKA and THA) for rheumatoid arthritis (RA) in the past eight years. However postoperative fragility fractures occurred in 6 patients. The purpose of this study is to analyze these cases in order to prevent these fragility fractures. (Methods) 1 male and 5 females (average age 78.2 years) were observed. We investigated the fracture site, injury mechanism, disease activity of RA, medication before fracture and treatment of each case. (Results) 2 vertebral, 3 femoral shaft and 1 tibial shaft fractures were oc-

curred. The disease activities were well controlled using MTX (2 cases), MTX+SASP (1 case), BUC (1 case) and ETN (1case). Although all patients received long-term glucocorticoid therapy only 2 patients were treated for osteoporosis. 3 fractures were treated conservatively and other 3 received some operations. 4 patients were treated using teriparatide. (Conclusion) It is extremely important to prevent fragility fractures in order to maintain good clinical results of RA patients who received TKA and/or THA. In particular for high-risk patients we have to stop glucocorticoid and to use more effective medication for osteoporosis as well as the patients of proximal femoral fractures with osteoporosis under the regional alliances.

W10-4

Total hip arthroplasty for the sarcoid arthritis

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Conflict of interest: None

We present a case of sarcoidosis with hip arthropathy. Chronic arthritis may occur in patient with sarcoidosis, such bone changes are relatively rare. We treated this patient by total hip arthroplasty. Histopathological specimens showed chronic synovitis. This case exhibited non-caseating epitheloid granuloma.

W10-5

Isolated proximal tibio fibular joint arthritis in a patient with juvenile idiopathic arthritis: A case report

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Conflict of interest: None

We report the case of a 14-year-old girl of juvenile idiopathic arthritis (JIA) with isolated proximal tibiofibular joint arthritis. The clinical history, magnetic resonance imaging, and pathological findings of the patient are presented. We should be careful to evaluate the patient for chronic lateral knee pain, and consider concomitant evaluation for JIA, including rheumatoid arthritis.

W10-6

Gastrocnemius Muscle Flap for the treatment of Skin defect and Reconstruction of the extensor mechanism following Second Revision Total Knee Arthroplasty with Rheumatoid Arthritis; a case report

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Conflict of interest: None

She had been diagnosed as having RA in 20xx. She had undergone cementless type TKA (Kyosera. inc) for left knee pain in 20xx+5. Cement type prosthesis (kyosera inc) was undertaken 6 years later because aseptic loosening. The patient was pain-free for 3 years, but she needed silvercar for walking. However, in 20xx+14 she presented with a swollen and painful right knee with the prosthesis was loose, with massive bone resorption. We decided to reconstruct the knee with a semiconstrained fixed-bearing revision knee system (OSSTM; Biomet, inc, Warsow, IN). Five days after surgery, the surgical wound showed a secretion and skin necrosis. Ten days, these things worsened and exposed patellatendon. Acinetobactor was found from swab at this days. Twenty-one days, the patient underwent the wound debridment and gastrocnemius muscle flap. The result was good, and after twenty days of flap operation the flap was lived. A total layer skin graft used to cover part of the skin defect. After sixty days of flap operation, the wound was heald. The patient has been followed for six months, there was also a functional recovery of the knee motion and stability, reaching a good active ROM (-10° - 90°).

W11-1

Interstitial pneumonitis in RA model animal, D1CC x D1BC homozygous transgenic mouse

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Conflict of interest: None

[Objectives] Collagen induced arthritis (CIA) which shows acute and transient disorder is used for study of rheumatoid arthritis (RA), however it has been reported that complications including rheumatoid lung. D1CC mouse shows RA with interstitial pneumonitis (IP), thus to test whether D1CC x D1BC homozygous transgenic mouse shows IP. **[Methods]** I established a novel RA mouse model called D1CC mouse, in which CIITA transgene as a master switch for MHC class II gene expression was introduced in chondrocytes. D1BC mouse also expressed immune checkpoint molecule, B7.1 in the same way. Bleomycin intratracheal instillation with sonoporation was performed in D1CC x D1BC homozygous mouse. The progression of disease was monitored by measurement of serum SP-D. **[Results]** D1CC mouse showed both of RA and IP, however they did not show IP during RA. Blips of serum SP-D was observed only in D1CC x D1BC homozygous mouse. Also chronic inflammation in lung was observed after bleomycin with sonoporation. **[Conclusion]** D1CC mouse showed IP and it need 30-35 weeks after RA-induction. On the other hand, chronic inflammation in lung was induced at any time in D1CC x D1BC homozygous mouse by Bleomycin with sonoporation. This model is useful tool for the screening new drugs for IP.

W11-2

The function of Leucine-rich α2-glycoprotein for the differentiation of Th17 in CIA model

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Conflict of interest: None

[Object] We have identified Leucine-rich alpha 2 glycoprotein (LRG) as a disease marker of rheumatoid arthritis (RA) and reported to bind with TGF-β and enhance of Smad2 phosphorylation. In collagen induced arthritis (CIA), phosphorylation of Smad 2 in CD4 T cells is important for the Th17 differentiation and the induction of arthritis. We aimed to elucidate the function of LRG on Th17 differentiation and to examine the involvement of LRG in the pathogenesis of RA. [Methods] We induced CIA in male C57BL6 or LRG KO mice. The Th17 differentiation in inguinal lymph nodes was examined. In the presence or absence of recombinant LRG, Th17 differentiation of naive T cells was analyzed. [Results] The serum level of IL17 and the weight of inguinal lymph nodes were significantly lower in LRG KO than in WT. The number of Th17 cells in inguinal lymph node was significantly fewer in LRG KO than in WT. In vitro study, LRG promoted the Th17 differentiation and TGF-β-induced Smad2 phosphorylation. In addition, LRG enhanced p38 MAPK phosphorylation which is also important in the Th17 differentiation and proliferation. [Conclusion] Our study suggested that LRG promotes both the proliferation and Th17 differentiation of naive T cells, leading to deterioration of arthritis.

W11-3

Soluble Sigles9 suppresses arthritis in collagen-induced mice model and inhibits M1 activation of RAW264.7 macrophages

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Conflict of interest: None

[Object] The aim of this study is to investigate the efficacy of Sigles9 on murine collagen induced arthritis (CIA) model *in vivo* and the activation of cultured murine macrophage *in vitro*. [Methods] We induced CIA on DBA1J mice and Sigles9 (5 ng/gm body weight or 50 ng/gm body weight) or PBS was administered intravenously. The mice were subject-

ed to clinical,histological, and serum examination.We performed stimulation tests using cell-line murine macrophage RAW264.7. M1 macrophage markers (TNFα, IL-6, and iNOS) and M2 markers (CD206, Arginage-1) were evaluated by RT-PCR and western blotting. We removed sialic acid using sialidase and then performed the stimulation test.As a result. [Results]Treatment with Sigles9 in CIA mice significantly suppressed the incidence rate and severity of arthritis in a dose-dependent manner. Serum levels of TNFα in CIA mice were significantly suppressed by Sigles9. Sigles9 decreased the mRNA expression of M1 markers in RAW264.7, however, there was no significant change in mRNA expression of M2 marker by treatment with Sigles9. The sialidase treatment canceled the inhibitory effect of Siglec9. [Conclusions]We clearly demonstrated the efficacy of Sigles9 in murine CIA model through the suppression of M1 macrophage activation.

W11-4

Leucine rich α2 glycoprotein (LRG) is involved in pulmonary fibrosis by enhancing TGF-β signaling in fibroblasts

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Conflict of interest: None

Objective Lung diseases related to connective tissue diseases are often accompanied by fibrosis and TGF-β is a major mediator in tissue fibrosis. In this study, we aimed to investigate the involvement of LRG, recently reported as a modulator of TGF-β, in a murine model of lung fibrosis. Methods Mice were intratrachally treated with bleomycin and fibrosis were evaluated histologically and biochemically. Furthermore, TGF-β signaling was investigated using L929 mouse fibroblast cell line. Results Bleomycin treatment increased LRG protein levels in bronchial alveolar lavage fluids (BALF) and lung tissues. When compared to wild type mice, fibrosis was significantly inhibited in LRG knockout (KO) mice. Although there was no significant difference in BALF TGF-β levels between WT and LRG KO mice, phosphorylation and nuclear translocation of Smad2 protein were attenuated in the lung of LRG KO mice. In vitro experiments using L929 revealed that LRG enhanced TGF-β-induced Smad2 phosphorylation and the expression of downstream genes. Furthermore, TGF-β-induced Smad2 phosphorylation was enhanced by LRG protein in a dose-dependent manner. Conclusion These data suggest that LRG enhances TGF-β signaling in fibroblasts leading to promote fibrosis in a murine model of lung fibrosis.

W11-6

The regulatory role of γδT cells in bleomycin-induced pulmonary fibrosis

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Conflict of interest: None

[Purpose] Interstitial pneumonia (IP) is one of the critical complications in patients with several autoimmune diseases. The purpose of this study is to clarify the role of γδT cells in bleomycin-induced IP murine models. **[Methods]** 1) C57BL/6 (WT) and TCRδ deficient (TCRδ$^{-/-}$) mice were treated with bleomycin. After 21 days, the pathology and collagen production in lungs were examined. 2) WT and TCRδ$^{-/-}$ mice were injected with bleomycin. At 3, 7, 14, 21 days, pulmonary IL-17A^{+} CD4^{+} T cells were analyzed by FCM. 3) Splenic CD4^{+} T cells were isolated from IFN-γ deficient (IFN-γ$^{-/-}$) mice. These cells were co-cultured with γδT cells isolated from WT or IFN-γ$^{-/-}$ mice in condition of Th17 cell differentiation. **[Results]** 1) TCRδ$^{-/-}$ mice showed pronounced hypercellularity and intimal thickening in lung parenchyma, and overproduction of collagen in lungs compared with WT mice. 2) In TCRδ$^{-/-}$ mice, pulmonary IL-17A^{+} CD4^{+} T cells increased at day 7 and 14 compared with WT mice. 3) After Th17 cell differentiation, γδT cells derived from WT mice suppressed IL-17A^{+} CD4^{+} T cells, whereas γδT cells derived from IFN-γ$^{-/-}$ mice did not. **[Conclusion]** IFN-γ^{+} γδT cells might play a regulatory role in the development of pulmonary fibrosis through the suppression of IL-17A^{+} CD4^{+} T cell activity.

W12-1

Searching of the epitopes and reactivity to the tissue using monoclonal anti-TRIM21/Ro52 autoantibodies isolated from collagen disease-patients with interstitial lung disease

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Conflict of interest: None

Anti-TRIM21/Ro52 antibodies appear in sera of various collagen disease patients. Many of these patients have interstitial lung disease (ILD) and some of ILDs are severe. Some reports have shown that anti-TRIM21/Ro52 autoantibodies may relate to morbidity and acuity of ILD, but its mechanisms are still unknown. To clear its mechanisms, some epitopes of anti-TRIM21/Ro52 autoantibodies have been determined by using human sera, but not by using monoclonal anti-TRIM21/Ro52 autoantibodies. In this study, we have obtained monoclonal anti-TRIM21/Ro52 autoantibodies from patients with anti-ARS antibody syndromes by immunospot-array assay on a chip (ISAAC) technology, and have tried to determine their epitopes using the peptide library by ELISA and found that at least three of them that were obtained from different three patients recognized the same peptide in the library. Next, we tried to determined segments that react to anti-TRIM21/Ro52 autoantibodies using segment protein of TRIM21/Ro52 by Western Blotting and found that most of these antibodies bonded to C-C domain of TRIM21/Ro52. We consider that these monoclonal antibodies have reactivity to the tissue of collagen diseases and now try immunohistostaining using salivary glands of shogren symdrome.

W12-2

Autoantibodies to the cohesion complex in patients with inflammatory myopathy and interstitial lung disease

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Conflict of interest: None

Aim: Several new myositis-specific autoantibodies (MSA) have been described recently. Nevertheless, ~50% of patients with PM/DM are still without known MSA. During screening of sera by immunoprecipitation (IP), a set of 3 proteins recognized by DM sera was noted. Target antigens were identified and clinical characteristics of the antibody-positive patients were analyzed. Methods: Sera of ~2600 patients including 514 PM/DM were tested by IP. The 3 protein bands of 140 -160kD, detected by a prototype DM serum were purified and identified by mass spectrometry (MS) and IP-western-blot (IP-WB) using mouse monoclonal antibodies (mAb). Results: Target antigens were identified as subunits of the cohesin complex (SA-1, SA-2, SMC-1, SMC3 and PBS5B) by MS. These subunits and an additional component Rad 21, were confirmed by IP-WB. IP patterns by anti-cohesin mAb were identical to those by autoimmune sera. Four anti-cohesin sera (3 females and a male; 2 Americans,1 Mexican and 1 Japanese) were identified. Diagnoses were PM-SSc, DM, ADM and ILD. All cases received steroid and 3 cases were also treated with immunosuppressive drugs. ILD was the main reason for treatment. Conclusion: The cohesin complex was identified as a new target of autoantibodies in inflammatory myopathy and ILD.

W12-3

Clinical analysis of antiaminoacyl tRNA synthetase antibody (anti-ARS antibody) syndrome in our department

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Conflict of interest: None

[purpose]Because ant-iARS antibodies have been discovered recently and the disease concept of antiARS syndrome has not been well defined yet, we evaluated characteristics of patients with antiARS antibody in our department clinically. [method] We measured each anti-ARS antibody except the anti-CADM140 antibody, and examined efficacy of the treatment on the suspected myositis with anti-ARS antibody profile. [patients] Seventy-two patients who had a diagnosis of polymyositis, dermatomyositis (PM/DM), systemic sclerosis (SSc) or anti-ARS antibody syndrome. mean 56.7±15.8 years old, men 29, women 43 [results] 1) Anti-ARS antibody-positive group consists of 12 PM patients,24 DM patients, 5 anti-ARS antibody syndrome,3 SSc. 2) The mean serum CK level of the anti-PL-12 antibody positive group was lower than that in other groups (355±637.2 U/L vs. 1,654±2,674 U/L). 3) Nine patients were associated with neoplasm and 8 of those were DM. Six out of these 9 showed anti-ARS ab-positive.4) There ase 38 anti-ARS antibody-positive cases. Of those, 2 were required gamma globulin high dose therapy, but 4 of 21 negative cases required gamma globulin high dose therapy. [conclusions] It was suggested that anti-ARS antibody is a predicting factor of refractory clinical condition.

W12-4

Consideration of chest high-resolution computed tomography scoring of polymyositis / dermatomyositis-associated interstitial lung disease

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Conflict of interest: None

【Objectives】Polymyositis (PM) / Dermatomyositis (DM) -associated interstitial lung disease (ILD) is a factor that affects life prognosis. In particular, anti-melanoma differentiation-associated gene 5 (MDA5) antibody positive cases become rapidly progressive ILD, so necessary to early diagnosis. In this study, we aimed to compare to the ILD-with anti-MDA5 antibody and ILD-with anti-aminoacyl-transfer RNA synthetase (ARS) antibody by scoring chest high-resolution computed tomography. 【Methods】In 25 patients with PM/DM-ILD (7 anti-MDA5 antibody; 18 anti-ARS antibody), We have divided the lungs into three zones (upper/middle/lower). Then, we scored using findings of the image being the exisiting reported. Lower ground-glass opacities (GGO) (two point), random GGO (four point), subpleural (three point), consolidation (three point). 【Results】Anti-MDA5 antibody positive patients scored (mean±Standerd Deviation) 7.0±3.54, 18 patients with anti-ARS antibody scored 2.71±2.02. There was a significant difference between the two groups ($p<0.05$). We calculate area under the curve to determine the most appropriate cutoff point. When the cutoff value is five points, 86% sensitivity and 67% specificity. 【Conclusion】This scoring might suggest an anti-MDA5 antibody positive cases.

W12-5

Platelet associated IgG in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the clinical significance of PAIgG in RA. [Methods] We checked PAIgG in 266 RA patients. We evaluated age at onset of RA, age of PAIgG test, disease duration, platelet number (PN), platelet bindable IgG, CRP, ESR, RF, MMP-3, DAS28-CRP, DAS28-ESR, SDAI, CDAI, and MTX dose between PAIgG (+) and (-). [Results] PAIgG were positive in 60.9%(162/266). There were significant differences only in RF and PN. RF were higher in PAIgG (+) than those in (-) significantly (126.4 IU/mL vs. 84.4 IU/mL, $p=0.03$). PN were lower in PAIgG (+) than those in (-) significantly (207,000/μL vs. 218,000/μL, $p=0.03$). However, the PAIgG (+) patients whose PN were under normal limit (NL) were only 11.1%(18/162). There was no significant difference compared with PAIgG (-) patients whose PN were under NL (8.7%: 9/104). [Conclusion] PAIgG show high value in immune thrombocytopenia. However, we found high PAIgG positive rate in RA which usually shows thrombocytosis. Although PN in PAIgG (+) were lower significantly, the mean value was within NL. The rates under NL between 2 groups were not different significantly. Although PAIgG had little effect on PN in RA, RF were higher in PAIgG (+) significantly. Further investigation is needed to evaluate the clinical significance of PAIgG in RA.

W12-6

Change of ACPA and rheumatoid factor by treat of various biological agents

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Conflict of interest: None

【Objectives】To evaluate the Change of ACPA and rheumatoid factor (RF) by treat of various biological agents (TNF inhibitor, Tocilizumab (TCZ), Abatacept (ABT) for rheumatoid arthritis (RA) patients. 【Methods】We examined retorospectively 62 (TNF inhibitor, Infliximab:6, Etanercept:28, Adalimumab:14, Golimumab:10, Certolizumab pegol:4), 31 (TCZ), 29 (ABT) RA patients. The change of ACPA and RF by treat were examined. 【Results】ACPA (U/mL) changed from 142.6±206.1 to 108.6±183.3 in group TNF inhibitor ($P=0.35$), from 244.8±273.1 to 162.5±161.1 in group TCZ ($P=0.18$), from 207.1±251.5 to 293.2±765.7 in group ABT ($P=0.61$). There were not significant changes in all groups. RF (U/mL) changed from 98.7±205.8 to 95.3±316.4 in group TNF inhibitor ($P=0.94$), from 144.0±298.1 to 214.6±423.3 in group TCZ ($P=0.45$), from 286.3±343.5 to 154.8±199.0 in group ABT ($P=0.08$). RF tended to decrease in group ABT. 【Conclusion】ACPA was not changed significantly in all groups. RF tended to decrease in group ABT.

W13-1

The expression and function of STEAP4(TIARP)-splice variant in arthritis in mice and humans

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Conflict of interest: None

Objective TIARP is a negative regulator in arthritis model mice. In human, STEAP4 (human counterpart of TIARP) is also expressed in CD14+ monocytes from patients with rheumatoid arthritis (RA). Recently, TIARP-splice variant (v-TIARP) has been found to be highly expressed in porcine lung. The aim of this study is to elucidate the role of v-TIARP/STEAP4 in the pathogenesis of arthritis. **Methods** 1) The expression of v-TIARP in spleen and joint from GPI-induced arthritis (GIA) was analyzed by qPCR and Western Blotting. 2) To detect v-STEAP4, CD14+ monocytes that collected from RA and healthy subject (HS) were analyzed by qPCR. 3) To analyze the function of STEAP4, we cloned the DNA and inserted that into lentiviral vectors. **Results** 1) The splicing form (lack of the encode of exon3) of TIARP was detected in spleen and joint from arthritic mice. **2)** The expression of v-STEAP4 was detected in CD14+ monocytes, expressed higher in RA than HS, and positively correlated with RF and CRP. **3)** We are analyzing the function by genes overexpressed monocytic cell lines. **Conclusion** A novel variant of TIARP/STEAP4 was identified in both GIA and RA, and might have a crucial role in the generation of arthritis. Currently, we are elucidating the

function of v-TIARP.

W13-2

A proteomic profile of synoviocyte lesions microdissected from formalin-fixed paraffin-embedded synovial tissues of rheumatoid arthritis

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Conflict of interest: None

We have conducted an HPLC/mass spectrometry based exploratory proteomic analysis focusing on synoviocyte lesions laser microdissected (LMD) from formalin-fixed paraffin-embedded (FFPE) synovial tissues (RA $n = 15$; OA, $n = 5$), where those of Osteoarthritis (OA) were used as the control. A total of 508 proteins were identified from the RA and OA groups. With the semi-quantitative comparisons, the spectral index, log2 protein ratio based on spectral counting, and statistical G-test, 98 proteins were found to be significant to the RA synovial tissues. These include MMP3, proteins S100-A8 and S100-A9, plastin-2, galectin-3, calreticulin, cathepsin Z, HLA-A, HLA-DRB1, ferritin, neutrophil defensin 1,CD14, MMP9 etc Network analyses of protein-protein interaction for those proteins significant to RA revealed a dominant participation of ribosome pathway, and, interestingly, the associations of the p53 signaling. An involvement of proteins including CD14, S100-A8/S100-A9 seems to suggest an activation of the NF-*k*B/MAPK signaling pathway. Our strategy of laser-microdissected FFPE-tissue proteomic analysis in Rheumatoid Arthritis thus demonstrated its technical feasibility in profiling proteins expressed in synovial tissues, which may play important roles in the RA pathogenesis

W13-3

Low molecular compounds identified by screening a panel of multiple inhibitors have therapeutic value for the treatment for RA

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Conflict of interest: None

[Objectives] We have screened a panel of multiple inhibitors (n = 330) to search for drugs that inhibit the invasion of synovial fibroblasts obtained from rheumatoid arthritis (RA). Several candidate inhibitors were identified, including inhibitors for the platelet-derived growth factor receptor (PDGFR), Akt, phosphoinositide 3-kinase (PI3K), and glycogen kinase synthetase-3β(GSK-3β). We investigated whether the inhibitors have therapeutic potential for treatment of RA. [Methods] Cell proliferation was investigated by EdU uptake, phosphorylation of intracellular signaling molecules was investigated by immunoblot, and the concentrations of cytokines were examined by ELISA. [Results] All of the Inhibitors for PDGFR, PI3K and GSK-3β inhibited proliferation, migration, phosphorylation of Akt and IL-6 production from synovial cells. Furthermore, in THP-1 cells (macrophage-lineage cells), these inhibitors suppressed production of IL-1β and TNF-a. Interestingly, GSK-3β increased anti-inflammatory cytokine, IL-10, production from THP-1 cells. [Conclusion] Blocking of PDGFR/PI3K/GSK-3β has a therapeutic value for RA treatment.

W13-4

TGF-β induces non-Tfh CXCL13-producing CD4$^+$ T cells

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Conflict of interest: Yes

【Object】 Chronic inflammatory conditions including synovium of rheumatoid arthritis frequently accompanies ectopic lymphoid like structures (ELSs), where non-Tfh cells are known to produce CXCL13. Recently, we have shown that TGF-β induces CXCL13-producing CD4$^+$ T cells. On the other hand, human Tfh cells are known to produce CXCL13. In this presentation, we investigated whether TGF-β-induced CXCL13-producing CD4$^+$ T cells harbor Tfh-cell features. 【Method】 Naïve CD4$^+$ T cells of healthy volunteers were differentiated with TGF-β. Tfh-cell signatures including PD-1, ICOS, CXCR5, and BCL6 were determined with flow cytometry or quantitative PCR. 【Results】 TGF-β-induced CXCL13-producing CD4$^+$ T cells were positive for PD-1 but expressed low levels of CXCR5 and ICOS, whereas tonsil Tfh cells or tonsil CXCL13-producing CD4$^+$ T cells express high levels of PD-1, CXCR5 and ICOS. In the time-course analysis, the expression of CXCR5 and BCL6 in TGF-β group was constantly low. Quantitative PCR analysis also demonstrated that TGF-β-induced CXCL13-producing CD4$^+$ T cells lack most Tfh cell-like features 【Concludions】 TGF-β in the chronic inflammatory conditions induces the differentiation of non-Tfh CXCL13-producng CD4$^+$ T cells.

W13-5

Synergistic regulation of humoral immune responses by TGF-β3 and IL-10

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Conflict of interest: None

[Objectives] TGF-β and IL-10 are famous immunosuppressive cytokines but they also possess pro-inflammatory effects. In this study, we aimed to investigate the synergistic effects of those cytokines on murine B cells. [Methods] *In vitro*, murine splenic B cells were cultured under different stimulation conditions in the presence or absence of TGF-β1, 3, and IL-10. *In vivo*, imiquimod, a TLR7 agonist, treated mice were administered with pCAGGS-Tgfb3 or pCAGGS-Il10 plasmid vector. [Results] TGF-β alone effectively inhibited B-cell antibody production under anti-CD40 and IL-4 stimulation condition. To the contrary, under stimulation with TLR agonists, coexistence of IL-10 was necessary to regulate B cell responses. TGF-β and IL-10 synergistically inhibited B cell responses by suppressing autophagy through inhibiting eIF2α-ATF4 pathway. *In vivo*, coadministration of pCAGGS-Il10 with pCAGGS-Tgfb3 suppressed autoantibody production in imiquimod treated mice. [Conclusion] Our results showed that TGF-β3 and IL-10 synergistically regulated humoral immune responses under TLR-stimulated conditions via regulation of autophagy in B cells. These findings suggest the combination therapy with TGF-β3 and IL-10 has a potential value for the treatment of autoantibody-mediated autoimmune diseases.

W13-6

The control mechanism of Th17 cell differentiation by T-bet independently of IFNγ

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Conflict of interest: None

[Object] To clarify the effect of Th1 specific transcription factor T-bet on the Th17 cell differentiation. **[Methods]** 1) CD4$^+$ T cells from B6 mice (B6), T-bet transgenic mice (Tg), and Tg/IFNγ$^{-/-}$ mice (Tg/γ$^{-/-}$) were cultured for Th17 cell differentiation. Then the transcription factor expression, cytokine production, and STAT3 phosphorylation were analyzed by flowcytometry, and the mRNA expression of relevant transcription factors were analyzed by quantitative PCR (qPCR). 2) IL-6R expression of CD4$^+$ T cells from B6, Tg, and Tg/γ$^{-/-}$ were analyzed by

flowcytometry. 3) Naïve CD4$^+$ T cells from B6 were transduced T-bet gene with retrovirus vector, and the cells were cultured for Th17 cell differentiation, then the transcription factor expression and cytokine production were analyzed by flowcytometry. **[Results]** 1) RORγt expression and IL-17 production were suppressed, and STAT3 phosphorylation by IL-6 stimulation was inhibited in Tg and Tg/$\gamma^{-/-}$ mice. qPCR analysis revealed SOCS3 expression was reduced in Tg and Tg/$\gamma^{-/-}$. 2) IL-6R expression was depressed in Tg and Tg/$\gamma^{-/-}$. 3) RORγt expression and IL-17 production were suppressed by T-bet transduction. [Conclusion] T-bet regulates the Th17 differentiation via the inhibition of STAT3 phosphorylation independently of IFNγ.

W14-1

Low inhibiting allele of Killer Immunoglobulin-like Receptor (KIR) may affect susceptibility to Rheumatoid Arthritis (RA) -KIR allele typing by Next Generation Sequencing (NGS) revealed the susceptible genes?

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Conflict of interest: None

【Purpose】KIR genes have been studied in association with RA in a number of studies because of potential function in controlling NK cytotoxicity. However, almost no similar study of RA in the Japanese population has been reproted. This may be due to the homogeneity of KIR gene in Japanese, and the difficulty of the allele typing of all KIR. To overcome this limitation, allele typing of KIR was carried out by NGS in a Japanese case and control study of RA.【Methods】Peripheral blood from 114 RA patients and 183 of healthy controls were collected and DNAs were extracted with informed consents. The KIR gene types, haplotypes and allele types, and HLA allele types were determined by Scisco Genetics KIR/HLA typing Kit using NGS of MiSeq (Illumina). 【Results】Significant associations in allele types were detected, though no association was found in genetypes or haplotypes. KIR2DS4*007 (P=0.0007, odds=3.57) and KIR3DL1*005 (P=0.001, odds =2.36) were increased, while KIR3DL1*029 was decreased (P=0.049, odds =0.13). 【Conclusions】The inhibitory receptor KIR3DL1*005 was reported as conferring weak ability of NK inhibition while the *029 alleles conferred strong inhibition. These results suggest that low inhibitory ability of KIR may affect RA susceptibility.

W14-2

CD11b$^+$Gr1^{dim}cells increase with the progression of pneumonitis in SKG mice, and are induced by GM-CSF

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Conflict of interest: None

【Object】To clarify the mechanism of progression of pneumonitis in SKG mice. 【Methods】SKG mice were induced pneumonitis by Zymosan A (ZyA) injection. The severity of pneumonitis were assessed three month after ZyA injection. The severity of pneumonitis was evaluated by the area of diffusely affected lesion, as follows: histological score (HS) 0: affected area <10%, HS1: 10-29%, HS2: 30-59%, HS3: ≥60%. Lung-infiltrating cells (T cells, myeloid cells, innate lymphoid cells (ILCs), etc.) were evaluated by flow cytometry. 【Results】Histological analysis revealed that ZyA-treated mice developed pneumonitis; HS1: 30%, HS2: 50%, HS3: 20%. Flow cytometric analysis revealed that CD11b$^+$Gr1$^+$cells, CD11b$^+$Gr1^{dim}cells, Th17 cells, regulatory T cells, ILC1s, and ILC3s were increased in the lungs. The proportion of these cells varied depending on the HS. GM-CSF (and IL-4) facilitated the differentiation of CD11b$^+$Gr1^{dim}cells from lung cells *in vitro*. Intracellular cytokine staining revealed that not only Th17 cells but also ILC1s and ILC3s produced GM-CSF. 【Conclusions】GM-CSF, produced by Th17 cells, ILC1s and ILC3s, induced pneumonitis by proliferating CD11b$^+$Gr1^{dim}cells in SKG mice.

W14-3

A new indole compound, MA-35 suppressed the collagen expression in SSc patient fibroblasts

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Conflict of interest: None

Systemic sclerosis (SSc) caused fibrosis of multiple organs and vascular disorders. Previous researches suggested that suppression of collagen overproduction can stop the disease progression. However, there has been no treatment for it. We found a new indole compound named MA-35, which has an anti-fibrotic function (Patent No. 2014-65688). Previous research revealed it has the anti-inflammatory and anti-fibrotic effect for TNF-sensitive cells and renal fibroblasts. Therefore, we examined the anti-fibrotic effect of MA-35 for fibroblast from the skin of SSc patients. The amount of mRNA of collagen typeI(Col I) was measured by RT-PCR. In addition, the amount of protein, Col I, was measured ELISA. First, the amount of Col I RNA and protein were measured after added TGF-β or IL-6. Then the amount of Col I RNA and protein were measured after added MA-35 in addition to TNF-β or IL-6. In the results of our research, MA-35 suppressed the expression of Col I RNA and protein induced by either TGF-β or IL-6, by its concentration. We found MA-35 was effective for the fibroblasts from SSc. In conclusion, we indicate new compound, MA-35 has the potential to be a novel treatment for SSc.

W14-4

Analysis of platelet activation and monocyte subset in Behcet's disease

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Conflict of interest: None

[Objectives] Platelets have function of activating inflammations. We reported platelets are activated in RA and promote IL-1b production of PBMCs. Although anti-IL-1b therapy is effective in Behcet's disease (BD), involvement of platelets in BD has not been reported. The main IL-1b producing cells in blood are monocytes and they are divided into classical (CD14++,CD16-), intermediate (CD14++,CD16+) and non-classical (CD14+,CD16+). The three subsets are different in the cytokine productivity, but there is no report in BD. The aim in this study is revealing the characteristics of platelet activation and monocyte subset in BD. [Methods] We compared platelet activation of BD patients with that of healthy donors by flow cytometry in CD62P / CD61 staining. We compared monocyte subsets of BD patients with that of healthy donors by flow cytometry in CD14 / CD16 staining. [Results] BD patients showed significantly higher expression of CD62P among CD61 positive cells than healthy donors. BD patients tended to have more intermediate subset than healthy donors. CD16+ monocytes had more IL-1b productivity. [Conclusions] Platelet activation is observed in BD. In addition, intermediate subset of monocytes increases in BD. Therefore, they may enhance IL-1b production in BD and they may exacerbate BD.

W14-5

Analysis of the expression of cytokines in cultured fibroblast-like cells derived from ossification of the posterior longitudinal ligament in cervical spine

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Conflict of interest: None

[Object] In the pathogenesis of ossification of the posterior longitudinal ligament (OPLL), ossification process was under enchondral ossification regulating under signal transduction. The present study used cultured ligamentum cells to test the hypothesis that cytokines or growth factors plays a role inossified process in OPLL. [Methods] We harvested specimens from 12 patients who underwent decompressive surgery for symptomatic cervical OPLL. Samples of non-ossified ligaments obtained from five patients were used as control.Cultured cells derived from OPLL were exhaustively analyzed for the expression levels of cytokines and growth factors by suspension array system. The harvested ligamentum sections were also investigated with immonohistochemical examination. [Results] Suspension array evaluation showed that the expression of IL-1, IL-6, MIP-1α, and VEGF were especially significant in cultured OPLL. Immunohistochemical examination revealed that these factors were positive in the macrophages or endothelial cells around ossification front. [Conclusion] We considered that cytokines or growth factors contribute to regulate the process chondrocytes differentiation, from mesenchymal cells to mature osteoblast in a very complex manner in the process of OPLL.

W14-6

Sterile inflammation is enhanced with soluble uric acid in vivo and in vitro

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Conflict of interest: None

[Object] Monosodium urate crystal induces sterile inflammation via activation of NLRP3 inflammasome. However it's still unclear whether soluble uric acid is associated with innate inflammation. [Methods] In vivo, we prepared uricase transgenic mice which levels of serum uric acid were lower than that of control mice (C57BL/6). Two types of uricase transgenic mice, one is secretable uricase (ssUOX Tg), another is intracellular uricase (intUOX Tg), and control mice were injected with cholesterol crystals into peritoneal cavity. The number of neutrophil infiltrating into the peritoneal cavity were counted. In vitro, human PBMCs were stimulated with LPS and cholesterol crystals with addition of low levels of uric acid, and IL-1β secreted by PBMCs was measured. [Results] The number of neutrophils infiltrating into peritoneal cavity were significantly decreased in uricase transgenic mice; ssUOX Tg 3.58 x 10^6 ± 1.19 x 10^6cells/mouse, control 4.85 x 10^6 ± 1.43 x 10^6cells/mouse [p= 0.015], intUOX Tg 3.23 x 10^6 ± 1.25 x 10^6cells/mouse, control 4.36 x 10^6 ± 1.04 x 10^6cells/mouse [p=0.0094]. Secretions of IL-1β were elevated in PBMCs cultured under over 1mg/dl of uric acid level. [Conclusion] It was shown that soluble uric acid augments sterile inflammation both in vivo and in vitro.

W15-1

Relationship between YKL-40 and Dermoscopy for Concurrent Interstitial Pneumonia(IP) and Pulmonary Arterial Hypertension(PAH) in Systemic Scleroderma(SSc)

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Conflict of interest: None

Purpose: While YKL-40, a chitinase-like protein, has been implicated in inflammation and tissue remodeling,reports on the relationship between SSc and YKL-40 in the Japanese population are unkown.Therefore, we examined YKL-40 and nailfold capillary in SSc patients with concurrent IP and PAH. **Subjects**: The sample of SSc patients at our hospital between August 2014 and June 2015 and included 41 SSc patients without concurrent IP and PAH,10 SSc patients with concurrent IP and PAH, and 8 healthy individuals. **Methods**: Serum YKL-40 levels were measured by ELISA, and nailfold capillary was measured using dermoscopy. **Results**: YKL-40 levels were 21.1±2.1ng/mL in healthy indiveduals, 58.9±8.9ng/mL in patients without concurrent IP and PAH (early/active/late pattern:39.9±13.0ng/mL (n=14)/58.8±16.3ng/mL (n=17)/61.7±21.8ng/mL (n=5)), and 186.5±49.6ng/mL in patients with concurrent IP and PAH (100.7±42.6ng/mL (n=3)/101.4±12.8ng/mL (n=2)/324.9±82.1ng/mL (n=5)). **Discussion**: Compared with healthy individuals, YKL-40 levels were significantly elevated in patients as well as in patients with concurrent IP and PAH. YKL-40 levels were significantly higher in patients with concurrent IP and PAH. YKL-40 and nailfold capillary findings of the present study suggest their utility in the diagnosis of IP and PAH in SSc.

W15-2

Subclinical damages at pulmonary artery of systemic sclerosis patients: an attempt at detecting elasticity with using stress Doppler echocardiography & an analysis of gene expression profile of peripheral blood

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Conflict of interest: Yes

Purpose: PAH is a leading cause of death in SSc. Although current studies focus on detecting early PAH, it is known that more than a half of the pulmonary circulation considered to be obstructed before a rise in PAP. So, in this study, we focused on subclinical damages at pulmonary artery. **Methods:** 50 patients categorized NYHA 1 with elevated BNP, Raynaud symptom, or sclerodactylia were included. With using stress DE, max-TRPG and the estimated sPAP/CO (eP/O) was calculated as an index of elasticity of PA. SSc patients (n=27) were compared with non-SSc (n=23). Some of the patients were also screened by RHC. 31 cases of gene expression signature were analyzed with using next-generation sequencing. **Results:** No significant difference was found in BNP or rest-TRPG between SSc and non-SSc. With stress DE, max-TRPG or eP/O was significantly high in SSc. The correlation between eP/O and mPAP/CO measured by DOB stress RHC was confirmed. By the gene expression analysis, correlation between eP/O and expression of genes including TGF-β activated kinase or DKK2 were found. **Conclusion:** Although detection of early damages at PA in SSc remains difficult, the eP/O may a candidate. The expressed genes corresponding with eP/O may play a role in a pathogenesis of early pulmonary damage.

W15-3

Clinical utility of serial KL-6 level measurement in systemic sclerosis (SSc)

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Conflict of interest: None

Objective. We investigated clinical utility of serial KL-6 level measurement in SSc. ***Methods.*** We enrolled 63 consecutive patients who were diagnosed as having SSc between 2007 and 2013. These patients were selected based on disease duration ≤8 years, follow-up period >2 years, availability of pulmonary function test (PFT) and chest high-resolution CT at diagnosis, and availability of serial PFT results. Serum KL-6 levels were serially measured. We examined the correlation between yearly change of % predicted forced vital capacity (%FVC) and KL-6 level at diagnosis and during follow-up. ***Results.*** Forty four had interstitial lung disease (ILD). Baseline KL-6 was higher in ILD (+) than in ILD (-). KL-6 was stable below 500 U/ml in ILD (-), but were sustained above 500 U/ml in 57% and changed with variation in ILD (+). In ILD (+), yearly change of %FVC was inversely correlated, not with baseline KL-6, but with final KL-6 to baseline KL-6 ratio and the coefficient of linear regression of serial KL-6. In 16 ILD (+) treated with cyclophosphamide, KL-6 was decreased at 1 and 2 years after treatment, while %FVC was stable. ***Conclusion.*** Serial measurement of KL-6 may be

useful in predicting progression of pulmonary function and in evaluating treatment response in patients with SSc-ILD.

W15-4

Quantitative assessment with HRCT scoring method in interstitial lung diseases complicated with systemic sclerosis

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Conflict of interest: None

[Objective] Systemic sclerosis (SSc) is characterized by progressive fibrosis in various organs such as skin, lung, digestive tract and heart. The interstitial lung diseases (ILD) are a crucial prognostic factor in SSc. This study aimed to validate a quantitative analysis using HRCT on SSc-ILD. [Method] Twenty-one patients who had been diagnosed as SSc-ILD in our institution from June 2010 to May 2015 were enrolled in this study and the clinical records were retrospectively analyzed. For HRCT scoring to ILD, the impaired volume of each lobe in lung was scored with 0 to 5 points by a radiologist and the sum was calculated. [Result] There were 5 men and 16 women included and the mean age at diagnosis was 57.2 years old. Ten patients out of them were classified into diffuse cutaneous SSc. Eight cases exhibited UIP pattern and the others showed NSIP pattern in chest HRCT. The median values of %FVC, %DLCO, KL-6 and SP-D were 78.8%, 75.3%, 648U/ml and 162ng/ml, respectively. The median of HRCT scores was seven points. HRCT scores highly correlated with %FVC, %DLCO and KL-6, but not SP-D, and also indicated 10 points in two cases of ILD-related deaths. [Conclusion] This study suggested that HRCT scoring method was a valuable assessment tool for lung impairment in SSc-ILD patients.

W15-5

Efficacy of PAH specific drugs combination therapy in PAH-SSc patients

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Conflict of interest: Yes

Purpose: We performed a study to evaluate the factors that influence the effect of combination therapy using PAH-specific drugs (C-Tpy) on survival of PAH-SSc. **Methods**: We analyzed 56 patients with PAH-SSc (41:dcSSc, 15:lcSSc), who were followed up from Jan. 1980 until Sep. 2015 in our hospital. We performed Cox's analysis for survival using propensity score for C-Tpy. **Results**: 16 patients were PAH alone. 29 patients were complicated with ILD, 11 were complicated with LHD, and 6 were complicated with both of them. 25 patients were treated under C-Tpy. Multivariate study demonstrated that C-Tpy significantly reduced the risk for death (HR 0.40, 95%CI: 0.15-0.89) in PAH. Coexistence of ILD and PAH significantly increased the risk for death (HR 2.03, 0.98-4.43) compared with PAH alone. Moreover, coexistence of ILD and LHD in addition to PAH increased the risk for death (HR 2.28, 0.25-17.80) compared with PAH alone. **Conclusion**: Our results demonstrated that C-Tpy improved survival of patients with PAH-SSc, while that coexistence of ILD and/or LHD are poor prognostic factor in C-Tpy. These results indicate that appropriate management of PH-ILD and/or PH-LHD must be important for improving survival of PH-SSc patients treated with PAH-specific drugs combination therapy.

W15-6

Efficacy of pulmonary vasodilators in skin ulcers complicated with connective tissue diseases

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Conflict of interest: None

[Object] Pulmonary vasodilators (PVs) are reported to be effective for treating skin ulcers in patients with connective tissue diseases (CTD) such as systemic sclerosis (SSc), but the efficacy hasn't been sufficiently evaluated. We examined the dosage and the effect of PVs in CTD patients with skin ulcers. [Methods] We referred to medical records of CTD patients, who were treated with PVs and examined the dosage of PVs and clinical course of skin ulcers. [Results] 60 patients with CTD (32 with SSc) were treated with PVs and 49 were complicated with pulmonary hypertension. In 26 patients who had skin ulcers, 25 were treated with endothelin receptor antagonists (ETRAs), 7 with phosphodiesterase-5 inhibitors and 10 with sustained-released prostaglandin I_2. Skin ulcers improved in 7 of 25 and all of them were treated with ETRAs (6 with bosentan and 1 with ambrisentan). In patients whose skin ulcers didn't improve by ETRAs, ulcers didn't improve if other PVs were added. Average dose of bosentan was 177.1mg in patients with improvement of skin ulcers, higher than 123.0mg in patients without improvement (p=0.046). [Conclusions] If ETRAs doesn't improve skin ulcers, combination of PVs wouldn't be effective. These results implied skin ulcers can be improved by sufficient dose of ETRAs.

W16-1

Association of T-bet (TBX21) gene polymorphism with systemic sclerosis (SSc) in Japanese population

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Conflict of interest: None

<Purpose> SSc is autoimmune disease characterized by fibrosis and peripheral circulation impairment. Dysregulation of Th1 and Th2 balance is known to contribute development of autoimmune diseases. Dominance of Th1 pathway is supposed to be associated with development of SSc. However, none of reports has been reported in terms with association between TBX21 and SSc. To elucidate the association between TBX21 and SSc in Japanese cohort, genotyping was performed. <Methods> 303 Japanese SSc patients and 499 healthy controls were recruited in this study. Five SNPs, rs4794067, rs17250932, rs2240017, rs11650354 and rs17244587, on the TBX21 gene were genotyped using Taqman assay. <Results> Haplotype of rs2240017 (C allele) and rs17244587 (G allele) was protective haplotype for Japanese SSc development. (OR 0.33 (95% CI 0.13-0.881) P=0.02). Haplotype of rs17250932, rs2240017, and rs11650354 was increased risk of anti Scl70 and anti centromere antibody ($p<0.05$). < Conclusions > Haplotype of rs2240017 and rs17244587 is known to be associated with Th1 dominant autoimmune diseases. In Japanese cohort, this haplotype reduces SSc development. Haplotype of rs17250932, rs2240017, and rs11650354 participated in autoantibody of Japanese SSc.

W16-2

The clinical significance of anti-U3-RNP antibody in systemic sclerosis

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Conflict of interest: None

Background: Previous studies reported in Western countries have suggested that anti-U3-RNP antibody (aU3-RNP) was associated with SSc patients having frequent muscle involvement and PAH, the latter sometimes leading to a fatal course. According to a case series in Japan, organ involvement of aU3-RNP-positive SSc patients is less severe, but further study remains to be required. Objectives: To investigate the clini-

cal features of Japanese aU3-RNP-positive SSc patients. Methods: We evaluated the sera of 12,379 patients diagnosed as or suspected of connective tissue diseases at Kyoto University Hospital during 2001-2015. aU3-RNP was detected by RNA immunoprecipitation. Then, we examined the clinical features of five Japanese SSc patients with aU3-RNP. Results: aU3-RNP was detected in 11 patients (SSc 5, SLE 2, unspecified 4). Among five SSc patients, muscle involvement, esophageal dysmotility, Raynaud's phenomenon, telangiectasia were frequently observed. In contrast, only one patient had severe interstitial lung disease, and no patient had renal crisis. Two patients had PAH, but both were alive during follow-up. Conclusions: aU3-RNP appears to be associated with muscle involvement and good prognosis in Japanese SSc patients.

W16-3

Role of nail fold capillary changes by dermoscopy in patients with systemic sclerosis

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Conflict of interest: None

To evaluate the role of nail fold capillary changes of patients with systemic sclerosis (SSc) we measured the semi-quantitative scale NFcA in hand finger of patients with SSc.by dermoscope. [Methods]SSc93 (dcSSc40,lcSSc53),control84 (RA,PM,DM,SLE, Raynaud's disease), We measured the Nail fold capillary activity: NFcA scale (nail fold giant capillary0-2, nail fold bleeding 0-2,total 0-40). These score assessed at every months for 6 months. [Results]The NFcA in patients with SSc significantly higher than that of control patients. Cut off point > 3.5 of NFcA score. NFcA score counter-correlated with disease duration. In 10 patients with dcSSc treated by IVCY and corticosteroids NFcA decreased in nail fold bleedings. The number of nail fold bleeding decreased in early5 diffuse cutaneous SSc. [Conclusion]These data suggested that changes of nail fold capillary might be concern with pathological changes of patients with SSc.

W16-4

The progression of nail foldcapillary abnormalities in patient with Systemic sclerosis (SSc) by Nailfold videocapillaroscopy (NVC)

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Conflict of interest: None

[Objectives] Association between nailfold capillary changes and dysfunction of organ involvement were reported in SSc. The aim of this study was to investigate the progression of NVC changes during 52 weeks. **[Methods]** 30 SSc patients were enrolled. The quantitative scoring was performed by calculating A score (early change; the number of Enlarged and giant capillaries, haemorrhages) and B score (advanced change; the number of loss of capillaries, disorganisation of the microvascular array, and capillary ramifications). Organ involvements and their profiles of anti-body were also examined. **[Results]** At the baseline, both A score correlated to skin score, and B score correlated to not only skin score but also pulmonary hypertension and gastrointestinal involvement. At week 52, half of the cases (15/30) showed a progression of nailfold capillary changes. Of note, anti Scl-70 antibody was associated with rapid progression of B score, whereas, anti-centromere antibody associated with slow progression of A score. **[Conclusion]** The progression of the nailfold capillary abnormalities in SSc reflects organ involvement. Antibodies were correlated with the progression of NVC changes. Early intervention of treatment could be into consideration in patient with rapid progression of NVC changes.

W16-5

Contribution of Nailfold Videocapillaroscopy to Diagnosing Systemic Sclerosis in Japanese Population

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Conflict of interest: None

[Object] Capillary abnormalities observed by nailfold videocapillaroscopy (NVC) are useful for the diagnosis of systemic sclerosis (SSc). However, there are few reports about NVC in Japan. In the present study, we aim to estimate whether NVC may contribute to the discrimination of SSc and other Connective tissue diseases (CTDs) in Japan. **[Methods]** NVC findings were collected from 49 adult Japanese patients with CTDs, including 28 SSc patients. NVC abnormalities were assessed in 6 aspects: enlarged capillaries, giant capillaries, hemorrhages, loss of capillaries, ramified capillaries, and disorganization of the vascular array. The association between clinical manifestations and NVC patterns were assessed. **[Results]** Forty-five patients (92%) had irregular NVC patterns. There were no differences in the frequency of patients who had irregular NVC patterns between SSc and non-SSc (96% vs. 88%, $p = 0.61$), but loss of capillaries was observed more frequently in SSc patients than that in non-SSc (75% vs. 40%, $p = 0.02$). Frequency of the patients whose fingers mostly had NVC abnormalities were higher among SSc patients than among non-SSc patients (66% vs. 36%, $p = 0.05$). **[Conclusion]** NVC may contribute to the diagnosis of SSc in the Japanese patients as reported in other ethnicities.

W16-6

Investigation of pseudo-obstruction in patients with systemic sclerosis

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Conflict of interest: None

<Objectives> Pseudo-obstruction is one of the gastrointestinal involvements with systemic sclerosis (SSc), and it is associated with a poor prognosis. Disease-specific antibodies such as anti-topoisomerase I antibody, anti-centromere antibody (ACA), anti-RNA polymerase antibody are well known with SSc. These antibodies are often correlated with some organ involvement and mortality, but relevance of pseudo-obstruction and disease-specific antibodies is unclear. <Method> We investigated that relation with disease-specific antibodies and pseudo-obstruction of patient with SSc. <Results> Nineteen SSc patients out of 228 were investigated. Positive rate of anti- topoisomerase I antibodies, ACA, nucleolar pattern of anti-nuclear antibody are 8.3%, 37.5%, and 20.8%. Disease duration is significantly long in ACA positive patients. SSc patients need to implant CV access port more than the other rheumatic disease patients. <Conclusion> Our study suggested that relation with pseudo-obstruction and ACA. ACA positive patients tend to have less complication, but we must be careful about gastrointestinal involvement with ACA positive SSc patients.

W17-1

Different serological activities between two onset-categories of lupus nephritis

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Conflict of interest: None

Objectives: We previously reported a poorer renal prognosis in lupus nephritis (LN) that develops after SLE onset (delayed, D-LN) compared

with LN manifesting at the time of SLE onset (early, E-LN) (Mod Rheumatol, 2009). The current study compared serological profiles in the active phase of SLE in E-LN and D-LN. Methods: Hospital records of 163 patients with LN (82 E-LN, 81 D-LN) were reviewed for serum C3 and anti-dsDNA antibody (Ab) levels on admission for each of 343 active SLE events. Results: The treated SLE conditions in the 82 E-LN patients included 91 renal events (including 36 flares) and 36 non-renal events, while those in the 81 D-LN patients comprised 110 renal events (52 flares) and 106 non-renal events. Serum anti-dsDNA Ab levels were higher in D-LN than in E-LN upon renal events (169 ± 139 *vs*. 118 ± 145 IU/mL, $p < 0.01$), particularly renal flare events (159 ± 126 *vs*. 46.8 ± 81.2 IU/mL, $p < 0.01$). C3 levels upon renal events were similar in the D-LN and E-LN groups. Serum C3 levels were lower and anti-dsDNA Ab higher upon renal events compared with non-renal events in both groups. Conclusion: Serum anti-dsDNA Ab levels upon renal events were remarkably high in D-LN patients. D-LN may reflect more active SLE than E-LN.

W17-2

Cleaved Form of Osteopontin in Urine as a Clinical Marker of Lupus Nephritis

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Conflict of interest: Yes

[Object] Several studies reported that osteopontin (OPN) is increased in plasma and urine of patients with systemic lupus erythematosus (SLE), and correlates with disease activity, implying association of OPN with pathophysiology of SLE. We assessed utility of two forms of OPN (OPN full and its cleaved form, OPN N-half) in plasma and urine as markers of disease activity of lupus nephritis (LN). [Methods] The plasma and urine were collected from SLE (LN: N=29, non-LN: N=27), minimal change nephrotic syndrome (MCNS) (N=4) and diabetic nephropathy (DMN) (N=5), and healthy volunteers (HC) (N=17). We measured the concentration of OPN full, OPN N-half in plasma and urine, and other markers in urine. [Results] There was no significant difference in urine OPN full levels among LN, non-LN and HC. Urine OPN N-half concentration was significantly higher in LN than HC ($p<0.01$) and it was higher in LN with overt proteinuria than LN with minimal proteinuria ($p<0.0001$), and also higher than in MCNS and DMN with overt proteinuria ($p<0.05$). Urine OPN N-half was correlated with urine IL-18 ($r^2=0.41$) and urine thrombin activity ($r^2=0.26$). Plasma OPN full was higher in SLE than in HC. [Conclusions] Urine OPN N-half reflects renal inflammation, and can be an activity marker of LN.

W17-3

Estimation of Kim-1 in the response to immunosuppressive treatment in lupus nephritis

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Conflict of interest: None

[Object] Kidney injury molecule-1 (Kim-1) is a biomarker useful for detecting early tubular damage and evaluating kidney injury in lupus nephritis (LN). We previously reported that the urinary Kim-1 excretion in active LN was increased compared that in inactive LN and urinary Kim-1 excretion is correlated with renal inflammation in the kidney. We therefore investigated whether treatment decreases urinary Kim-1 excretion in LN. [Methods] We prospectively enrolled 40 patients with biopsy-proven LN. Urinary KIM-1 was assessed before and after immunosuppressive treatment (0, 6, 12 months). [Results] Urinary KIM-1/creatinine (Cr) was significantly decreased in patients with LN after treatment compared to baseline. There was a decrease in the amount of proteinuria after treatment, but it was not statistically significant. Estimated glomerular filtration rate (eGFR) did not change with treatment. Urinary KIM-1 was not correlated with proteinuria and eGFR at baseline or follow up. [Conclusions] Immunosuppressive treatment decreases urinary Kim-1/Cr in patients with LN. The results suggested that urinary Kim-1 is the useful biomarker as the predictor treatment response because we previously reported that urinary Kim-1 is correlated with glomerular injury and intersitial inflammation.

W17-4

Long-term renal outcome and efficacy of induction therapies in patients with lupus nephritis

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Conflict of interest: None

[Object] To clarify long-term outcome, prognostic factors and efficacy of induction therapies in patients with lupus nephritis (LN) [Methods] This retrospective study comprised 206 patients treated in our hospital between 1984 and 2012 with a mean observation period of 13.4±8.1 years. Endpoint was defined as death or end-stage renal disease (ESRD). Complete renal remission (CR) was defined as proteinuria <0.5g/gCr and normal or near normal GFR (within 10% of normal GFR if previously abnormal). [Results] Fifteen deaths and eleven ESRD occurred. Ten-year overall survival and renal survival was 96.1% and 93.7%, respectively. Male gender and nephrotic proteinuria at baseline were identified as independent poor prognostic factors for renal survival. Of 183 patients with clinical data, 151 (82.5%) achieved CR in the first year: CR rate of those treated with corticosteroids (CS) and cyclophosphamide, 81%: CS and mycophenolate mofetil, 100%: CS and tacrolimus or cyclosporine, 50%: CS only, 81%. Male, Class V, Cr >0.8 mg/dl were predictors of non-remission. [Conclusions] Long-term renal outcome of LN was acceptable. Male gender and nephrotic proteinuria were predictive of poor renal outcome. Male gender, Class V and Cr were identified as non-remission predictors.

W17-5

Predicting urinary protein and renal function in lupus nephritis after treatment using urinary podocyte markers

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Conflict of interest: None

Objectives: We investigated whether urinary podocyte number and podocalyxin were useful biomarkers to predict urinary protein creatinine ratio and estimated glomerular filtration rate after 30 months treatment (30MuPCR and 30MeGFR respectively). Methods: Involved in this study were 11 LN patients diagnosed by renal biopsy from May 2010 to Dec 2012 and could be followed up for 30 months (ISN/RPS class III: 1, IV: 8, V: 1, IV+V: 1). Urinary podocyte number (U-Pod/Cr) was counted by indirect immunofluorescence. Urinary podocalyxin level (U-PCX/Cr) was measured by sandwich ELISA. Results: Cumulative U-Pod/Cr for 12 months was not correlated with either 30MuPCR or 30MeGFR. There was positive correlation between U-PCX/Cr after 12 months of medication and uPCR after 30 months (r=0.8787, P=0.0034). There was no correlation with between U-PCX/Cr at the initiation of treatment and uPCR after 30 months of treatment. Conclusions: Cumulative U-Pod/Cr was not reflected either uPCR or eGFR after treatment. U-PCX/Cr at 1 year of treatment initiation may correlate with uPCR at 2.5 years.

W17-6

Lack of partial renal response by 12 weeks after induction therapy is an indicator to switch the treatment in lupus nephritis class III or IV

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Conflict of interest: None

Objectives: To determine appropriate period and targeted clinical status to switch the treatment in patients with lupus nephritis class III or IV. **Methods:** Eighty patients with biopsy-proven lupus nephritis class III or IV were retrospectively recruited and divided into 2 groups, with complete renal response (CR) or non-CR at 3 years after induction therapy. We investigated when clinical responses were obtained at each observational period from the baseline to year 3. Clinical responses were divided into 3 groups, CR, partial renal response (PR), and non-PR. Patients were assessed by systemic damage and steroid dose. **Results:** Forty-four patients with CR and 36 with non-CR were included. Cumulative CR rate was 85.0%. PR rates of patients with CR were significantly higher than those with non-CR from week 12 to year 3 ($p<0.01$). When patients with non-PR at week 12 were all excluded, the cumulative CR rate gained to 96.5%. Although 6 of patients with non-PR at week 12 achieved CR at year 3, their SDI and prednisolone dose at year 3 were high. **Conclusions:** Lack of PR at week 12 less likely predicts CR at year 3. Even CR is obtained at year 3 in those patients, their systemic damage and steroid dose may be high. Switching treatment for those patients should be made at week 12.

W18-1

Predictive factors for progression of atherosclerosis in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objective] To clarify the predictive factors for progression of atherosclerosis in patients with SLE. [Methods] This retrospective cohort study comprised 53 cases (female 50) with SLE (20-59 years old) underwent carotid ultrasonography (CUS) at baseline and at follow-up, between 2012 and 2015. Clinical data, traditional atherosclerotic factors, presence of antiphospholipid antibodies (aPLs) and disease treatment were evaluated at baseline. Outcome was defined as both increase of maximum carotid intima-media thickness (max IMT) and any increase of carotid plaque. [Results] The median age, disease duration were 42 years old, 9 years, respectively. 22 cases (41.5%) had aPLs. CUS at follow-up was performed, after a median of 22.2 months. Progression of both max IMT and plaque occurred in 10 cases (18.9%). Multiple logistic regression analysis showed the presence of plaque ($p = 0.009$), phosphatidylserine-dependent anti-prothrombin antibody (aPS/PT) ($p = 0.013$) were identified as predictive factors for progression of atherosclerosis, on the other hand, statins ($p = 0.011$) against progression of atherosclerosis. [Conclusion] In SLE patients, the presence of carotid plaque and/or aPS/PT favors the acceleration of atherosclerosis and statins protect against progression of atherosclerosis.

W18-2

Blood brain barrier injury and inflammatory mediators in cerebrospinal fluid in patients with neuropsychiatric SLE

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Conflict of interest: None

【Objective】Blood brain barrier (BBB) injury could be involved in the pathogenesis of neuropsychiatric SLE (NPSLE). We examined association of permeability of BBB and inflammatory mediators (IMs) in cerebrospinal fluid (CSF). 【Methods】We used 62 CSF samples from NPSLE patients (30 of diffuse, 38 of focal and 10 of peripheral manifestations). BBB injury was determined by albumin quotient (*Q*alb), defined normal range as less than 0.0076. IL-6, MCP-1, MIG and fractalkine were measured by quantitative multiplex cytokine analysis. 【Results】1) BBB breach was recognized in 15 patients (24.2%), but not in 47 patients (75.8%). IL-6 (74.7 vs 23.8pg/ml, P=0.003), MCP-1 (396 vs 247pg/ml, P=0.017), MIG (4736 vs 222pg/ml, P=0.0035) and fractalkine (64.4 vs 11.6pg/ml, P=0.0025) levels were higher in BBB injury group than non-BBB injury group. 2) *Q*alb correlated with CSF concentrations of MIG (r=0.67, P<0.01) and fracktalkine (r=0.70, P<0.01), but not with IL-6 and MCP-1. 3) Diffuse NPSLE was not more frequent in BBB injury than in non-BBB injury group. 【Conclusion】The permeability of BBB is associated with the concentrations of MIG and fractalkine. Both IMs may not be involved in pathogenesis of diffuse NPSLE, suggesting that other critical factors associated with NP manifestations in SLE.

W18-3

Examination of the brain MRI in Acute confusional state (ACS) patients in Neuropsychiatric systemic lupus erythematosus (NPSLE)

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Conflict of interest: None

Object: NPSLE, especially ACS is a serious organ involvement in SLE. In ACS, We performed a retrospective study to examine whether there is any difference in manifestation at brain MRI findings or not. **Method**: We analyzed clinical data of 16 patients with ACS, who were followed from 2006 until 2015 in our hospital. We classified 16 patients into the group with brain MRI findings (MRI+) and few group (MRI-), and compared clinical presentation and parameter between MRI+ and MRI-.**Result**: Number of patients in MRI+ and MRI- was 9 and 7, respectively. There was no significant difference between MRI+ and MRI- in following parameters: age at onset SLE, serum autoantibodies, IgG level, IL-6 level (sera and cerebrospinal fluid (CSF)), and protein level of CSF. In MRI+, MRI findings improved in 5 patients, 3 patients died. However no patients died in MRI-. Each cause of death is severe infection, acute renal failure and pulmonary hypertension. One MRI- patient had new findings on MRI in follow-up period.**Conclusion**: There is no difference in manifestation between MRI+ and MRI- group.Each death example was a group of MRI+.The abnormality of brain MRI might be poor prognosis factor of ACS.

W18-4

The mechanism of C5a elevation in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] In patients with SLE, it has been shown that the breakdown of BBB integrity is associated with the development of neuropsychiatric manifestations (NPSLE), especially diffuse NPSLE, involving

inflow of autoantibodies from systemic circulation into CNS. C5a has been reported as an important factor which can cause BBB damage. We have clarified serum C5a from NPSLE patients increased compared with patients without NPSLE. This study was undertaken to examine levels of C5a, C5 and C4 in sera obtained from NPSLE and LN patients. [Methods] We examined serum C5a, C5 and C4 by ELISA in 84 patients with SLE (30 with NPSLE, 28 with LN and 26 without NPSLE nor LN [SLE alone]) and 21 healthy controls. [Results]Serum C5a from NPSLE and LN patients were significantly elevated than those from SLE alone patients, whereas there were no significant differences in serum C5 levels among the three groups. Serum C4 from LN patients were significantly lower than those from NPSLE patients. [Conclusions] These results indicate elevation of serum C5a in LN patients might be caused by activation of classical pathway. On the other hand, there might be another mechanism of C5a elevation without classical pathway in NPSLE patients because there were little decline of serum C4 from those patients.

W18-5

Efficacy of mycophenolate mofetil for Neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

Objective: To evaluate the efficacy of mycophenolate mofetil (MMF) for Neuropsychiatric systemic lupus erythematosus (NPSLE). Methods: Of the 25 patients with NPSLE who were treated in our hospital from 2010 until 2015, 4 patients were treated with MMF. We reviewed their medical records retrospectively, and analyzed their clinical feature and course. Results: All 4 patients showed acute confusional state, 1 patient was also complicated with transverse myelitis. All of them were resistant to high-dose corticosteroid and 3 patients were also resistant to azathioprine (AZA). 1 patient was resistant to CY, 1 patient had allergic reaction to CY, and 2 patients cannot be used CY because of fertility, then all patients were treated with MMF. Following the adoption of MMF, CSF IL-6 and serum anti-DNA antibody levels were decreased, serum complement levels were increased and improved neuropsychiatric manifestations. In 1 patient, MMF was withdrawn because of thrombocytopenia. On the other hand, 3 patients had no recrudescence and adverse experience in a follow-up period of up to 1.5 years. Conclusions: Our results demonstrate that MMF is also effective for NPSLE. Further data are needed to establish the long-term safety and efficacy of MMF in the treatment of NPSLE.

W18-6

Retrospective analysis of post-steroid neuropsychiatric manifestations in patients with Systemic Lupus Erythematosus

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Conflict of interest: None

[Objective] To clarify the characteristics of post-steroid neuropsychiatric disease (PSNP) in patients with SLE. [Methods] This retrospective observation study comprised SLE patients with (48) or without (148) any neuropsychiatric manifestations before treatment and 168 other systemic autoimmune diseases without neuropsychiatric manifestations. All patients were treated with high-dose corticosteroids more than 40mg/day, between April 2002 and March 2015. [Results] The prevalence of PSNP was significantly higher in patients with SLE than those with other autoimmune diseases (24 % vs.7.3 %, OR 4.01, $p<0.0001$). In SLE-PSNP, the frequency of mood disorder and anxiety disorder were significantly higher than those with NPSLE (52.8 % vs 23.2 %, 30.6 % vs 7.0 %, $p<0.05$). In 66.6 % of lupus patients with PSNP, one or more abnormal findings in spinal fluid, electroencephalogram, MRI or SPECT were observed. Eighty percent of lupus patients with PSNP were treated with immunosuppressant drugs such as steroid pulse therapy or IVCY. SLE-PSNP had better event-free survival than those with NPSLE ($p<0.05$, Log Rank Test). [Conclusion] PSNP was significantly more frequent in patients with SLE and treated with immunosuppression, indicating that SLE-PSNP is one of the features of NPSLE.

W19-1

Predictive factors of radiographic progression after treatment with abatacept in bio-naïve 120 patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To detect the predictive factors of radiographic remission (REM) or clinically rapid radiographic progression at 48 weeks treatment with abatacept (ABT) in bio-naïve patients (Pt's) with rheumatoid arthritis (RA). [Method] We evaluated 120 RA Pt's enrolled in the ABROAD study who were treated with ABT for 48 weeks and assessed van der Heijde modified sharp score (TSS). We defined REM if one year change of TSS was lower than 0.5, and CRRP if they were higher than 3. We evaluated predictive factors of REM or CRRP. [Results] Predictive factors of REM (81 Pt's, 67.5%) were disease duration (less than 3 years), ACPA (negative), Class classification (lower) and baseline TSS in addition with progression speed until baseline, in which disease duration and progression speed of joint space narrowing score were detected as independent predictive factors by multivariate analysis. Those of CRRP (14 Pt's, 11.7%) were serum titers of MMP-3 and total cholesterol, and baseline TSS in addition with progression speed until baseline, in which progression speed of TSS was detected as independent predictive factor. [Conclusion] Disease duration or progressive radiographic change in baseline state was predictive factors for sustained joint damage after ABT therapy.

W19-2

Biologic-naïve rheumatoid arthritis patients with anti-citrullinated protein antibody in elderly and with concomitant use of Methotrexate in younger significantly affect the achievement of sustained clinical remission by abatacept treatment

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Conflict of interest: None

[Objective]To determine the predictive factors associated with sustained clinical remission by the abatacept (ABT) treatment in bio-naïve RA patients in each age groups (age $\geq$ 65 vs < 65 years old).[Methods] We evaluated 277 RA patients with high or moderate disease activity enrolled in the ABROAD study who were treated with ABT for 48 weeks. DAS28-CRP remission rate after the initiation of ABT were examined. Then, patient profiles at baseline associated with sustained clinical remission defined as a continuous clinical remission (DAS28-CRP<2.3) of more than 12 weeks during the last 24 weeks in the whole treatment period were determined by logistic regression analysis.[Results]The proportion of patients who achieved sustained clinical remission was 29.5% in elderly ($\geq$ 65 years old) and 37.2% in younger patients (< 65 years old), respectively. In elderly patients, ACPA positivity (Odds ratio [OR] =5.34, $p=0.024$) was significantly associated with sustained clinical remission.

In younger patients, however, concomitant MTX use (OR=4.98, p=0.010) was the predictive factor for sustained clinical remission.[Conclusion]We recommend treatment with ABT particularly for biologic-naïve RA patients who are elderly and have ACPA, and also for those who are younger and have received MTX.

W19-3

Is positivity of rheumatoid factor and anti-cyclic citrullinated peptide associated with the response rate of infliximab, tocilizumab, and abatacept in treatment of rheumatoid arthritis?

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Conflict of interest: Yes

Objectives: This study examined whether RF+ and ACPA+ statuses in patients with RA impacted the clinical efficacy of anti-TNF-α, anti-IL-6, and T-cell costimulation modulator therapy. **Methods:** We retrospectively evaluated 295 patients with RA who were observed through 52 weeks of follow-up after infliximab (IFX), tocilizumab (TCZ), and abatacept (ABT) treatment (IFX, n = 142; TCZ, n = 93; ABT, n=60). **Results:** Among patients who achieved remission at 52 weeks in the IFX group, DAS28-ESR remission was seen in 36% and 59% RF+ and RF- patients (p = 0.02), respectively, and in 36% and 62% ACPA+ and ACPA- patients, respectively (p = 0.01). The proportion of patients who achieved remission was significantly lower in RF+ and ACPA+ patients. In the TCZ group, no efficacy index between RF+ and RF- patients or between ACPA+ and ACPA- patients significantly correlated with remission. In the ABT group, however DAS28-ESR remission was seen in 33% and 75% RF+ and RF- patients (p = 0.02), respectively, no efficacy index between ACPA+ and ACPA- patients significantly correlated with remission. Conclusions: RF+ statuses are likely to be risk factors that affect the clinical efficacy of both IFX and ABT treatment, and ACPA+ statuses are those of IFX treatment, but not TCZ treatment.

W19-4

Association between serum levels of *Porphyromonas gingivalis* peptidylarginie deiminase and responses to biologic DMARDS in patients with rheumatoid arthritis

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Conflict of interest: None

【Objective】Autoimmunity against citrullinated proteins through peptidylarginine deiminase (PAD) may be involved in the pathophysiology of rheumatoid arthritis (RA). *Porphyromonas gingivalis,* a periodontopathogen, has been shown to express PAD known as PPAD. The present study evaluated whether serum levels of anti-PPAD antibodies affect responses to biologic DMARDs in patients with RA. 【Methods】Rheumatologic parameters and serum levels of anti-PPAD antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, CRP, and matrix metalloproteinase-3 were evaluated in 60 patients with RA who received medication with inhibitors of tumor necrosis factor and interleukin-6 receptor at baseline and 3 months later. 【Results】Based on the median (0.82 ELISA unit) of anti-PPAD titer at baseline, 60 patients were divided into two groups (H and L groups, 30 and 30 patients). Changes in DAS28-CRP and tender joint count (TJC) were significantly lower in the H group than in the L group, although these parameter values were comparable at baseline. Additionally, changes in DAS28-CRP and TJC were significantly correlated positively with the baseline anti-PPAD titer. 【Conclusions】These results suggest an effect of anti-PPAD titer on responses to biologic DMARDs in patients with RA.

W19-5

Association of anti-SSA antibody with response to three different biologics in patients with rheumatoid arthritis

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Conflict of interest: Yes

Objective. To clarify the association of anti-SSA antibody (SSA) with response to biologics (Bio) in patients (Pts) with rheumatoid arthritis (RA). *Methods.* The subjects were Bio naïve RA Pts who started treatment with infliximab (IFX), tocilizumab (TCZ), or abatacept (ABT). 1) We compared baseline characteristics between 3 Bio groups or SSA -positive and -negative Pts. 2) We compared changes in DAS28, SDAI, and CDAI for 12 months between SSA -positive and -negative Pts. 3) Human anti-chimeric antibody (HACA) and seroconversion rate for autoantibody were examined in IFX Pts. *Results.* We examined 59 Pts (9 were SSA -positive/50 were -negative) treated with IFX, 27 Pts (5/22) with TCZ, and 24 Pts (13/11) with ABT. 1) There was no significant difference in baseline characteristics between groups. 2) In IFX group, these parameters significantly decreased from baseline in SSA -negative Pts, while not in -positive. In TCZ, these parameters significantly decreased in both groups. In ABT, SDAI and CDAI significantly decreased in both groups. 3) HACA was detected in 3 of 6 SSA -positive Pts, and seroconversion rate of anti-nuclear antibody was significantly higher in SSA -positive than -negative. *Conclusion.* Positivity of SSA in RA seems to confer resistance to IFX, but not to TCZ and ABT.

W19-6

Prediction of the early remission in the initial treatment with certolizumab pegol for rheumatoid arthritis in multicenter study TBCR

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Conflict of interest: Yes

Objectives: We evaluate the efficacy of the loading dosage with certolizumab pegol (CZP) for rheumatoid arthritis (RA). Methods: 60 patients with RA who underwent CZP treatment were enrolled in this study. Those patients had not received previous biologic treatment. We assessed parameters that could potentially affect DAS28-CRP at 12 weeks, as follows: CRP at 0, 4, 8 weeks, DAS28-CRP at 0, 4, 8 weeks, class using the multiple logistic regression analysis. Results: Logistic regression found DAS28-CRP at 12 weeks (odds ratio, 0.003; 95% CI, 0.00-0.18) to be significant. The best cut-off value of DAS28-CRP at 8 weeks for predicting remission at 12 weeks was 2.41 (sensitivity: 89%, specificity: 87%, accuracy: 92%) by ROC analysis. Conclusions: We suggested that DAS28-CRP at 8 weeks can be useful for predicting the remission at 12 weeks in RA patients with the initial treatment in CZP therapy.

W20-1

Examination effectiveness according to the dose of etanercept and the weight of patient in the rheumatoid arthritis

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Conflict of interest: None

[Objective] Using NinJa2014, to examine the patient ratio according to the dose of etanercept and the effectiveness according to the weight [Methods] In 15023 examples registered with NinJa2014, I intended for 837 etanercept use patients. I examined 50 mg/W, 25 mg/W, the ratio of patient of 25mg/2W. I divided into three groups less than 40 kg, 40-60 kg,more than 60 kg according to the weight and the disease activity according to the dose. [Results] 50 mg/W52.2%, 25 mg/W28.7%, 25mg/2W were 7.5%, and the average weight was 54.8kg, 53.4kg, 55.0kg in patients receiving etanercept. In the disease activity of 50 mg/W,less than 40 kg: remission (R)52.2%, low disease activity (L)4.3%, moderate disease activity (M)26.1%, high disease activity (H) 17.4%, 40-60 kg: R44.9%,L22.2%,M23.6%,H9.3%,more than 60kg:R43.0%, L26.8%,M23.9%,H6.3%. In the disease activity of 25 mg/W, less than 40 kg: R37.5%, L12.5%, M37.5%, H12.5%, the group of 40-60 kg: R51.0%,L23.4%, M22.4%,H3.1%,the group more than 60kg:R61.1%,L1 4.8%,M22.2%,H1.9%. In the disease activity of 25 mg/2W, there is no case in less than 40 kg,40-60 kg: R75.0%,L9.6%,M13.5%,H1.9%,more than 60kg:R52.4%,L19.0%,M28.6%,H0%. [Conclusion] The effective dose of etanercept does not relate to the weight of the patient.

W20-2

Precision treatments for Rheumatoid arthritis patients of Etanercept IR by using a parameter of serum non-binding TNFα concentrations

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Conflict of interest: None

[Objective] to assess the precision treatments for active RA patients despite of Etanercept treatment. **[Method]** Non-binding serum TNFα with soluble TNF receptors in Etanercept might be tried to detect by the two-steps sandwich ELISA method. **[Results]** Serum TNFα concentrations in 17 cases who showed secondary insufficient response (IR) against Etanercept were 143.20±93.33pg/ml. Those in anti -TNF monoclonal antibody treated groups (4 cases), non-TNF biologics treated group (9 cases) (Tocilizumab (4), Abatacept (5)) and DMARDs treated group (8 cases) were 1.23±0.2pg/ml, 1.09±0.29pg/ml (1.00±0.29, 1.10±0.22) and 1.33±0.45pg/ml. **[Conclusion]** It is important to mind that non-binding TNFα particles are remarkably increasing in the RA patients treated by Etanercept, and decreasing to the same levels (1.30±0.24pg/ml) of most active inflammatory RA patients in 2-3 months after a Etanercept stop. These findings are suggestive of lower risks of infection for Etanercept-treated patients. However, these results lead to the following conclusion that it is not easier to achieve a goal of significant improvement for patients of Etanercept IR. It is also important to mind which biologics and when should be tried for the next.

W20-3

A strategy of rheumatoid arthritis with early infliximab dose increase to 10 mg/kg is available. - acount of baseline TNFα and IL-6 levels-

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Conflict of interest: None

OBJECTIVE: To attain early induction of remission and maintenance in RA patients, early infliximab (IFX) dose increase to 10 mg/kg was conducted and the efficacy and safety were compared with those in patients before approval of dose increase IFX. Baseline TNFα and IL-6 levels and blood trough levels before IFX dose increase were measured. METHODS: This study included 19 RA patients with inadequate efficacy to ³6 mg/wk of methotrexate. IFX dose was started 3 mg/kg and increased to 10 mg/kg at 14 wks for non-remitted patients. Changes in scores of DAS28 and HAQ were compared before and 22 and 54 wks after IFX dosing. RESULTS: Remission rates based on DAS28 in the Z- and S-groups were 90 and 44% at 22 wks (P<0.05), and 60 and 44% at 54 weeks (NS); respectively. ΔDAS in the Z- and S-groups were -2.7 and -0.9 at 22 wks (P<0.05), and -2.8 and -1.2 at 54 weeks (P=0.051), respectively. In the Z-group, IFX dose was increased to 10 mg/kg in 4 patients (40%); 2 (Za-group) at 14 wks and 2 (Zb-group) at 22 wks with baseline TNFα levels of 1.27 and <0.55 pg/mL and IL-6 levels of 86.9 and 3.11 pg/mL, respectively. CONCLUSION: Significant differences in the remission rate and change in DAS28 between the groups were observed at 22 wks.

W20-4

Drug sparing effects of tocilizumab in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To evaluate the drug sparing effects of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA). *Methods:* We retrospectively studied 60 patients with RA treated with TCZ over 1 year (median: 170.5 weeks), focusing on DAS28-CRP, doses of co-used drugs (prednisolone; PSL, methotrexate; MTX), and interval of TCZ injections between the first and last doses of TCZ. *Results:* The median DAS28-CRP level decreased from 4.90 to 1.68 during the period of TCZ injection (p=0.000), and 85.0% of patients achieved remission. In parallel, the median dose of PSL was reduced from 5.0 to 2.0 mg/day (p=0.000). The median dose of MTX was also reduced from 8.0 to 5.0 mg/week (p=0.000). In 19 patients (31.6%), the spacing (i.v.: ≥5 weeks, s.c.: ≥2.5 weeks) of TCZ injection was maintained over 12 weeks. Variables that correlated with achievement of TCZ spacing were Steinbrocker stage Ior II at initiation of TCZ (p=0.008) and changes in DAS28-CRP level between the first and last TCZ injections over 12 weeks (p=0.03). *Conclusion:* TCZ significantly reduced RA disease activity with a high remission rate, and allowed significant decreases in the doses of PSL and MTX. Spacing of TCZ injection was maintained in nearly 30% of the patients.

W20-5

The analysis of extension of intravenous abatacept® (ABA iv) therapy in RA patients

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Conflict of interest: None

【Object】We examined effects of extension of therapy period in patients with rheumatoid arthritis (RA) who had achieved clinical remission (CR) by intravenous abatacept® (ABA iv) therapy. 【Methods】We investigated into 24 RA patients who took treatment of ABA iv. in our hospital for past 5 years. 11 patients of them achieved CR at almost 16.6 months by ABA iv therapy, and then treatment interval was extended to every 6 weeks. We compared RA disease activity scores and their backgrounds of extension group (Group E) with those of non-extension group (Group N). 【Results】DAS28ESR at first time of ABA therapy had no significant difference between both groups (5.7 vs 5.9). Nonetheless, DAS28ESR at week 24 of ABA therapy had significantly difference from Group E and N (2.9 vs 4.3, p<0.01). And more, only Group E got good EULAR response. In their backgrounds, duration of RA, ACPA titer, JHAQ score, MTX combination ratio and PSL usage rate had statistical significant differences (p<0.05), respectively. 【Conclusion】We suggested that early onset of RA, low level of ACPA titer, and good EULAR response at early period of therapy, respectively, might be factors for extension of ABA therapy period.

W20-6

Investgation on factor for maintaining remission after discontinuation of infliximab(IFX) following clinical remission in RA

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Conflict of interest: None

[Objectives] To detect factor for keeping remission after discontinuation of IFX following remission (DAS28ESR <2.6) more than 6 months in RA.[Methods] Patients: group 1 (G1);132 cases treated with IFX, group 2 (G2);29 discontinued IFX following remission, G3;15 of G2 which have maintained remission without restart of IFX, G4;14 of G2 which restarted IFX against flare. [Results]1) Age (y) at IFX start: G1;55.1, G2;52.1, G3;51.8, G4;52.5. 2) Ratio of stage 3+4 (%): G1;75.8, G2;79.3, G3;66.7, G4;92.9. 3) Disease duration (y): G1;8.7, G2;4.1, G3;2.9, G4;5.5 (G1:G2 p=0.007, G1:G3 p=0.01, G3:G4 p=0.04). 4) DAS at IFX start: G1 4.75, G2 4.53, G3 4.22, G4 4.85. 5) MTX (mg/w) at IFX start: G1; 8.5, G2; 9.2, G3; 9.4, G4; 8.9. 6)Of G3, 6 cases needed MTX escalation or adding other DMARDs to sustain remission. 7) Of G4, restarted IFX was switched to other biologics due to insufficient effect in 5 cases. Second remission after second discontiuation of restarted IFX against flare was observed in 3 cases. 8) DAS28 at IFX discontinuation:G3 1.53 vs G4 2.33 (p=0.02). [Conclusion]Maintaining remission after discontinuation of IFX without restart of IFX is expected by starting IFX in early stage and attaining deep remission. Second remission following second discontinuation of IFX is possible.

W21-1

MEFV gene analysis in Japanese patients with unexplained fever

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Conflict of interest: None

Objective: To determine the diagnostic contribution of molecular analysis of MEFV, the gene responsible for familial Mediterranean fever (FMF), in patients with unexplained fever. Methods: We evaluated 630 patients with unexplained fever or rheumatic manifestations for the presence of MEFV mutations. Direct sequencing of exon1, 2, 3, 10 of MEFV gene was performed. Results: Among total 630 patients, 198 patients (31.4%) were diagnosed as FMF according to the FMF diagnostic criteria. According to the Tel-Hashomer criteria clinical diagnosed FMF patients (n=198) were divided into typical FMF (49.5%, n=98) and incomplete FMF (50.5%, n=100). 26 FMF patients (13.1%, 26/198) had concomitant rheumatic diseases (RA 7, SLE 6, Sjögren's synd 5) and presented with fever (90.9%) or serositis (39.4%). Majority of FMF patients (92.4%, 183/198) carried at least single MEFV mutation. The allele frequencies of M694I (13.4% vs 0%) E148Q (37.6% vs 20.0%), E84K (3.8% vs 0.6%) were significantly higher in FMF patients compared to those in non-FMF patients. Conclusions: We suggest that a significant number of FMF cases were included in Japanese patients with unexplained fever.

W21-2

Exhaustive analyses of 11 responsible genes derived from autoinflammatory syndrome in the patients with unknown fever

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Conflict of interest: None

Purpose: Autoinflammatory syndrome is characterized by 1) the episodes of seemingly unprovoked inflammations, 2) the absence of high titer of autoantibody or auto-reactive T cell. Autoinflammatory syndrome is known to be important for the differential diagnosis of unknown fever. Methods: We examined the responsible genes including *MEFV*, *TNFRSF1A*, *NLRP3*, *MVK*, *NOD2*, *IL1RN*, *NLRP12*, *PSTPIP1*, *PSMB8*, *NLRC4*, and *PLCG2* in the genomic DNA derived from 102 patients with unknown fever using the next-generation sequencer (MiSeq). Results: 1) We diagnosed as FMF (M694I) in 3 patients (2.9%) and detected another *MEFV* mutations, such as E84K, R202Q, E225K, R304R, R354Q, P369S, and R408Q in 30 patients (29.4%). 2) We identified *TNFRSF1A* mutations, such as T61I and V125M in 3 patients. 3) We identified less than 1% of frequency of mutations derived from East Asia healthy individuals in 5, 4, 5, 3, 3, and 1 location of *NLRP3*, *NOD2*, *NLRP12*, *PSTPIP1*, *NLRC4*, and *PLCG2*, respectively, in the patients with unknown fever, however, none of patients has clinical symptoms in each autoinflammatory syndrome. Conclusions: These exhaustive analyses suggest that we could find the MEFV mutations from 11 responsible genes derived from autoinflammatory syndromes in 32.4% of the patients with unknown fever.

W21-3

The relationship between febrile attacks and menstruation in patients of familial Mediterranean fever

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Conflict of interest: None

【Objectives】In familial Mediterranean fever (FMF), some of female patients show the febrile attacks on their menstrual cycles. Our aim was to elucidate the relationship between FMF attacks and menstruation by investigating their clinical and genetic characteristics.【Methods】We analyzed clinical features and genetic mutations about 181 female patients clinically diagnosed as FMF who fulfilled Tel-Hashomer diagnostic criteria.【Results】Sixty-three patients (34.8%) experienced the febrile attacks relating to menstruation. They indicated higher frequencies of peritonitis (79.4%), p.Met694Ile mutation (30.2%), and the use of colchicine (60.3%) compared with those in patients whose attacks were independent of menstruation (p <0.05). In patients relating to menstruation, 5 patients were free of attacks during their pregnancy, and 7 patients had been treated with progestational agent due to the suspicion of dysmenorrhea or endometriosis (before the diagnosis of FMF).【Conclusion】Menstruation induces febrile attacks in female FMF patients. FMF is definitively diagnosed in some patients who have been thought as dysmenorrhea. Therefore, we need to recognize FMF in patients having febrile episode on the menstrual cycle.

W21-4

Analysis of predictive factor for life prognosis in patients with adult onset Still's disease at a tertiary medical center

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Conflict of interest: None

[Objective] To analyze short-term prognostic factors of patients with adult onset Still's disease (AOSD). [Methods] A total of 23 consecutive patients who were diagnosed as AOSD in our department between April

2007 and October 2015 were analyzed retrospectively. We divided the patients into every two groups according to age, gender, each item of Yamaguchi's classification criteria, and serum ferritin level. We drew Kaplan-Meier curves and compared them by log-rank test. [Results] The mean age of the 23 patients was 58.7 (range; 21-87) years old. Five were male and 18 were female. Male patients and patients with high serum ferritin level (over 10,000 ng/mL) followed worse clinical course than female patients ($p<0.001$) and patients with low ferritin level ($p=0.035$), respectively. There was a tendency that suggested worse life prognosis of old people. [Conclusions] In AOSD patients, male gender and high serum ferritin level may predict poorer short-term life prognosis.

W21-5

Case study in suspected Familial Mediterranean fever at private Rheumachi clinic

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Conflict of interest: None

Objective: We studied the clinical features and final diagnosis of six cases that visited to my private clinic whose chief complaint was total body pain, joint pain or fever of unknown origin (FUO). Methods: We investigated in the 6 cases the chief complaint, family history, and blood examination test at first visit, treatment courses and final diagnosis. Results: 6 cases were all female, average age 53 years, average duration 2.6 years. Chief complaints were joint pain in 3 cases, total body pains in 2 cases and FUO in 1 case. Average ESR was 67 mm/hr and CRP was 3.3mg/dl. Colchicine were effective in 5 cases. Finally one case was found to be relapsing polychondritis (RP). Genetic diagnosis showed no abnormal TRAPS genetics and FMF gene abnormality was found in two cases. In 5 cases, colchicines were effective to their fever and pain complaint. Only prednisolone was effective in the case of RP. Conclusion: In our clinic, which advocated rheumatoid department, there is a possibility to visit various unknown causes. In such cases, we should be noted to mix such a case like FMF.

W21-6

Atypical Familial Mediterranean Fever: A report of 2 cases

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Conflict of interest: None

It has been reported that there are more atypical Familial Mediterranean fever (FMF) patients in Japan than Mediterranean countries. Here we report 2 cases of atypical FMF, one of which is a rare case of a male FMF patient who showed ambulant myalgia with fever. One case was 62-year-old man, who was referred to our department due to recurrent high fever lasting 2 to 5 days every 10 to 14 days for 5 months, which started after the operation of infectious endocarditis. With the fever, he had limited myalgia the lesion of which was different every time and was confirmed by PET-CT that showed accumulation of PET at relevant spot. He had no serositis, arthritis, and skin lesion. We performed muscle biopsy from the tender muscle when he had a fever attack, revealing the muscle fiber and fascia had a severe infiltration of inflammatory cells. Another case was 58-year-old woman, who was referred due to recurrent high fever following influenza infection at intervals of 10-30 days. She had pericarditis and non-localized peritonitis with the fever, but had no skin lesion, arthritis and myalgia. Both cases had no family history. Genetic tests revealed both cases had heterozygous for the E148Q mutation, and diagnosed as atypical FMF. We treated with colchicine for both cases.

W22-1

Transition of clinical manifestation in Japanese Behcet's disease: a retrospective study of 584 patients

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Conflict of interest: None

[Object] To evaluate phenotype transition of Behcet's disease (BD) in Japanese population. **[Methods]** We retrospectively analyzed 584 patients, who fulfilled Japanese Diagnostic Criteria for Behcet's disease. Presence of clinical manifestations, such as oral ulcer, genital ulcer, etc, HLA-B51 positivity,observation period, and date of diagnosis, were selected as variables. **[Results]** The patients' characteristics were as follows: female n=334, male n=250, average of disease onset, 36.9±12.3 y.o, frequency of oral ulcer 98.5%, genital ulcer 72.3%, uveitis 60.5%, skin rash 88.5%. We further divided the patients who were diagnosed with BD before and after 2009. Univariate analysis showed significant differences in observation period, age of onset (before 2009, 36.7 y.o vs after 2009, 39.6 y.o), and HLA-B51 positivity (before 2009, 52.6% vs after 2009, 34.3%). Other clinical manifestation did not show significant differences. **[Conclusions]**HLA-B51 positivity maybe decreased in recent-onset BD.

W22-2

Cognitive Impairment in Chronic Progressive Neuro-Behçet's Disease: Comparative Study of Brainstem and Hippocampus Region using Brain MRI

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Conflict of interest: None

Purpose: We examined volumes of brainstem and hippocampus in order to identify the responsible lesions for neurobehavioral changes in chronic progressive neuro-Behçet's disease (CPNB). **Methods:** The subjects were 32 patients, including 13 with CPNB, 13 with BD without NB (non-NB), and 6 with Alzheimer's disease (AD). CPNB was defined as slowly progressive neurobehavioral changes and ataxia accompanied by persistent elevation of CSF IL-6 of > 20 pg/ml. AD satisfied DSM-IV criteria. The area of brainstem was measured on mid-sagittal sections of T1-weighted images using image analysis software (Image J). Severity of hippocampal region atrophy (Z score) was investigated using VSRAD software. **Results:** Brainstem area was significantly decreased in CPNB compared with those in AD and non-NB. VSRAD showed that Z score was significantly increased in CPNB and AD compared with non-NB. There was no significant correlation between the area of brainstem atrophy and Z score. **Conclusion:** These results indicate that hippocampus and brainstem is a common site for lesions in CPNB, accounting for the progressive cognitive dysfunction in this disease. The lack of correlation between brainstem atrophy and hippocampal atrophy suggests that predisposing factors might determine the lesion site in CPNB.

W22-3

Efficacy of anti-TNF agents in neurogenic, vascular, and intestinal Behcet's disease

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Conflict of interest: None

Objectives: Neurogenic, vascular, and intestinal Behcet's disease (BD) can be lethal or leave irreversible deficits. We assessed the efficacy of anti-TNF treatments [infliximab and adalimumab] in neurogenic, vascular, and intestinal BD. Methods: We investigated retrospectively our neurogenic, vascular, and intestinal BD patients treated with infliximab and adalimumab from April 2008 to October 2014. We assessed efficacy and cumulative proportion in anti-TNF treatments. Results: Of 151 BD patients, fifty-six patients (37.1%) were included in this study. Thirteen patients were treated with infliximab, and 6 patients were treated with adalimumab. Clinical manifestation requiring the use of infliximab included intestinal (n = 10), neurogenic (n = 3), and vascular manifestation (n = 1). Adalimumab was administered to only intestinal manifestation. Anti-TNF agents allowed improvement in the majority of patients. In intestinal manifestation, only one patient did not response to infliximab. The cumulative proportion of patients continuing infliximab and adalimumab at one year was 100%, respectively. Infliximab had a significant corticosteroid sparing effect. Conclusion: In intestinal manifestation, anti-TNF agents allowed improvement in the majority of patients.

W22-4

Contributable Factors for Irreversibility of Visual Function in the Treatment of Behcet's Disease

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Conflict of interest: None

[Background] Chronic inflammation needs to be treated within reversible states. Early intervention improves prognosis of rheumatoid arthritis. With regard to Behcet's disease, the strategy will be needed. [Purpose] To assess factors for irreversibility of visual function in Behcet's Disease. [Method] Thirty-one patients who received infliximab were observed, and cases whose visual acuity (VA) could not reach 0.2 over 1 year treatment were defined 'poor visual prognosis'. Monovariate and multivariate analysis were conducted. [Result] Among available 26 cases (52 eyes), 17 eyes were poor visual prognosis and 35 eyes were not. Differences were; $p<0.01$ for VA at administration, $p=0.10$ for deviation of VA, $p=0.28$ for age, $p=0.37$ for CRP and $p=0.42$ for disease duration. Odds ratios (OR) for poor visual prognosis by logistic regression analysis were OR 11.2 [2.72,126] in low VA at administration, OR 17.6 [2.13,498] in wide deviation of VA, OR 3.08 [1.04,14.7] in age, OR 1.46 [1.01,2.61] in low CRP, OR 1.15 [0.99,1.37] in long disease duration. Lower VA, unstable VA, higher age and longer disease duration contribute to the poor visual prognosis. [Conclusion] Factors for irreversibility of visual function in Behcet's Disease suggest Window of Treatment Opportunity of this disease.

W22-5

A single endoplasmic reticulum aminopeptidase-1 protein allotype is a strong risk factor for Behçet's disease in HLA-B*51 carriers

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Conflict of interest: None

[Object] To determine the naturally occurring ERAP1 protein allotypes and their contribution to Behçet's disease (BD) in Turkey. **[Methods]** Genotypes of all reported *ERAP1* gene missense variants with 1000 Genomes EUR super-population frequency greater than 1% were determined in 1,900 BD cases and 1,779 controls from Turkey. Protein allotypes of ERAP1 and their contributions to BD were determined by haplotype identification and disease association analyses. **[Results]** One ERAP1 protein allotype with 5 non-ancestral amino acids was recessively associated with disease ($P = 3.13 \times 10^{-6}$, odds ratio 2.55, 95% CI 1.70 to 3.82). The ERAP1 association was not found in individuals who lacked HLA-B*51. Individuals who carry HLA-B*51 and who are also homozygous for the haplotype had 10.96 (95% CI, 5.91 to 20.32) fold increased disease risk compared with those with neither risk factor. **[Conclusions]** The BD-associated ERAP1 protein allotype was previously shown to have poor peptide trimming activity. Combined with its requirement for HLA-B*51, these data suggest that a hypoactive ERAP1 allotype contributes to BD risk by altering the pool of peptides available for binding to HLA-B*51.

W22-6

Characteristic compositional alteration of gut microbiota in patients with Behcet's disease

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Conflict of interest: None

[Background] We have presented evidence that high frequency and overactivity of helper T (Th)17 cells in patients with BD (BD). Recently, some researchers clarified the relationships among several gut bacteria, skewed Th17 cell function and local inflammation. We conducted fecal metagenomic analysis of BD and compared the data with that of normal individuals (NI). [Methods] We explored fecal microbiota of 12 patients with BD and 12 NI by sequencing of 16S ribosomal RNA gene. We calculated bacterial diversity of each sample (alpha diversity) and each group (beta diversity). We compared the relative abundance of bacterial taxa with fecal secretary IgA (sIgA) concentrations. [Results] The sequencing data showed that the genera Bifidobacterium and Eggerthella increased significantly in BD compared with NI. Fecal sIgA concentrations increased significantly and correlated positively with the Eggerthella population in BD. There was no significant difference in alpha diversity between BD and NI. An exploratory analysis showed a significant difference between the two groups in beta diversity. [Conclusions] We suggest that the compositional change of gut microbe may be unfavorable for BD patients (dysbiosis) and have a relationship with the skewed Th cell differentiation of BD.

W23-1

Relationship between atypical femoral fracture and bisphosphonates in patients with collagen diseases

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Conflict of interest: None

Introduction; There are many reports for atypical femoral fracture (AFF). In those reports, long-term bisphosphonate (BP) use is listed as one of the risk factors. Although the collagen diseases or administration of glucocorticoids (GCs) also may be risk factor of AFF, there are limited reports for those factors. **Patients;** 501 patients with collagen diseases treated with BPs for more than 2 years were involved in this study. We investigated the relationship between AFF and the variety of BPs, the duration of BPs therapy, the history of lower limb surgery, and the administration of GCs. **Results;** There were 326 cases with alendronates, 166 cases with risedronates, and 9 cases with other BPs. The mean duration of BPs treatment was 1272 days (737-4985). 214 cases were administrated GCs as well as BPs. Two cases (0.40%) with rheumatoid arthritis, who

underwent hip arthroplasty had AFF. These cases were received BPs and GCs for more than 7 years. **Conclusion;** The incidence of AFF in collagen disease cases treated with long-term BPs revealed 0.40%, which is consistent with previous reports. Further careful study will be needed for analyzing the relationship between AFF and BPs, GCs, and orthopaedic implant surgery for lower limb.

W23-2

Effect of sequential treatment of teriparatide and denosumab on bisphosphonate-resistant osteoporosis in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Several lines of evidence have reported the efficacy of bisphosphonate on osteoporosis associated with rheumatoid arthritis (RA). The purpose of this study is to examine the effect of sequential treatment of teriparatide and denosumab on bisphosphonate-resistant osteoporosis in RA patients. [Methods] RA patients (n=13; mean age, 71; mean duration of RA, 20 years) whose bone mineral density (BMD) did not increase even with the bisphosphonate treatment for more than a year, received subcutaneous teriparatide injection for two years followed by denosumab injection for more than a year. Mean value of daily amount of steroid is 2.0 mg/day. The patients had 4.5 vertebral compression fractures on the average. Assessment includes dual x-ray absorptiometry scans of the lumbar spine and femoral neck, and yearly change of BMD was calculated. [Results] Even in patients who showed the bisphosphonate-resistance for osteoporosis treatment, not only teriparatide but also denosumab treatment significantly increased BMD in lumber spine and femoral neck. [Conclusion] These results suggest that sequential treatment of teriparatide and denosumab might be quite effective for bisphosphonate-resistant osteoporosis in RA patients.

W23-3

The effect of Weekly Teriparatide, Denosumab, and Bisphosphonates for Prevention of Vertebral Fractures in Glucocorticoid-Induced Osteoporosis

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Conflict of interest: None

[Object] To clarify the effect of weekly teriparatide (56.5ug, wTPTD), denosumab (DMAB) and bisphosphonates (BIS) on vertebral fractures (vFx) in Glucocorticoid-Induced Osteoporosis (GIO). [Methods] A oneyear cohort study recruiting 232 patients (208 women) with GIO. Means of age, disease duration, total prednisolone (PSL) dosages, and daily PSL dosages (dPSL) of the subjects were 65+/-15 (yo,+/), 11+/-11 (y), 25+/-29 (g), and 6.7+/-5.9 (mg/day), respectively. vFx were defined from Xray films with the SQ method. Lumbar BMD were measured with Lunar 3030 (GE). Prevalent vFx were seen in 107 (46%) patients. [Results]1)The BMD was showed no difference between treatment groups at the base line. The dPSL was significantly higher ($p<0.03$) in the group of wTPTD than in the group of BIS and DMAB (11.6, 6.2 and 6.1, respectively). 2) Incident vertebral fractures were observed in 24 (BIS16%), 2 (DMAB3%), 2 (wTPT9%). 3) A multivariate logistic regression analysis revealed that statistically significant factors for incident fractures were DMAB or wTPTD (vs BIS, 0.12, 0.03-0.45), prevalent fractures (3.09, 1.14-8.41), daily PSL (1.13, 1.041.23), BMD (OR; 0.95, 95%CI; 0.910.99). [Conclusions] wTPTD and DMAB might be more effective than BIS for prevention of osteoporotic vFx in GIO.

W23-4

Trabecular Bone Structure Analysis, The predictor for vertebral fracture in Glucocorticoid-Induced Osteporosis

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Conflict of interest: None

[Object] To clarify a role of TBS in GIO. [Methods] Patients with GIO was subjected for one year longitudinal cohot study. The subjects (female; 204, age; 65+/-15 (mean +/- SD), prednisolone (PSL) dosage at base line; 9.1+/-12.8 mg/day, PSL dosage during 1y; 6.7+/-5.9mg/day, prevalent vertebral fracture; 46.7%. Lumbar bone mineral densities (lBMD) were measured with Lunar 3030 (GE). TBS values were calculated with TBS (medimaps). Incident vertebral fractures were analyzed with XP at thoracic and lumbar spines. Medications during this study were bisphosphonates (65%), denosmab (26%), weekly teriparatide (9%). [Results]1) The value of lBMD (%Young Adult Mean; %YAM) at the base line was 81.5+/-15.6%, and that of TBS was 1.268+/-0.107. The rate of incident fractures during the follow-up period was 14.1%.2) TBS was significantly correlated with lBMD ($r=0.695$, $p<0.001$) and the age ($r=-0.603$, $p<0.001$).3) Logistic regression analysis revealed that incident fractures could be predicted (87.1%) with TBS (1.78; 1.10-2.86; $p<0.02$), daily prednisolone dosages (per 5mg/day increase; 1.47; 1.20-1.81; $p<0.01$), and the prevalent fractures (3.63; 1.33-9.89; $p<0.02$). [Conclusions]TBS analysis of the lumbar spine DXA data might be useful for prediction of prevalent fractures in GIO.

W23-5

The cross-sectional study of glucocorticoid-induced osteoporosis female rheumatoid arthritis patients using the FRAX® tool and femoral neck BMD measurement

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Conflict of interest: None

[Objective] To clarify the fracture probability of female RA patients that was defined as a glucocorticoid induced osteoporosis (GIO) Guidelines. [Method] The female RA patients of 40-90 years of age during treatment with MTX or biologics are surveyed. All spine X-ray imaging and BMD measurement, and interview by the FRAX tool were performed. [Results] GIO group 164 women, average age 67.6 ± 9.5 years, and age-matched control group 170 women, average age 66.8 ± 9.7 years (U-test, ns). There was no significant difference in body weight. Prophylaxis of osteoporosis drug has been performed at the time of glucocorticoid introduced at 75% of the cases. T- Score femoral neck of the GIO group was -2.3 ± 1.0SD, it was lower than the control group -2.0 ± 1.0SD ($p<0.01$). Risk of major osteoporotic fractures and femoral neck fracture within 10 years GIO group was 29.4 ± 18.1% and 11.8 ± 12.3%, it was a high rate compared with that of the control group (16.8 ± 12.3%, 5.6 ± 8.0%, $p<0.00$). There was no significant difference in combination of biologics. [Conclusion] For the GIO that occur in long-term administration of glucocorticoid of low-dose we think the need is more powerful strategy than prophylactic administration of bisphosphonates.

W23-6

The therapeutic effect of denosumab in osteoporosis patients

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Conflict of interest: None

Purpose: Denosumab is a fully human monoclonal antibody against RANK-Ligand which was released as a therapeutic drug of the osteoporosis in Japan. We examined the usefulness of it, based on a use experi-

ences. **Patients and Methods:** In 148 osteoporosis patients who started denosumab from July 2013 to July 2014 in our hospital, we investigated a difference of bone mineral density (BMD), bone metabolism markers, for before and after one year denosumab administration. We also observed a cancellation reason and a continuation rate. Then, patients were divided into two groups: rheumatoid arthritis (RA) group and non-RA group. Furthermore, statistical analysis was performed between two groups. **Results:** Although lumbar vertebrae BMD were significantly increased, but the trans-cervical BMD were not significantly increased. All bone metabolism markers were significantly decreased. **Discussion:** Because of previous Teriparatide (TPD) use in 84% of patients, it was considered that higher effect could be expected in previous TPD users, compared with non-TPD users. **Conclusion:** The curative effect of denosumab for the osteoporosis was shown in increasing of BMD and reducing of bone turnover, significantly in TPD users compared with non-TPD users, regardless of RA or non-RA patients.

W24-1

Verification of the capacity of lysyl oxidase to induce osteoclastogenesis

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Conflict of interest: None

Objective: Although RANKL (encoded by the *Tnfsf11* gene) is an essential cytokine for osteoclastogenesis and a key pathological factor for bone destruction in rheumatoid arthritis, the existence of a RANKL-independent pathway of osteoclastogenesis has been argued. A recent study claimed that lysyl oxidase (LOX) potently induces osteoclastogenesis in a RANKL-independent manner (Cox, *Nature*, 2015). However, it lacks sufficient experimental evidence for the RANKL-independence. Thus, we investigated the detailed mechanism in which LOX induces osteoclastogenesis by using *Tnfsf11*-deficient cells. **Methods:** Wild-type or *Tnfsf11*-deficient mice-derived bone marrow cells were stimulated with RANKL, LOX or both of them. Three days or three weeks later, osteoclast differentiation and bone resorption activity were evaluated. **Results:** LOX alone failed to induce osteoclastogenesis. LOX synergistically promoted RANKL-induced osteoclastogenesis in 3-week culture of wild-type cells but not of *Tnfsf11*-deficient cells. In addition, long-term LOX stimulation upregulated *Tnfsf11* expression in bone marrow cells. **Conclusion:** LOX alone fails to induce osteoclastogenesis. On the other hand, long-term treatment of LOX induces endogenous RANKL expression and promotes osteoclastogenesis indirectly.

W24-2

IL-35 inhibits human osteoclastogenesis

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Conflict of interest: None

【**Background and Objective**】IL-35 is a potent inhibitory cytokine produced by Treg cell populations. In RA patients, however, the role of IL-35 is controversial (Filkova M et al. 2015) (Nakano S et al. 2015). 【Objective】To investigate the effect of IL-35 for differentiation and function of human osteoclasts (Oc). 【**Methods**】1) Human monocytes (Mo) were cultured with M-CSF for 3 days. Next, Mo were cultured with M-CSF and sRANKL. We simultaneously added rhIL-35. After 10 days, Oc formation was evaluated by IHC for anti-CD51/61 Ab. 2) Oc were cultured with M-CSF, sRANKL and rhIL-35 for 4 days on Osteoassay™ and pit formation was evaluated. 3) The expression of various molecules in Mo stimulated with rhIL-35 was analyzed by RT-PCR. 4) The expression of various molecules in pre-Oc stimulated with rhIL-35 was analyzed by RT-PCR. 【**Results**】1) rhIL-35 significantly inhibited human Oc-genesis. 2) rhIL-35 also significantly decreased the area of pit formation by mature Oc. 3) rhIL-35 significantly decreased mRNA expression of RANK in Mo and FOS in pre-Oc. 【**Conclusion**】Our findings suggest that IL-35 inhibits Oc-genesis and Oc activation by inhibiting RANK and/or FOS. IL-35 has the inhibitory effect for osteoclastic-bone resorption.

W24-3

The effect of rebamipide in osteoporosis model mouse

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Conflict of interest: None

[Objective] In this study, we investigated the effects of rebamipide in vivo. [Methods] Female Sprague-Dawly rats (n=27) were used for ovariectomized (OVX) experiments. Six rats underwent sham operation for control. OVX rats (n=/group) were randomized to 1) vehicle control (CT); 2) low dose of rebamipide (10mg/kg; R10); 3) high dose of rebamipide (100mg/kg; R100). Vehicle or rebamipide were given by intraperitoneal administration once a daily for 5 weeks. Peripheral blood were collected at operation. After prescription, all animals were scarified and collected both thighbone. Histomorphometric measurements were performed to obtain the data of the number of osteoclasts, BV/TV%, DXA and micro CT. [Results] Oc.N/B.Pm (100mm) were 77.2 in group CT, 94.6 in R10, 81.5 in R100 and 44.9 in Sham respectively. BV/TV (%) were 12.0 in CT, 12.8 In R10, 12.3 in R 100 and 19.9 in Sham group. The BMD by DXA and micro CT showed no difference between these groups. [Conclusion] In the current study, using the OVX rats, rebamipide did not show the significant effect on osteoclastogenesis in vivo.

W24-4

Influence of Wnt signaling pathway in secondary osteoporosis of patients with rheumatoid arthritis

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Conflict of interest: None

[Object] Since rheumatoid arthritis (RA) is one of the major causes of secondary osteoporosis, it is important to prevent not only joint damage but also bone loss. The bone metabolism in RA was reported as the results both by decreased bone formation and by the increase of bone resorption. We investigated whether Wnt signaling pathway influenced on metabolisms of RA. [Method] Serum levels of bone formation markers (OC, P1NP, BAP), bone resorption markers (NTX, TRACP-5b) and Wnt signaling inhibitors (Dickkopf-1, sclerostin) were measured in 112 RA patients and 29 healthy controls (HC). [Result] Serum OC levels in RA were significantly lower than that in HC (5.2±2.9 vs 8.6±2.3: $P<0.001$). Serum P1NP and BAP levels in RA were significantly lower than those in HC, respectively (46.2±29.9 vs 57.8±21.0: $P<0.01$, 4.4±2.2 vs 14.3±3.7: $P<0.001$). However, serum levels of bone resorption markers and Wnt signaling inhibitors in both were not significantly different each other. [Discussion and Conclusion] It is suggested that the disturbed bone formation was more important than the increased bone resorption in the secondary osteoporosis in RA. However, our data suggested that Wnt signaling inhibitors were not directly associated with suppression of bone formation in these patients.

W24-5

The Influence of biologics and SDAI on the efficacy of Denosumab (anti-RANKL-antibody) for the osteoporosis in collagen disease and rheumatoid arthritis patients

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Conflict of interest: Yes

[Objectives] It is unclear whether biologics and the activity of rheumatoid arthritis (RA) have the effect on the efficacy of Denosumab (Anti-RNKL antibody) for the osteoporosis patients. [Methods] We analyzed the 74 patients (RA26, SLE21, others27, F:M=59:15, 55±14 years old, BMI 21.3±2.7) from 113 patients in treatment with Denosumab from July 2013. We investigated the relationship among the bone mineral density (BMD) change of L2-4 and Femur 12months after treatment of Denosumab (ΔBMD of L2-4 and Femur) and the various clinical parameters (biologics, DAS-28CRP, SDAI, the serum levels of CRP, MMP-3 and so on). [Results] The combination therapy of biologics significantly increased ΔBMD of L2-4 (Bio-group 0.062±0.0083 vs. non Bio-group 0.039±0.0055 (g/cm2), Wilcoxon signed ranked test, p=0.0431) but notΔBMD of Femur (0.012±0.023 vs. 0.016±0.024 (g/cm2) p=0.8017). ΔBMD of Femur was related to age and the serum level of MMP-3 (-0.3058 p=0.0091,-0.3848 p=0.0090, Spearman Rank-Order Correlation). ΔBMD of L2-4 was associated with DAS-28CRP and SDAI (-0.4178 p=0.0241,-0.4672 p=0.0106). [Conclusion] Our results indicate that bone mass increase of the lumbar spine due to denosumab is enhanced by the combination therapy of biologics and the low disease activity of SDAI.

W24-6

Efficacy of denosumab in patients with rheumatic diseases: observational study

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Conflict of interest: None

[Object] Denosumab, an anti-RANKL monoclonal antibody, was reported to offering a favorable efficacy in postmenopausal osteoporosis. This observational study was conducted to clarify the efficacy of denosumab in patients with rheumatic diseases. [Method] Serum levels of bone turnover markers and lumber bone mineral density (BMD) in 100 patients with rheumatic diseases [mean age 67.5±12.9 (S.D), male 8, postmenopausal female 85, mean prednisolone dose: 5.1±6.4 mg/day]] at baseline and 6th month after denosumab therapy, respectively. [Result] Serum levels of NTX (17.3±8.7→14.1±8.7 nmolBCE/L) and TRACP-5b (276.7±176.8→151.1±105.2 mU/dL) were significantly decreased. Serum levels of PINP (34.5±12.6→17.4±9.3 μg/L) and BAP (12.8±4.39→9.46±2.42 μg/L) were also significantly decreased. BMD was significantly increased from baseline (0.773±0.129→0.792±0.127 g/cm^2). On the other hand, BMD in 19 patients were decreased. These patients who resistant to denosumab had trend of aged, lower BMD, and lower mean prednisolone dose. [Conclusion] Denosumab acted on the both sides of osteoblastogenesis and osteoclastogenesis at bone turnover markers and increased BMD in patients with rheumatic diseases. Existence of 19% patients who were resistant to denosumab remained to be studied.

W25-1

Can bone mineral density of whole body predict the fractures in patients with rheumatoid arthritis from the TOMORROW study?

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Conflict of interest: None

[Objectives] RA is an independent risk factor of osteoporosis. RA patients have high risk of fracture. We investigated whether BMD could predict the fracture within 5-years. [Methods] We analyzed date from TOMORROW study, which is a 10-years prospective cohort for age and sex matched RA and volunteers. BMD, lean mass, and %fat were measured by whole body DXA. We investigated BMD, lean mass, and %fat between fracture and non fracture groups, and revealed cut-off value of increase fracture risk. [Results] There were not significantly differences of fracture rate between RA and volunteers (14.9%, 10.4%: p=0.231). The BMD of fracture group was significantly less than that of non fracture group (0.914g/cm^2, 0.995g/cm^2: p=0.001) in 358 subjects. It was observed same tendency in RA. There were not significantly differences of lean mass and %fat between groups. When cut-off value was determined 0.869g/cm^2, AUC was 0.734, sensitivity was 72.2%, and specificity was 65.7%(p=0.01). The fracture risk within 5-years was 5.3 compared BMD over and under 0.869g/cm^2 in RA. [Conclusion] BMD of fracture group was significantly higher than that of non fracture group. However, there were not significantly differences of lean mass and %fat. Baseline BMD was useful for predict of fracture within 5-years.

W25-2

Atypical femoral fracture is associated with rheumatic diseases

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Conflict of interest: None

[Purpose] Patients having a rheumatic disease are likely to present with osteoporosis. Atypical femoral fracture (AFF) is known to occur during the treatment of osteoporosis. We investigated the clinical features of AFF experienced in our hospital. [Subjects] We surveyed 323 limbs in 297 patients (215 women and 82 men; average, 78 years old) who suffered from a fragility femoral fracture during the past 10 years, and found 6 limbs in 5 patients of AFF (four women and one man; average, 64 years old). [Result] The incidence of AFF was 1.9%. The underlying diseases included rheumatoid arthritis in 3 patients, mixed connective tissue disease in one, and dermatomyositis in one, all of whom were given bisphosphonate (BP) and/or proton pump inhibitor (PPI). Alendronate had been used in all patients, with a mean duration of 11 years. Prednisolone (PSL) had been used in 4 patients, with a mean duration of 13 years and a mean dose of 7.2 mg. All the AFF occurred in the subtrochanteric region. Thus, all the patients with AFF had a rheumatic disease, had taken BP, PSL, and PPI for years, and had developed AFF in the middle age. [Conclusion] Care must be taken for a possible AFF in patients with a rheumatic disease who receive bone turnover inhibitors.

W25-3

The prevalence and the risk factor of new vertebral fracture in RA patients: a 5-year follow-up data in TOMORROW study

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Conflict of interest: None

[Objectives] We have previously reported the prevalence of vertebral fractures was significantly higher in patients with RA than control group. We analyzed the prevalence and the risk factors of new vertebral fractures in patients with RA and control. [Methods] This study compared the thoracolumbar spine radiograph and clinical data in 189 RA patients and 182 controls to evaluate the prevalence of new vertebral fracture and the risk factors associated with new vertebral fracture in five year follow-up. [Results] Prevalence of new vertebral fractures was 14.3%(26 cases) in RA group and 7.4%(14 cases) in control group (P=0.033). Moreover the number of fractures was likely to be multiple and more severe in patients with RA. In the logistic regression analysis, existing vertebral fracture (adjusted OR 7.88, 95% CI 2.00 to 31.0), continuation of low bone mineral density (adjusted OR 5.11, 95% CI 1.13-23.1), glucocorticoid use (adjusted OR 3.71, 95% CI 1.14-12.0) and age (adjusted OR 1.07, 95% CI 1.01-1.14) were risk factors for new vertebral fracture. [Conclu-

sion] New vertebral fractures were significantly found in patients with RA during five year follow-up. The existing vertebral fracture and the continuation of low bone marrow density was the risk factor of new vertebral fractures.

W25-4

Incidence and risk factor analysis of fracture in osteoporotic patients with rheumatoid arthritis receiving bisphosphonate: 71-month mean follow-up results

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Conflict of interest: None

Bisphosphonate therapy (BP) reduces fracture risk but does not eliminate fracture occurrence in rheumatoid arthritis (RA). The objective of this study was to investigate incidence and risk factors for fracture in RA patients receiving BP. A retrospective cohort study of 106 patients with RA receiving BP was conducted. Patients were followed until a 3-month gap in therapy. The incidence of fracture was evaluated from Kaplan-Meier analysis, and the risk factors for fractures were identified by multivariate logistic regression model. During a mean of 71.2-month follow-up, 29 patients (26.9%) developed new fracture. The incidence of fracture at 1 / 2 / 3 / 5 / 10 years after administration was 0 / 3.2 / 7.5 / 19.7 / 44.0%, respectively. Daily glucocorticoid usage, long disease duration, and lower lumbar BMD were at higher risk of fracture. Our findings indicate that persistent BP users remain at risk of fracture. Thus, we conclude that an alternative medication should be considered, especially in RA patients with glucocorticoid, long-standing disease, and lower BMD.

W25-5

Efficacy of daily teriparatide treatment in osteoporosis of RA patients -Comparison between TKA-performed patients and non-TKA-performed patients-

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Conflict of interest: None

【Objectives】One of pathogenesis of osteoporosis in RA patients (RA-OP) is disuse due to joint disorder. Residual disorder is often seen in some RA patients after TKA. This study investigated the influence of past history of TKA on efficacy of daily teriparatide (dTPTD) in RA-OP. 【Methods】31 female RA-OP cases treated with dTPTD were used. These cases were divided into two groups, TKA group (n=7) and non-TKA group (n=24). Comparson between two groups were performed. 【Results】Mean age, BMI, FRAX, PSL use and DAS28-CRP in TKA group/non-TKA group were 68.6/70.1, 21.9/21.0, 36.1/31.8, 85.7/62.5 and 2.67/2.31. There were significant differences between groups in RA duration (22.4y/13.3y) and mHAQ (1.54/0.73). Baseline THBMD in TKA group was low compared with that in non-TKA group (0.544 vs. 0.635, p=0.08). % increase of LSBMD every 6m was 4.9/5.9/7.9/10.2% in TKA group and 7.4/12.5/13.2/14.3% in non-TKA group.There was a significant difference in % increase at 6m between two groups. % increase of THBMD every 6m was 1.6/2.8/4.8/5.2% in TKA group and 0.5/2.3/2.7/3.3% in non-TKA group. There was no significant difference in % increase of THBMD. 【Conclusions】TKA group had longer RA duration, lower ADL and lower THBMD. Efficacy of dTPTD was good enough in TKA group.

W25-6

Risk of bone mineral density reduction in patients with rheumatoid arthritis treated with biologics

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Conflict of interest: None

Background: Osteoporosis is a complication of rheumatoid arthritis (RA). We identified risk factors for reduction of bone mineral density (BMD) during treatment with biologics. **Methods**: Lumber spine and femoral neck BMD was measured in 153 patients with biologics-treated. We examined age, BMI, type of RA, disease duration, dose of prednisolone, duration of biologics use, change of DAS-CRP, change of SDAI, and change of CRP. We undertook multivariable logistic regression analysis to identify risk factors. **Results**: BMD of lumber spine was increased during 12 months. The average increase of lumber spine BMD was 0.004g/cm^2. In the multivariable analysis, no risk factor for bone loss of lumber spine was found. BMD of femoral neck was decreased during 12 months. The average reduction of femoral neck BMD was 0.005g/cm^2. In the multivariable analysis, lower BMI, longer disease duration, and high dose of prednisolone use are the risk factors for bone loss of femoral neck. **Discussion**: We recommend that patients with RA who possess these risk factors be considered for earlier and more intense treatment to prevent bone loss.

W26-1

Long term result of CR type Total Knee Arthroplasty for the Rheumatoid Arthritis Patients

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Conflict of interest: None

[Object] We investigated long term results of CR type TKA for the RA patients. [Methods] We performed 154 TKA using CR type Kinemax or PFC Σ from 1993 to 2004. All patella were displaced, and all cases used cement but did not use cement for the keel in PFC Σ. The examples which we can follow up to date were 47 knees (an average of intraoperative age was 59.6 years old; the average of follow-up period was 10 years 9 months; 32 Kinemax type and 15 PFCΣ type). [Results]The complications of all cases were one infection, two supracondylar fracture of Femur, and four revisions (2 Kinemax type, 2 PFCΣtype). Final average of Japan Orthopaedic Association score was 75.8 points, and average extension was -1 degree, flexion was 111 degrees. In X ray, 4 knees were seen clear zone in Femur, 7 knees in Tibia, but no loosening on Kinemax type. In contrast, one knee was seen clear zone in femur, 5 knees in tibia, 2 knees loosening in tibia on PFC Σ. [Conclusions]Long-term results of TKA by Kinemax CR type are satisfied. But there were 4 loosening on PFCΣ.We thought that cruciate keel of PFCΣtibia component kept bone stock and raise rotation homeostasis. Therefore we did not use comment for the keel, but in RA patients, bone quality was bad and loosening of tibia component ware occurred.

W26-2

Change of knee alignment on patients with rheumatoid arthritis from historical study

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Conflict of interest: None

[Objectives] DMARDs contained biologics have led and maintained remission and inhibited of joint destruction in RA. When TKA was performed in RA, knee alignment was valgus, previously. However, TKA due to complicated medial osteoarthritis (OA) and varus alignment increase, recently. We investigated radiograph and considered whether medial OA and varus knee alignment increased. [Methods] There were 67 patients and 87 knees performed TKA from 2003 to 2015. We divided to two groups by operation period. Early group (EG) was 47 knees and late group (LG) was 40 knees. We compared preoperative FTA, position of

Mikulicz line, medial OA (over KL grade 3), and femorotibial joint space width. [Results] Average age was same. Disease duration of EG was significantly longer than that of LG (15.8 and 10.1 years: p=0.012). FTA of EG and LG was 173.3 and 176.9° (p=0.019). Mikulicz line of LG passed more medial than that of EG (7.9 and -1.4mm: p=0.033). Medial OA in LG was significantly higher than that in EG (60.0 and 31.9%: p=0.01). Usage rate of MTX in LG was higher than that in EG. Whereas, usage rate of PSL and biologics was same. [Conclusion] We revealed that medial OA and varus knee alignment increased in RA patients performed TKA. TKA due to medial OA may more increase in controlled RA.

W26-3

Simultaneous bilateral total knee arthroplasty for windswept deformity knee with rheumatoid arthritis

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Conflict of interest: None

[Object] Windswept deformity (WD) of knee is relatively rare. We will report the cases performed simultaneous bilateral TKA for WD with RA (RA-WD). [Methods&Materials] We evaluated 17 cases. WD was defined that FTA was >175° at one knee and <170° at the other knee according to KSS. [Results] The causes of WD were traumatic and coxitis in 1 case, respectively. But we could not detect the specific causes for the other cases. Valgus knee side was 12 knees at right side (70.6%) and 5 knees at left side (29.4%). The overall range of motion (ROM), Knee score, and JOA score were improved postoperatively compared with preoperation, however, there were not significant difference between valgus and varus side. [Conclusion] We could find that the cause of RA-WD was vague in many cases and observe that the valgus knee frequently exist on the right side for RA-WD. As results of surgery, the meaningful difference for ROM and clinical score were not seen between the valgus and varus knee.

W26-4

Minimum 10 years results of cementless total hip arthroplasty in patients with rheumatoid arthritis: mortality and implant survival

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Conflict of interest: None

PURPOSE To evaluate the outcome of cementless total hip arthroplasty (THA) for patients with rheumatoid arthritis (RA) and postoperative mortality. METHODS A total of 247 cementless THAs were performed in 195 patients between 1998 and 2005. 45 patients were lost to follow-up and remaining 191 hips in 150 patients were included. Mean age at surgery was 58.5 years and mean follow-up was 12.3 years. Kaplan-Meier survival analysis was performed with the following three endpoints:(1) revision of the stem and (2) revision of the cup and (3) revision of the liner. RESULTS 43 patients died within 10 years and 19 patients died between 10 and 17 years. Patient survival rate was 57.3% at the last observation. One stem was revised due to loosening after periprosthetic fracture. Acetabular revisions were performed due to aseptic loosening in 6 hips, recurrent dislocation in 5 hips. Three alumina liners were revised in 3 hips. Subsequent implant survivals with the endpoint of any revision of the stem, cup and liner at 15 years were 99.5 % and 92.6 % and 92.4 %, respectively. CONCLUSIONS In follow-up of minimum 10 years, RA patient survival after THA was 57.3%. The use of the cementless stem proved successful, while acetabular revision were performed in various reasons.

W26-5

Postoperative change of femoral canal filling ratio in cementless total hip arthroplasty for patients with rheumatoid arthritis

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Conflict of interest: None

[Object] In cementless THA,cortical atrophy is concerned due to osteoporosis and the means of stem fixation, especially in rheumatoid arthritis (RA) patients. The purpose of this study was to investigate the postoperative change of canal filling ratio in cementless total hip arthroplasty for patients with RA.[Methods]Twenty-four THAs in 23 RA patients observed more than five years were included in this study (average age 61.0 y.o, 5 males, 18 females, average follow-up period 7.6 years). Natural hip stem in 12 hips and Mallory-Head XR stem in 12hips were used. Canal filling ratio at 20 mm proximal from the center of the lesser trochanter (CLT) (P20), 20 mm distal from the CLT (D20) and the isthmus were estimated on the radiographs at 1 year postoperatively and final follow-up. [Results]Canal filling ratio changed from 1 year postoperatively to the final follow-up, 60.8% to 61.2% at P20, 67.2% to 63.9% at D20, 74.2% to 72.1% at isthmus.[Conclusions]Canal filling ratio reduced at D20 and isthmus from 1 year postoperatively to the final follow-up in this study. It indicated cortical atrophy at these levels and was caused by the means of the cementless stem fixation and osteoporosis caused by the disease.

W26-6

Long and mid-term results of total joint arthroplasties of lower extremity in patients with rheumatoid arthritis and systemic lupus erythematosus operated before forty-years old

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Conflict of interest: None

[Purpose] To study the clinical results of joint arthroplasties patients with rheumatoid arthritis (RA) and systemic erythematosus (SLE) operated before 40 years old. **[Materials and methods]** SLE patients, 5 patietns,8 joints (male; 2 patients, 2 joints, female; 3 patients 6 joints), RA patients, 9 patients, 14 joints (male 2 patients, 4 joins, female 7 patients, 10 joints). THA; 18joints, TKA; 2 joints, 1st toe MTP Swanson implants 2 joint. An average age at operation was 32.3 years old (20-39 years old). A follow up period was an average of 11 years 5 months (5 years 8 months-17 years 8 months). We have studied the clinical course and results, ADL change, and complication. **[Result]** One TKA of RA was infected, one THA of SLE was become loosening and revision and another one THA of SLE dislocation. At operation period, patients were treated with prednisolone (PSL) using average 8.2mg and two patients were with biological agents. At the time of investigation, PSL using 6,5mg and Biological agents using six patients. ADL of one SLE and 4 RA patients were worsened cause by joint damage progression and vertebra compression fracture. **[Discussion]** RA and SLE patients' bone quality and the other joint damage influences on clinical results some patients were worsened daily activities.

W27-1

Deformity of lesser toe after Silicone implant and resection arthroplasty of the metatarsophanlangeal joint for rheumatoid arthritis

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Conflict of interest: Yes

Silicone implant arthroplasty of the first metatarsophalangeal joint combined with resection of the metatarsophalangeal joints of the lesser toe was performed. Follow-up evaluation was available for 27 feet in 15 patients. Their average age at the time of operation was 58.6 years, their average follow up period after the operation was 10.3 years. Weight-

bearing radiographs of foot were made preoperatively and postoperatively at 6 month and final follow-up. The HVA was improved from 45.3 degree preoperatively to 23.6 degree at the 6 month after operation, and the corrected HVA was kept throughout post-operation. By contrast for lesser toe, both the MTP-2 and proximal phalanx angle were improved at 6 month after operation, but recurrence of deformity was admitted at the final follow-up (MTP-2; 26.4 degree preoperative, 13.4 degree at 6 month after operation, 22.5 degree at final follow-up, proximal phalanx angle; 40.0 degree preoperative, 22.4 degree at 6 month after operation, 34.5 degree at final follow-up). This operation improved the deformity of both the first toe and the lesser toe, but the deformity of lesser toe was admitted in the long term follow-up.

W27-2

Planter pressure and surgical indication of toe arthroplasty for the rheumatoid forefoot deformity

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Conflict of interest: None

【Objectives】To clarify the surgical indication for the rheumatoid forefoot deformity, the preoperative plantar pressure of the foot treated with toe arthroplasty later was compared to the pressure without operation. 【Patients and methods】Using F-Scan®, planter pressure of 93 feet in 67 patients with toe arthroplasty and 258 feet in 153 patients without arthroplasty were measured. The average age in the surgical group and the non-surgical group was 63 and 64 years old. The average hallux valgus angle (HVA) in the weight bearing dorsoplantar radiograph of the foot was 35.6˚ and 20.7˚. Distribution of the peak and the integrated pressures were measured in 9 sections each, including the 1st IPJ, the 1st through the 5th MTPJs, the medial and the lateral midfoot, and the hindfoot. 【Results】The peak and the integrated pressures was high at the 1st MTPJ and low at the 5th MTPJ in the surgical group compared to those in the non-surgical group. The integrated pressure at the hind foot was high in the surgical group. In the foot with HVA less than 20˚, the pressure at the 5th MTPJ was low, and in the foot with HVA 20˚ or more, the pressure at the hindfoot was high. 【Conclusion】Plantar pressure was high at the medial forefoot and the hind foot in the surgical group.

W27-3

Change of hallux alignment after metatarsal shortening osteotomy of lesser toe without hallux surgery for rheumatoid forefoot deformity

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Conflict of interest: None

[Background] Among the rheumatoid forefoot deformity, occasionally, the hallux MTP joint may have minimal deformity. Resection arthroplasty of lesser MTP joint without hallux surgery is unfavorable because of the high probability of deterioration of hallux valgus deformity. We examined the hallux alignment after shortening metatarsal osteotomy of lesser toe. [Methods] Thirteen feet of 13 RA patients were included. Metatarsal shortening osteotomy from 2nd to 5th toe without great toe were underwent. Hallux valgus angle (HVA), intermetatarsal angle (IMA), sesamoid position (Hardy grade), shortened length of 2nd metatalsus were examined. [Results] HVA was significantly deteriorated from 15.9 preoperatively to 18.4 at 3 months postoperation, and 22.9 at 1 year postoperation. IMA was deteriorated from 6.0 at preoperatively to 8.2 at 3 months postoperation. Mean amount of 2nd metatarsus shortening was 8.7mm. Eight cases showed over 20 degree of HVA at 1 year postoperation. [Discussion] The influence of decrease of outside support of shortened 2nd toe and increase of the load of 1st metatarsal head supposed to appear at early time point after operation. [Conclusion] Metatarsal shortening osteotomy of lesser toe without hallux surgery aggravate the hallux valgus deformity..

W27-4

The Clinical Outcomes of Joint-preserving Arthroplasty for Rheumatoid Forefoot Deformities

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Conflict of interest: None

Object: The clinical outcomes of joint-preserving surgery for rheumatoid forefoot deformities was assessed in comparison to resection arthroplasty. **Methods:** We retrospectively evaluated 23 feet in 17 patients with rheumatoid forefoot deformities who underwent surgery between Jan 2010 and Dec 2013. The patients included one male (1 foot) and 16 females (22 feet), with a mean age of 62 years. The mean length of follow-up was 28 months. Joint-preserving procedures were performed in 10 feet (JP group). Resection arthroplasty was performed in 13 feet (RA group). The clinical outcomes of the patients were evaluated using the Japanese Society for Surgery of the Foot (JSSF) hallux and lesser toe scales. **Results:** There were no significant differences in the preoperative total JSSF scores for either the hallux (54.5 and 61.4 points) or the lesser toe (45.2 and 57.4 points) between the RA and JP groups, respectively. Postoperatively, the total JSSF scores for both the hallux (79.4 and 88.2 points) and lesser (73.6 and 87.7 points) showed significant improvement in both the RA and JP groups, respectively. The scores relating to the function category on the hallux scale and the alignment category on the lesser toe scale were significantly higher in the JP group.

W27-5

Results of salvage replacement of all toes MTP joints by Swanson implant for failed arthroplasties of forefoot in rheumatoid arthritis

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Conflict of interest: None

【Object】Arthroplasty for forefoot deformities of RA patients (Pts) is effective treatment. Recurrence of pain or deformities, however, sometime needs revision. We report the results of replacement of all toes MTP joints by Swanson implant (RMSI) in salvage situations. 【Methods】We retrospectively looked at 5 RA Pts, 6 foot who underwent RMSI after failure of an arthroplasty of forefoot. We assessed clinically American Orthopaedic Foot and Ankle Society (AOFAS) clinical rating system, and radiographically hallux valgus angle (HV angle), M1M2 angle and M1M5 angle. 【Results】All Pts are female, mean age is 65.5 years (range 62-71 years). Pts were followed up for 17-83 months (mean, 47 months). There was neither infection nor implant breakage. One Pt had recurrence of pain. Average AOFAS Hallux Metatarsophalangeal-Interphalangeal Scale improved significantly from 40 points preoperatively (pre-op) to 73.8 points postoperatively (post-op). Average AOFAS Lesser Metatarsophalangeal-Interphalangeal Scale improved significantly from 27 points pre-op to 72.3 points post-op. Average HV angle, M1M2 angle, M1M5 angle decreased post-op from 21.7˚ to 17.5˚, from 10.3˚ to 8.8˚, from 27.7˚ to 25.3˚, respectively. 【Conclusions】 Salvage RMSI for failed arthroplasty of forefoot would be of use.

W27-6

The instrument using after operations to the forefoot deformity of rheumatoid arthritis patients

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Conflict of interest: None

Objective: The shortening oblique osteotomies of metatarsal bones for lateral toes are performed to the forefoot deformities of rheumatoid arthritis (RA) patients in our hospital. We inhibit to weight at forefoot for 3 weeks. Patients wore instruments which were made by therapist, but they were not so strong and safety. On the other hand, ready-made instruments were very expensive. So we tried to reform more effective instruments. ***Methods:*** In new instruments, we chose slippers with counter heel and attach the hard soles to bottom of them. We picked up 10 ordinary person and they wore new instruments, old instruments and ready-made instruments. Under wearing them, we searched the functional reach test, timed up go test, walking 10m test, and standing on one foot test. After then, we use them to several patients and reform again. ***Results:*** In the functional reach test and timed up go test, there were no significant. In walking 10m test and standing on one foot test, new instruments are superior to other instruments. We used them to RA patients and all of them could walk from next day. Some patients had pain at their ankles, so we changed the other type of soles. ***Conclusion:*** The new instruments are effective and we can use to RA patients.

W28-1

Effectiveness of surgical reconstruction for the lower extremity - a prospective study using various evaluations?

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Conflict of interest: None

【Objectives】To investigate the effectiveness of surgical reconstruction for the lower extremity in the patients with RA, a prospective cohort study was performed. 【Patients and methods】During the period between October 2012 and September 2014, 126 primary surgical reconstructions were scheduled. The average age was 66 YO and the average disease duration was 18 yrs. The surgical procedure was THA in 12 patients, TKA in 47, ankle arthrodesis in 11, toe plasty in 51, and synovectomy in 5. Assessments using DAS28-CRP (4) and SDAI for disease activity, JOA score and JSSH scale for joint function, J-HAQ and EQ-5D for QOL, and BDI-II for depression were performed just before surgery and at one year after surgery. 【Results】DAS28-CRP (4) and SDAI decreased significantly ($p<0.01$). JOA score for the hip/knee, JSSF scale for the toe improved significantly ($p<0.01$). There was no significant change in J-HAQ, however, EQ-5D and BDI-II improved significantly ($p<0.01$). Within the subgroup of surgical site, J-HAQ improved in the knee, EQ5-D in the knee/ankle/toe, and BDI-II in the toe ($p<0.01$). 【Conclusion】The surgical reconstruction ameliorated disease activity and joint function. The knee/ankle/toe surgeries improved QOL and the toe surgery made depressed feeling better.

W28-2

QOL of Joint-Preserving Arthroplasty for Rheumatoid Forefoot Deformities

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Conflict of interest: None

[Object] To compare clinical outcomes of joint-preserving surgery for rheumatoid forefoot deformities with those of resection arthroplasty. [Methods] 26 feet in 16 patients with rheumatoid forefoot deformities who underwent shortening osteotomy of 1-5 metatarsals (joint-preserving group) were retrospectively compared with 33 feet in 17 patients who underwent resection arthroplasty of 1-5 metatarsal heads (resection group) using patient-oriented QOL questionnaire. [Results] Five subscale (pain and pain-related, physical functioning and daily living, social functioning, shoe-related and general health and well-being) scores were not statistically different between joint-preserving and resection group. More patients of joint-preserving group achieved more than 80 points in general health and well-being subscale score than those of resection group. [Conclusions] Joint-preserving surgery for rheumatoid forefoot deformities may provide better results for QOL than resection arthroplasty.

W28-3

Risk factor for late deep infection after total hip arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: The aim of this study was to investigate the correlation between TNF-α inhibitor therapy and serious postoperative late infection in patients with RA who underwent total hip arthroplasty (THA). **Methods:** Ninety-nine patients with RA who enrolled in our institution's THA registry between January 2003 and December 2012 were eligible to participate. Data collected included clinical parameters and medications, including biological drugs, disease-modifying antirheumatic drugs, and glucocorticoids. Logistic regression was performed to examine the association between clinical parameters, medications, and the development of postoperative late infection. **Results:** Two risk factors were identified in multivariate analysis. Etanercept therapy and glucocorticoid dose were found to be significantly associated with the development of late infection after THA (etanercept: odds ratio [OR]: 16.9, 95% confidence interval [CI]: 1.4-205.7; glucocorticoid dose: OR: 2.0, 95% CI: 1.1-3.4). **Conclusion:** The use of TNF-α inhibitor therapy, especially etanercept, is associated with an increased rate of late infection after THA. When the use of TNF-α inhibitor therapy is considered, rheumatologists need to pay special attention to patients after THA.

W28-4

Investigation of patient specific instrument in total knee arthroplasty for rheumatoid arthritis

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Conflict of interest: None

【Introduction】PSI is introduced as the significant improvement in TKA.We evaluated the issue of PSI-TKA by comparing between the cases for RA and OA.【Patients and Method】23 patients in PSI-TKA for RA and 32 patients for OA were compared. The mean age of RA was 69.9 and OA was 72.0. The analysis was performed by NTX and BMD, surgical time, blood loss,FTA,component size and position, osteotomy changes.【Results】The time (min) for RA and OA was 86.2 and 88.9. The blood loss (ml) was 463 and 499. FTA was 174.6 and 174.6. Osteoporosis was found in RA. Component size was changed in RA (14 cases) and OA (26 cases). The component positioning was corrected in RA (11 cases) and OA (12 cases). In RA recut was done for 1 case and 3 cases in OA.【Discussion】In RA, bone quality loss seems to cause an error of the fixed defectiveness by the pin or the bone excision felt uneasy about on the occasion of using PSI, but the problem was not seen in this examination in particular. In valgus knee deformity of RA,it was necessary to release the tibia.【Conclusion】PSI is in effective treatment for TKA of the RA. However, in case of RA with bone density loss or in case pannus forms in

bone,using PSI must be caution, and further validation such as the pin insertion, removal of soft tissue nearby bone, should be performed.

W28-5

Clinical results and problems of arthroscopic debridement for pyogenic arthritis of the knee

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Conflict of interest: None

Objective: Good clinical outcomes have been reported about arthroscopic debridement (A.D.) for pyogenic arthritis of the knee. We assessed clinical results and problems retrospectively. Materials and methods: Seventeen patients (OA: 12 knees, RA: 2 knees, trauma: 3 knees) who underwent A.D. for pyogenic arthritis were divided into two groups: group A (only once A.D.: mean age 68.3 years old, 9 knees) and group B (several times surgery such as open debridement or arthrodesis for treatment: mean age 72.6 years old, 8 knees). Blood examinations, the time interval between onset and A.D., pathologic agent, immunocompromised patients (RA, DM or liver disease etc.) and clinical results were evaluated. Results: The serum level of Hb and Alb were significantly higher in group A (Hb 12.2±2.0 g/dl, Alb 3.5±0.4 g/dl) than in group B (Hb 9.8±1.3 g/dl, Alb 2.4±0.5 g/dl). There were no significant differences in other factors. The clinical results according to Ballard's evaluation were better in group A than in group B. Conclusions: It was difficult to treat pyogenic arthritis of the knee only by A.D. in the case of patients with severe anemia or low serum albumin level. Another treatment such as open debridement or arthrodesis, would be selected for these patients at an early stage.

W28-6

Clinical and radiographical results of tibiotalocalcaneal arthrodesis for the patients with rheumatoid arthritis by retrograde intramedullary nail

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Conflict of interest: None

[Object] For rheumatoid patients, ankle joint disorder often cause the impairment of activity of daily life (ADL). Previously, ankle arthrodesis has been performed for these patients. In this study, we aimed to evaluate the safety and efficasy of tibiotalocarcaneal arthrodesis using retorograde intramedullary nail. [Methods] From January 2006 to December 2014, we performed tibiotarocarcaneal arthrodesis for 13 patients (15 feet), consistent with 13 females. The mean age was 59.8 years old, disease duration was 15.9 years, JSSF RA foot and ankle scale was 42.6 points and DAS 28 CRP was 4.13 at index surgery.[Results]The mean postoperative follow up period was 61.3 months. In one patient, 2 feet, nonunion had been exhibited. In other 12 cases, the mean JSSF RA foot and ankle scale was increased to 54.5 points and DAS 28 CRP was improved to 3.26 at the final examination [Conclusions] It's considered that tibiotalocarcaneal arthrodesis was great benefitical procedure for the rheumatoid patients with ankle joint disorder, releaving its severe pain and improving whose ADL.

W29-1

Development of prevention strategy of non-traumatic osteonecrosis of the femoral head

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Conflict of interest: Yes

[Object] We previously reported that innate immunity via toll-like receptor (TLR) has a role in the pathogenesis of non-traumatic osteonecrosis of the femoral head (ONFH). Moreover, we demonstrated that the repression in IRF7 activity by BAY11-7082 interfered with the development of ONFH. In the present study, we hypothesized that lansoprazole could prevent to the development of ONFH through a repression in IRF7 activity. [Methods] Male wistar rats were divided into four groups. Each group rats were given LPS or Imiquimod on Day 1 and methylprednisolone (MPSL) with or without lansoprazole. Histopathological and NF-kB and IRF7 activity assay were performed. [Results] ONFH was observed in almost 50% in the LPS+MPSL and Imiquimod+MPSL group. On the other hand, no ONFH was observed in the group treated with lansoprazole. The activity of IRF7 was repressed significantly at 1 day in rats administered lansoprazole. [Conclusions] Lansoprazole belongs to a group of drugs called proton pump inhibitors. It was also reported that lansoprazole has anti-inflammatory activity. In the present study, we also observed anti-inflammatory activity of Lansoprazole. In results, lansoprazole could prevent to the development of ONFH. Based on this result, we conduct a clinical trial.

W29-2

Clinical Trial: Lansoprazole Prevents the Development of Corticosteroid-Induced Osteonecrosis of the Femoral Head

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Conflict of interest: Yes

[Object] We reported that a repression in IRF7 activity by the use of lansoprazole (LPZ) could prevent the development of ONFH in rats. In the present study, we conducted a clinical trial for preventing ONFH in patients with corticosteroid-treated immune diseases. [Methods] All patients required primary high-dose corticosteroid treatment for immune diseases. All 30 patients were administered LPZ intravenously a total of 6 times. Subsequently, all were administered LPZ orally once a day for 25 days. [Results] ONFH was found in 4 of 30 patients treated with high dose corticosteroid, which was a significantly lower incidence than that in the control group. ONFH in MRI was not observed at pre-corticosteroid treatment or at 4 weeks after treatment. It was observed in 3 patients at 12 weeks after treatment, and in another one at 24 weeks. [Conclusions] The present study showed that co-treatment of LPZ with corticosteroid prevents ONFH development in patients having immune disease treated with corticosteroid, although the study is preliminary. Several limitations of our clinical study should be noted. It has small sample size, is single-center and historically controlled. Furthermore, we could not evaluate transcriptional factors activity in patients.

W29-3

Analysis of our forty cases with aseptic necrosis of femoral heads during steroid tharapy

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Conflict of interest: None

«Object» The object is investigating aseptic necrosis of femoral heads during steroid therapy. «Methods» We retrospectively analyzed clinical data of our forty patients with aseptic necrosis of femoral heads. «Results» Main chief complaint was hip pain. Some had no symptom. Main basic disease was Systemic Lupus Erythematosus, Dermatomyositis/Polymyositis, Vasculitis Syndrome and Mixed Connective Tissue Disease. The number of cases was 13, 6, 6 and 3 respectively. Average age at the onset was 46.7±16.6 years old. Thirty three had bilateral necrosis. Average maximum dose of prednisolone (PSL) was 51.8±22mg. Average PSL dose at the onset was 10.9±7.5mg. Thirteen patients took steroid pulse therapy. Duration from beginning of steroid to diagnosis was wide

(2-192 months). Median duration was 16 months. Twenty one needed total hip arthroplasty (THA). Fifteen of them took bilateral THA. Type A, B, C-1 and C-2 at the onset was 5, 11, 30 and 25 joints and rate of THA was 20, 0, 33 and 60% respectively. «Conclusions» Aseptic necrosis of femoral heads by connective tissue disease was more frequent. The dose of PSL was high. Type C was more common. MRI was useful to predict future THA. Since half of femoral necrosis require operation, we should try to find prophylactic measures.

W29-4

Serum adipokine level is associated with arterial stiffness in systemic autoimmune diseases undergoing glucocorticoid therapy

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Conflict of interest: None

[Objectives] We investigated the association of adipokines and glucocorticoid (GC) therapy with premature atherosclerosis in patients with systemic autoimmune diseases. [Methods] Thirty eight patients with systemic autoimmune diseases who had started GC therapy were enrolled. Ankle-brachial pressure index (ABI) and Cardio-vascular ankle vascular index (CAVI) were measured to detect premature atherosclerosis after a follow-up of mean 3 years. Serum levels of adipokines [resistin, leptin, and high molecular weight adiponectin] were measured with enzyme-linked immunosorbent assay kits. [Results] The mean value of CAVI and ABI was 7.8±1.5 and 1.2±0.1, respectively. Five of the 38 patients (13.2%) had a low ABI (ABI<1.0). CAVI was positively associated with age, diabetes mellitus, and the yearly change in serum resistin levels, independently. Cumulative prednisolone dose was significantly higher in the subgroup of patients with ABI≧1.0 than in that with low ABI <1.0. In contrast, there was no significant difference in serum levels of 3 adipokines between the subgroups. [Conclusion] Rsistin might be positively related to CAVI as an index of arterial stiffness, while GC might not adversely affect CAVI or ABI in patients with systemic autoimmune diseases.

W29-5

Prophylaxis of pneumocystis pneumonia by TMP/SMX in immunocompromised patients with rheumatic diseases

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Conflict of interest: None

Pneumocystis pneumonia is one of most serious complications during the treatment with high doses of corticosteroid or immunosuppressants in rheumatic disease patients. TMP/SMX is a useful drug for prophylaxis of PCP, although a lot of adverse events may cause the cession of the administration. We studied the adverse events of daily administration of TMP/SMX on the patients treated with high doses of corticosteroid. We enrolled 208 patients between Jan 2011 and Dec 2014. There were 62 males and 72 females. Mean age was 55.8 years old. Eighty two patients discontinued the administration of TMP/SMX because of adverse events, such as hyponatremia, hyperkalemia, liver dysfunction and skin eruption. The cessation rate of the administration was 39.4%. Mean duration before discontinuation was 18.06 days. Next we included 13 patients who were administrated TMP/SMX in 3 days per week. None of them discontinued TMP/SMX. Thus the administration of 3 days per week of TMP/SMX is a tolerable and useful method for the prevention of PCP.

W29-6

3 cases of interstitial pneumonia with amyopatic dermatomyositis (DM-IP) controlled by immuno-adsorption therapy (PMX-DHP)

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Conflict of interest: None

[Background] DMIP is still one of refractory diseases, in spite of several immunosuppression used. The Polymyxin B immunoadsorption column can remove various kinds of inflammatory cytokine including endotoxin in a case of the sepsisrelated shock. This way is called PMXDHP. There are only a few cases of DMIP are included in several reports. [Cases] Three DMIP cases that PMXDHP could contribute to prevent acute exacerbation. The case 1 is a 54 years old man, the case 2 is 57 years old woman, and case 3 is 71 years old women. PMXDHP were performed two times of six hours in each. As the outcome, only case 1 died because of reexacerbation, although once his condition was recovered. Other two cases have been survive. The specific autoantibody was positive with anti-MDA only in Case1. As combination medication, methylprednisolone (mPSL) pulse, cyclophosphamide IV infusion (IVCY), prednisolone (PSL) were given in Case1. IVCY and PSL in cyclosporin A were given Case 2 and 3. Before PMXDHP, AaDO2 was 74.9, 29.95, 34.85Torr, refractory. They were improved after in 626.0, 39.7, 49.25Torr. P/F ratio was 244, 368.5, 350 before PMXDHP. After they were improved to 49.6, 328.0, 293.0. PMXDHP could recover the severe condition of DM-IP.

W30-1

Cessation of pre-emptive therapy for patients with rheumatic disease with previously resolved HBV

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Conflict of interest: None

[Methods] Examined the rate of HBVDNA reappearance after the cessation of entecavir (ETV) for rheumatic disease (RD) patients with resolved HBV treated with ETV. The criteria for cessation of ETV were as follows:(1) at least 6 months of administration of ETV;(2) undetectable HBVDNA;(3) negative HBeAg;(4) negative HBsAg; and (5) negative HBV crAg. After cessation of ETV, HBVDNA were monitored on a monthly [Results] All patients (RA;n=3 and PMR).For case 1, after prednisolone had been tapered and discontinued, the five ETV discontinuation criteria were met and ETV was stopped. At 39 months after cessation of ETV, HBVDNA reappearance had not occurred.For case 2, HBVDNA reappearance developed once 8 months after cessation of ETV while the patient was being treated with dexamethasone palmitate and MTX; however, it was not seen in the next 9 months. For case 3, reappearance of HBV DNA was noted at 27 and 34 months after cessation of ETV while being treated with tocilizumab. HBV DNA became negative immediately thereafter at both time points without readministration of ETV. For case 4, reappearance of HBV DNA has not developed since cessation of ETV [Conclusion] Our criteria for cessation of ETV may be effective for protecting against hepatitis onset in RD patients with resolved HBV.

W30-2

Prevalence and Pathophysiology of Reactivation of Hepatitis B Virus (HBV) in Patients with Resolved HBV Infection on Immunosuppressive Therapy for Connective Tissue Disease

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Conflict of interest: None

[Objectives] We are performing multicenter observational, prospective study, by 16 Japanese Red Cross hospitals to clarify the prevalence and pathophysiology of HBV reactivation in connective tissue disease (CTD) patients. We report the results of one year observation in the patients with resolved HBV infection. [Methods] Patients with CTD, treated with steroids, and/or synthetic or biological immunosuppressive drugs (ISD), with negative HBs antigen and positive anti HBs and/or HBc antibody (Ab) were enrolled. HBV-DNA (RT-PCR) and related data were registered regularly. [Results] Among 847 patients, detection of HBV-DNA, were found in 22 patients (2.6%) and positivity more than 2.1 log copy/ml were seen in 7 cases (0.83%). None of reactivated patients, including three started nucleic acid analogue, showed hepatitis. Low titer of HBs Ab and advanced age seemed to be risk factors for HBV reactivation. The intervals from start of ISD to reactivation were longer than previous reports, four to 157months, 58.9 months in average. [Conclusions] HBV reactivation with ISD was 2.60% per year in CTD patients with resolved HBV infection. Overt hepatitis was seen in none of reactivated patients, criteria for preventive treatment for HBV reactivated patients may be reconsidered.

W30-3

Hepatitis B virus reactivation associated with anti-rheumatic therapy for rheumatoid arthritis in our institute

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Conflict of interest: None

[Purpose] The present study investigated the prevalence of HBV reactivation associated with anti-rheumatic therapy in our hospital. [Method] All patients with RA received the screening for HBV infection including serological test and HBV-DNA before the initiation of treatment and were followed up carefully. [Results] 1. 5 patients with RA who had resolved HBV infection during the treatment with MTX,PSL and bDMARDs without antiviral prophylaxis. 2 patients who had clinically apparent hepatitis were defined as de novo hepatitis. The HBV replication disappeared in all 5 patients who were treated immediately with nucleoside analogue. 2. 8 patients with RA who were inactive HBV carriers were treated with anti-rheumatic therapy and without antiviral prophylaxis. The HBVPCR became detectable in 3 patients and increased in 5 patients in the absence of ALT elevation.The HBV-DNA replication disappeared with entecavir therapy. 3. 7 patients who were inactive HBV carriers were simultaneously treated with nucleoside analogue and csDMARDs. The HBVPCR became undetectable in all patients. [Conclusion] The present study supported that the implication of antiviral prophylaxis for patients with resolved HBV infection and inactive carriers might be effective in prevention of HBV reactivation.

W30-4

Risk factors for cytomegalovirus (CMV) reactivation in 165 patients with connective-tissue disease (CTD)

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Conflict of interest: None

Objectives: To investigate risk factors relevant with CMV reactivation in patients with CTD. **Methods:** CTD cases who started immunosuppressive therapy with CMV PP65 antigen tested from January 2012 until October 2015 were enrolled. Risk factors for CMV reactivation were investigated. **Results:** 165 cases were enrolled. Patients characteristics were following; mean age 57.1 years old, female 115 (69.7%), SLE 41, AAV 35, RA 21, PM/DM 20, AoSD 10, others 38, new-onset 110 (66.7%), of the mean PSL dose 49.4 mg/day, mPSL pulse therapy 56 (33.9%), concomitant immunosuppressants 113 (68.5%). Among 62 CMV-reactivated cases, CMV infection occurred in 17 cases (hematopoietic injury 14, liver injury 2, retinitis 1, others 3). mPSL pulse therapy (p=0.001), initial PSL dose (p=0.002), lymphocyte count (p=0.026), albumin (p=0.000), CRP (p=0.035), and oral candidiasis (p=0.001) were relevant with CMV reactivation. Among asymptomatic 33 cases, 10 cases finally needed antiviral therapy. Their initial WBC (p=0.017) and lymphocyte (p=0.019) count were significantly less, and CMV reactivation occurred more rapidly after the start of immunosuppressive therapy (p=0.000) than 27 cases whose CMV disappeared spontaneously. **Conclusions:** The risk factors for CMV reactivation with CTD were detected.

W30-5

Clinical Features of Cytomegalovirus Infection in Patients with Rheumatic Diseases during Immunosuppressive Therapy

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Conflict of interest: None

Objective: To analyze the clinical features of cytomegalovirus (CMV) infection in patients with rheumatic diseases during immunosuppressive therapy. Methods: We retrospectively analyzed 64 patients who had admitted in our department from December 2011 to December 2014. 25 patients who were positive for CMV antigenemia (C10/C11 assay) received Ganciclovir (GCV) during immunosuppressive therapy (infection group). 39 patients did not received GVC regardless of the result of C10/C11 assay (non-infection group). Results: There were no significant differences in age and the interval from the start of treatment to the C10/C11 assay between the groups. RA complicated with acute interstitial pneumonia (RA/AIP) was more frequent in infection group than non- infection group (32% vs 7.6% p=0.018). In comparison with non- infection group, lymphocyte and platelet counts at C10/C11 assay were significantly decreased in infection group (p=0.003 and p=0.005, respectively). In multivariate analysis, thrombocytopenia (p<0.01, OR 9.8), lymphocytopenia (p<0.01, OR 13.6) and RA/AIP (p<0.01, OR 46.5) indicated the risk factors for CMV infection. Conclusion: Thrombocytopenia is a useful marker of active CMV infection in patients with rheumatic diseases during immunosuppressive therapy.

W30-6

Effects of TNF-alfa inhibitors to a Human T-lymphotropic virus I infected cell line

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Conflict of interest: None

Background: Human T-lymphotropic virus I (HTLV-I) is widely spread in western Kyushu in Japan. It is unknown if HTLV-I can prolifer-

ate when biologics are used. Objectives: To evaluate effects of TNF-alfa inhibitors (TNFi) to HTLV-I infected cell. Method: We used an HTLV-I infected cell line named HCT-5, which is derived from cells in spinal fluid of a patient with HTLV-I associated myelopathy. We also used Jurkat as a control cell line. Result: In multiple cytokine assays, supernatant of HCT-5 showed time-dependent elevations of IL-6, RANTES and sICAM-1. Supernatant of HCT-5 with infliximab, adalimumab, etanercept (ETN), golimumab and certolizumab pegol showed no differences in levels of IL-6, RANTES, sICAM-1 compared to that of HCT-5 with PBS. By fluorescence-activated cell sorting, expressions of TNFR1 in HCT-5 with each TNFi did not change, but expressions of TNFR2 were elevated except for ETN. Expressions of mRNA of tax and HBZ, which is needed to immortalization and proliferation of HTLV-I infected cells respectively, did not have differences compared to the control. Proviral loads also were not changed. DNA ladder which shows apoptosis was not detected. Conclusion: In vitro, TNFi did not affect the cytokine profiles, associated proteins, proviral load and apoptosis of HCT-5.

W31-1

Diagnostic performance of measuring antibodies to the glycopeptidolipid core antigen specific to *Mycobacterium avium* complex in patients with rheumatoid arthritis: results from a cross-sectional observational study

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Conflict of interest: None

[Objective] To investigate diagnostic performance of measuring antibodies (ab) to glycopeptidolipid (GPL) core antigen specific to *Mycobacterium avium* complex (MAC) in patients with rheumatoid arthritis (RA). [Methods] We cross-sectionally investigated anti-GPL core IgA ab and radiographs of 396 RA patients (pt). MAC pulmonary disease (MAC-PD) was diagnosed by criteria of American Thoracic Society. The ab was measured by EIA. RA pt with abnormal shadows on chest x-rays underwent CT.Bronchoscopy was performed on pt with negative for MAC by sputum and positive CT compatible with MAC-PD.[Results]Eight who had MAC-PD at entry and19 who refused bronchoscopy were excluded in the analysis.Ten pt were newly diagnosed with MAC-PD.The ab was detected in 12 of 369 pt.Eight of the 10 pt with MAC-PD and 4 of 359 pt without MAC-PD tested positive for the ab.Specificity and sensitivity were 99% and 80%. Twelve pt underwent bronchoscopy.Six pt positive for the ab were positive for MAC in bronchoalveolar lavage fluids (BALF), whereas 6 pt negative for the ab were negative for MAC in BALF.[Conclusion] Measuring the ab is useful as a supplementary diagnostic tool for MAC-PD and may provide a new strategy, in combination with pulmonary imaging, for differentiating MAC-PD in pt with RA.

W31-2

Outcome of RA patients suspected of having nontuberculous mycobacteria pulmonary disease (NTM-PD) by screening before starting biologic DMARDs

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Conflict of interest: None

【Objectives】To assess the clinical characteristics of RA patients (pts) suspected of having NTM-PD and effects of treatments for RA. 【Methods & Results】2069 RA pts were screened using CT scan before starting biologics in our hospital from April 2005 to January 2015. 18 pts were suspected of having NTM-PD according to CT findings. After further evaluation, NTM infection was diagnosed in 9 pts (definite 2, PCR-positive 3, after treatment 4; Species, M.avium 7, M.Kansasii 2). Clinical characteristics of 9 pts (mean age 65years; disease duration 131months; DAS28ESR 5.97) were not significantly different from those of 2069 RA pts. 4 pts developed NTM infection during treatment with biologics (ETN 3, TCZ 1). 5 pts were treated with a combination of three drugs (RFP, CAM, and EB). After obtaining informed consent, biologics were started in 9 pts (ETN 5, ABT 4). Although in 2 patients ETN was discontinued due to worsening CT findings and repeated pneumonia, the other 7 patients had no adverse events. 6 out of 7 patients continuing biologics remained LDA in RA. [Conclusion] RA pts complicated with or without NTM-PD could not be distinguished from clinical characteristics. Adequate therapy and following up NTM-PD could enable disease control of RA with biologics.

W31-3

Study on clinical significance of mycobacterium avium complex antibody in patients with rheumatoid arthritis (RA) associated with nontuberculous mycobacterial diseases

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Conflict of interest: None

[Purpose] Nontuberculous mycobacterial (NTM) diseases in RA patients (pts) are prevalent but it is difficult to distinguish the bronchiectasis associated with NTM from those with RA. Mycobacterium avium complex (MAC) are most common among NTM. We aim to evaluate the efficacy of MAC antibody (ab). [Methods] The 1,855 sera from RA pts randomly collected during the one or two months in 2014, in the 7 hospitals enrolled in NinJa. Those sera were examined with the enzyme immunoassay (EIA). [Results] 80 (4.3%) of 1,855 RA pts were positive with MAC ab. 1,414 pts, which have information of NTM complication, were analyzed. MAC ab positive rate was significantly high in RA pts with NTM [20 (39.2%) of 51] compared with non-NTM [41 (3.0%) of 1,363] ($p<0.001$). Sensitivity and specificity were 39.2% and 97.0%, respectively. It is suggested that high rate of positivity in RA pts should be due to high prevalence of NTM in RA pts. It is possible that false negative pts of NTM were included because of the strict diagnostic criteria. [Conclusion] Using randomly collected sera from RA pts on a large scale we clarified the positive rate of MAC ab in RA pts. Sensitivity was relatively low but specificity was high and it is considered that measuring MAC ab is useful for the diagnosis of MAC disease in RA pts.

W31-4

Effect of latent tuberculosis infection treatment in the immunosuppressive therapy of patients with articular rheumatism in this hospital and directly observed treatment, short-course (DOTS) conference

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Conflict of interest: None

Objectives: As our hospital has no pulmonologist, we cooperate with external respiratory disease specialists in respiratory infection screening (RIS) before introducing immunosuppressive therapy (IST). We conduct directly observed treatment, short-course conferences (DOTS-C) with public health center (PHC) for latent tuberculosis infection (LTBI) cases treated with isoniazid (INH) regularly from 2013. Therefore we examined the RIS situation and the effect of DOTS-C gave in a treatment outcome of LTBI. Methods: We investigated LTBI and IST of 250 cases who underwent RIS for 2010-14. Results: The LTBI patients treated with INH were 58. As IST among these cases, methotrexate were 37, and 7.57±2.28 mg/week (mean ± standard deviation), prednisolone were 6, and 2.17±0.85 mg/day and biologics were 45 as of October 31, 2015. The INH treatment planned period was 270 days in all cases. DOTS-C was performed in 23 cases. The cases with completion of treatment with 100% were 19 (82.6%) in DOTS-C enforcement group and 11 (31.4%) in DOTS-C non-enforcement group. Conclusion: In completion treatment for LTBI was possible by cooperating with PHC in the hospital which pulmonologist was not registered. It was suggested that enforcement of DOTS-C was useful in treatment successful execution of LTBI.

W31-5

Effect of directly observed treatment, short-course (DOTS) to a proper medical offer of a latent tuberculosis infection in immunosuppressive therapy

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Conflict of interest: None

Objectives: Tuberculosis (TB) screening is essential before introducing immunosuppressive therapy (IST). Public health center has been provided health care services performing directly observed treatment, short-course (DOTS) to all TB patients, including latent TB infection (LTBI) patients. We examined the effect of DOTS on treatment outcome among the LTBI patients. Methods: We investigated 81 LTBI cases enrolled for 2010-14 and evaluated them according to the treatment outcome categories we established newly. Results: The cases during IST in LTBI were 0.0% until 2011, 35.0% in 2012, 58.1% in 2013 and 76.9% in 2014. The number of cases who completed treatment within the specified periods were 0 (0.0%) in 2010, 7 in 2011 (50.0%), 18 in 2012 (90.0%), 24 (77.4%) in 2013 and 11 (84.6%) in 2014. The IST cases of them were 5 (71.4%) in 2012, 14 (77.8%) in 2013 and 9 (81.8%) in 2014. Enough DOTS was performed in 57 cases of them. Six cases could not be evaluated due to insufficient information. Enough DOTS was not performed to them. Conclusion: The proportion of the patients during IST to total LTBI patients is considerably high, indicating the effect impacts on overall treatment outcome. Our results showed that enforcement of enough DOTS was useful in completion of treatment.

W31-6

Extrapulmonary nontuberculous mycobacterial infection in patients with rheumatic diseases

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Conflict of interest: None

[Object] To investigate the clinical characteristics of musculoskeletal nontuberculous mycobacterial (NTM) infection in patients with rheumatic diseases undergoing immunosuppressive therapies. [Methods] Patients who were diagnosed and treated with musculoskeletal NTM infections in our center were identified and retrospectively reviewed. [Results] 5 patients (2 rheumatoid arthritis, 1 systemic lupus erythematosus, 1 dermatomyositis, 1 polymyalgia rheumatica) were identified. The initial diagnosis was flare of underlying rheumatic diseases in all patients and among these three patients received escalation of immunosuppressive therapies. Synovectomy of joint and tendon sheath was performed in four patients. *M. intracellulare* was found in two patients, *M. avium* complex in two, *M. marinum* in one. In all patients, anti-NTM drugs were administered without discontinuation of immunosuppressive agents. In all patients but one, both conditions of NTM and rheumatic disease were adequately controlled. [Conclusions] To diagnose musculoskeletal NTM infection correctly, debridement of synovial tissue should be considered. Continuation of immunosuppressive agents may represent an option for patients with otherwise uncontrolled rheumatic diseases.

W32-1

Clinical characteristics of Otitis media with ANCA associated vasculitis

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Conflict of interest: None

[Object] The aim of this study is to clarify the clinical characteristics of Otitis media with ANCA associated vasculitis (OMAAV), and to investigate the differences of clinical manifestations between OMAAV and microscopic polyangitis (MPA)/granulomatosis polyangitis (GPA). [Methods]Six patients with OMAAV, 33 those with MPA and 8 those with GPA were enrolled in this study. OMAAV was defined as following: initial symptom was hearing loss, other symptoms were not remarkable, and OM and the positivity of ANCA were revealed. **[Results]** The median age at disease-onset was 67 in OMAAV subset. The positivity of MPO-ANCA was revealed in all of OMAAV patients. The median titer of MPO-ANCA was significantly lower in OMAAV subset than that in MPA subset. The levels of inflammatory marker and anemia were significantly milder in OMAAV subset than in MPA subset. Regarding other organ involvement, mild interstitial lung disease was complicated in 3 OMAAV patients. Prednisolone, median dose of 30 mg/day, was administered in OMAAV subset.The remission is maintained in 5 of the 6 patients with OMAAV. Other symptoms are still not found in those with OMAAV. **[Conclusions]** In OMAAV, the main symptom is hearing loss. Systemic inflammatory response and other organ involvement are slighter than in MPA.

W32-2

The clinical features of otitis media with ANCA-associated vasculitis in our hospital

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Conflict of interest: None

【Objectives】To investigate clinical characteristics and treatment response in patients with otitis media with ANCA-associated vasculitis (OMAAV) in our hospital.【Methods】13 patients (three males, ten females) who were diagnosed with OMAAV between July 2009 and October 2015 were retrospectively evaluated.【Results】Mean age was 65.8 year old. The durations from the onset to the diagnosis were 3 months (median value). The initial symptoms were impaired hearing, congested feeling, or tinnitus. MPO- and PR3-ANCA were positive in 11 and 0 cases, respectively. Hypertrophic pachymeningitis and facial palsy was observed in 4 and 2 cases, respectively. Otitis media was involved in bilateral ears in 8 cases. All patients were treated with corticosteroid (mean prednisolone 0.77mg/kg/day), 10 with methlyprednisolone pulse therapy, 9 with azathioprine, 1 with cyclophosphamide, 3 with intravenous cyclophosphamide, and 2 with rituximab. In 9 patients, audibity test was improved one month after initial treatments. After treatments, all patients

survived, and 2 re-exacerbated.【Conclusion】Although therapies with corticosteroid and immunosuppressants were almost effective against OMAAV, further study on strategy for safety and efficacy is needed.

W32-3

Clinical features of patients with ANCA associated vasculitis accompanied by otitis media

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Conflict of interest: None

[OBJECTIVE] To clarify the clinical features of otitis media with ANCA associated vasculitis (OMAAV). [METHODS] We examined 23 patients with newly onset AAV who admitted to our department from 2012 to 2015. We divided them into with or without OMAAV groups by the criteria suggested by Japan Otological Society in 2013. We retrospectively compared 1) background, 2) ANCA and BVAS, 3) organ involvements, 4) induction therapy and responses, between groups. [RESULTS] We identified 5 patients with OMAAV (Group A) and 18 without OMAAV (Group B). 1) Background of Group A (69.0±4.3 years old, 1 male/4 female, 3 MPA/2 GPA) was similar to that of Group B (65.4±15.1 years old, 10 males/8 females, 13 MPA/1 GPA/4 EGPA). 2) ANCA status (MPO+ in 5 cases, PR3+ in none of cases) and BVAS at baseline (16.0±8.2) in Group A were comparable to those in Group B (MPO+ in 15, PR3+ in 4, BVAS 17.9±10.7). 3) Frequency of hypertrophic pachymeningitis was significantly higher, whereas neuropathy was significantly lower in Group A than in Group B (60% vs 0%, 0% vs 50%, $p<0.05$, respectively). 4) All patients with OMAAV were treated with PSL, and otitis media improved in 80%. [CONCLUSIONS] Patients with OMAAV were preferably accompanied by hypertrophic pachymeningitis, and well responded to corticosteroid.

W32-4

What kind of immunosuppressants should be chosen for otitis media with ANCA associated vasculitis?

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Conflict of interest: None

[Objective] To clarify the suitable immunosuppressive therapy for otitis media with ANCA associated vasculitis (OMAAV). [Methods] Twenty nine patients (fourteen males, fifteen females) with OMAAV who were admitted to Niigata University Medical and Dental Hospital from 1989 through 2015 were recruited. Treatment for granulomatosis with polyangiitis (GPA) (definite or probable) group and otitis media (E) only group were analyzed. [Results] Maximum prednisolone dose was 50 ± 16 mg/day in GPA group and 35 ± 9.2 mg/day in E only group ($P<0.01$). Cyclophosphamide was used in 67 % of GPA group and 25 % of E only group ($P=0.02$). Azathioprine was chosen in 48 % of GPA group and 88 % of E only group ($P=0.03$). No significant differences were observed in steroid pulse therapy, methotrexate, intravenous immunoglobulin, or rituximab for both groups. Relapse was observed in 57 % of GPA group and 25 % of E only group ($P=0.07$). In relapsed two cases of E only group, cyclophosphamide was administrated in one case, and intensive immunosuppressive therapy was avoided because of cardioembolic stroke in another case. [Conclusion] Although cyclophosphamide is a standard immunosuppressant for GPA, azathioprine might be enough for E only OMAAV.

W32-5

Scoring system of pulmonary lesions with HRCT in ANCA associated vasculitis

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Conflict of interest: None

[Object] The aim of this study is to clarify the usefulness of scoring system of pulmonary lesions with HRCT (HRCT score) in patients with ANCA associated vasculitis (AAV). [Methods] We enrolled 52 patients with AAV in our hospital since January 2010 to September 2015 in this study. HRCT were reviewed by experienced radiologist without knowledge of clinical parameters. The pulmonary lesion was scored on a scale of 0-5 for both alveolar depending on the percentage of each lobe involved. HRCT score was made into a total of each lobe score. [Results] The patient's mean age was 68.3 years old. The diagnosis of AAV according to Watts's algorithm revealed MPA in 22 patients, EGPA in 8, GPA in 14 and unclassified in 8. Forty five patients revealed pulmonary lesions on HRCT. Mean HRCT score was 4.1 and the score with unclassified type was significantly higher than those with GPA. Mean HRCT score of 36 patients after initial therapy was 2.8 and 21 patients improved the score. Six patients died during follow up period. Patients with high HRCT score showed poorer prognosis than those with low HRCT score. [Conclusions] Our data indicated that HRCT score were effective measurement for evaluation of pulmonary lesions with AAV. Moreover, high HRCT score showed the possibility of poor prognosis.

W32-6

Responsiveness to immunosuppressive treatment of lung abnormalities on chest computed tomography in patients with microscopic polyangiitis

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Conflict of interest: None

Objectives: A wide variety of lung abnormalities on the chest computed tomography (CT) can be identified in patients with microscopic polyangiitis (MPA). In this study, we aimed to determine the responsiveness of lung abnormalities to immunosuppressive therapy. Methods: We retrospectively identified 76 MPA patients whose chest CT images before and within 3 months after treatment were available in three centers in Japan. We evaluated the CT images in detail and determined the presence and the responsiveness to treatment (improved/unchanged/worsened) of a total of 22 imaging components for interstitial lung lesions, airway lesions, emphysematous lesions, pleural lesions, and miscellaneous lesions. Results: Three out of 4 components for airway lesions were responsive to treatment: bronchiolitis improved in 42 % of patients, bronchial wall thickening in 28 %, and bronchiectasis in 12 %. For interstitial lung lesions, grand glass opacity improved in 29 % of patients, interlobular septal thickening in 29%, and consolidation in 28%. No emphysematous lesions improved within the same period. Conclusions: Airway lesions in MPA patients can improve after treatment. These data suggest that airway lesions identified in MPA patients represent inflammation that is characteristic of MPA.

W33-1

Effects of Rituximab Administration in ANCA-Associated Vasculitis.

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Conflict of interest: None

(Purpose) To evaluate the efficacy of rituximab (RTX) for ANCA-associated vasculitis (AAV), we examined the cases in our hospital retrospectively. (Methods) Eleven AAV cases treated with RTX, including 8 cases with recurrent vasculitis in spite of cyclophosphamide (CY) therapy and 3 cases who were not able to be treated with CY for some reason, were examined (age:60.9±9.2-year-old, male 7 cases, female 4 cases, MPA 3 cases, GPA 8 cases). The remission rate at 3 months and the flare-up rate within the following 27 months were analyzed. Safety and outcome of RTX treatment were also observed. (Result) CRP was 3.98±7.43 mg/dl, S-Cr was1.31±1.04 mg/dl and BVAS was 11.7±7.43 before the RTX therapy. Remission rate at 3 months was 81.8 %. Infectious disease occurred in 2 cases (18%) and liver damage in 3 cases (27%). Flare-up was found in 4 cases (40%). Sudden death occurred 2 cases, but it was not certain that RTX was involved in the cause of death. (Conclusion) RTX could be effective for the remission induction in the recurrent AAV cases in spite of CY treatment and AAV cases who cannot be treated with CY.

W33-2

The efficacy of rituximab in ANCA associated vasculitis

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Conflict of interest: None

[Objective]To estimate efficacy of Rituximab (RTX) in treating ANCA associated vasculitis (AAV). [Methods]Of 110 patients admitted to our hospital and diagnosed as AAV between January 2005 to October 2015, eleven were administrated RTX. 375 mg /m^2 administered once a week for 4 weeks, then once in 6 months.[Results] The base line of the diseases were followed: MPA in 5 (45 %), GPA in 6 (55 %). Six were male and 5 were female. The average age on administlation was 71.2±3.5 y.o. and the average BVAS was 11.9±2.4. RTX was used as the first induction therapy in 2 patient, as reinduction therapy in 9. Ten achieved complete remissions, one attained a partial remission, none had a relapse. Six months after the therapy, CD19 was negative in all measured 6 cases, and the mean dose of prednisolone (PSL) was significantly reducted from 18.8±3.6 mg/day to 8.1±1.4 mg/day (*p=0.017)*. Eight patient had underwent remission-induction pre-treatment with cyclophosphamide (CY), the mean dose of which was 15.4±8.6 g. One patient died 19 months after the first administlation of RTX due to aspiration pneumonia. [conclusion] RTX has a noteworthy efficacy both in the first induction therapy and in re-induction therapies in addition to the decreasing of PSL with statistical significance.

W33-3

Analysis of efficiency and safety of rituximab for ANCA associated vasculitis

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Conflict of interest: None

(Objective) We studied the efficiency and safety of rituximab (RTX) for ANCA associated vasculitis (AAV) through the comparison with those of cyclophosphamide (CY). (Methods) Retrospectively we recruited AAV patients, who were followed for more than 6 months after treatment with RTX or CY in the rheumatology centers between June/2012 and March/2015. (Results) We recruited 17 AAV cases, 8 males and 9 females. The average age was 69.4 years old. They were consisted of 4 GPA, 12 MPA and 1 unclassified vasculitis. The average BVAS was 13.25, and the median BVAS was 14.5. CY was used 15 times, and RTX was used 7 times. CY was used 13 times for initial remission induction therapy, and twice for disease relapse. RTX was used twice for initial remission induction therapy, twice for CY resistance vasculitis and 3 times for disease relapse. Although the remission rate of CY was 73%(11/15), that of RTX was 100%(7/7). During one year after these treatment, CMV infection, UTI, drug fever and bone fracture appeared in CY cases, and none did in RTX cases. (Conclusion) RTX treatment is effective for the remission induction of initial, refractory and relapsed AAVs.

W33-4

Safety of azathioprine for treatments of ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] Azathioprine (AZA) is a standard immunosuppressant for the maintenance treatments of ANCA-associated vasculitis (AAV) in worldwide. The objective of this study is to evaluate safety of AZA for treatment of Japanese patients with AAV. [Methods] We included 64 AAV patients initiated AZA and followed up for over 1 year at our hospital from January 2006 to August 2014. We evaluated the continuation rate of AZA for 1 year and explored the risk factors for discontinuation caused by adverse effects of AZA.[Results] Median age of total was 70 years (male; 17, female; 47) and median initial dose of AZA was 25 mg/day. AZA was discontinued in 27 (41%) patients (30 cases) because of the adverse effects within one year; myelotoxicity (n=10), liver damage (n=10), infections (n=4), digestive symptom (n=3), and others (n=3). The patients with discontinuation caused by the adverse effects showed higher levels of aspirate transaminase and lower levels of neutrophil than those without discontinuation of AZA (27±4 vs. 19±1 U/L, p=0.05 and 6137±357 vs. 7384±404 /μl, p=0.03; respectively). [Conclusions] Continuation rate of AZA in the present study was substantially lower than previous western reports. Alternative maintenance therapy may be required in clinical practice in Japan.

W33-5

A study of the clinical course after rituximab treatment for refractory or recurrent ANCA-associated vasculitis - one year follow up-

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Conflict of interest: None

【Objective】We followed up the clinical course of patients with refractory or recurrent ANCA associated vasculitis after rituximab treatment.【Background of patients】10 cases of granulomatosis with polyangitis (GPA) and 2 cases of microscopic polyangitis (MPA) were followed (Male/Female 2/11, median age 72 years old).【Results】All patients improved clinically and serologically and the dose of prednisolone was under 10mg per day after rituximab treatment. Two patients were treated with only prednisolone and 10 patients were treated with prednisolone and immunosuppressive drugs (cyclosporine 4 cases, tacrolimus 3 cases,

azathioprine 3 cases). One patient died of pneumonia due to pneumocystis jirovecii. Five patients were treated with rituximab once or twice as the maintenance treatment.【Conclusion】Rituximab therapy for refractory or recurrent ANCA-associated vasculitis patients was useful to control disease activity and reduce the dose of prednisolone and immunosuppressive drugs.

W33-6

The availability of readministration of rituximab as an adjuvant therapy to protect the recurrence of refractory ANCA-associated vasculitis

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Conflict of interest: None

【Objective】It is very difficult to treat patients with refractory or recurrent ANCA associated vasculitis continuously. Rituximab is the hopeful drug for them, but someone suffered a relapse about one year after the initial rituximab treatment. Then we studied the availability of readministration of rituximab as an adjuvant therapy. 【Background of patients】4 cases of granulomatosis with polyangitis (GPA) and 2 cases of microscopic polyangitis (MPA) were readministrated with rituximab (Male/Female 0/6, median age 69.5 years old). 5 patients took prednisolone and immunosuppressive drugs orally. The serological data was as follows; CRP≥0.5mg/dl was found in 4 cases, ANCA≥3.5U/ml was found in 5 cases, CD20 positive population≥0.5% was found in 4 cases, and CD19 positive population≥0.5% was found in 4 cases. The average interval between initial RTX treatment and RTX adjuvant treatment was 14.5±1.9 months. 【Results】All patients improved clinically and serologically. The dose of prednisolone could be reduced. 【Conclusion】The readministration of rituximab was very useful as an adjuvant therapy for refractory or recurrent ANCA-associated vasculitis.

W34-1

TNF-a induced miR-155 promotes IL6 signaling in rheumatoid synovial fibroblasts

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Conflict of interest: None

Objective. The present study was undertaken to elucidate the role of miRNAs in the rheumatoid cytokine network. We analyzed miRNA expression in rheumatoid synovial fibroblasts (RASFs). Methods. miRNA array-based screening was used to identify miRNAs differentially expressed between TNFα-activated RASFs and untreated RASFs. Transfection of RASFs with miR-155 was used to analyze the function of miR-155. Levels of interleukin-6 (IL6) were analyzed by protein chip assay. Real-time polymerase chain reaction (PCR) was used to measure the levels of miR-155 in RASFs. Results. miRNA microarray analysis revealed that miR-155-5p was the most highly induced miRNA in TNFα-stimulated RASFs. TNFα-induced miR-155 expression in RASFs was time-dependent and TNFα dose-dependent, whereas, IL6 stimulation did not affect miR-155 expression in RASFs. Transfection of miR-155 mimics into RASFs augmented IL6 production after TNFα-activation. miR-155 over-expression resulted in sustained STAT-3 phosphorylation in IL6-stimulated RASFs. Conclusions. Our data show that up-regulation of miR-155 enhances TNFα-mediated IL6 secretion, as well as IL6-mediated sustained STAT3 activation. These findings suggest that miR-155 contributes to the cross-talk between TNFα and IL6-mediated inflammatory pathways in RA.

W34-2

Regulatory roles of IL-35 in T Cells of Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Object] Interleukin (IL)-35 is the member of IL-12 family. It was reported that recombinant IL-35 effectively attenuated CIA, a mouse model of RA, via mechanisms involving the suppression of T cell proliferation and Th17 cell differentiation. We investigated whether IL-35 enhances the in vitro immunosuppressive function of patients with rheumatoid arthritis (RA). [Methods] Peripheral blood was harvested from 17 active and 10 inactive RA patients, and IL-35 concentrations were quantified using an enzyme-linked immunosorbent assay (ELISA). The function of IL-35 was then evaluated in a suppression assay using CD4+ CD127- CD25+ Treg and CD4+CD127+CD25- responder T (Tres) cells isolated from human RA patients with CD2, CD3, and CD28 antibodies. [Results] Serum IL-35 levels and the number of regulatory T cells (Treg) were decreased significantly in patients with active RA. There was a significant correlation between serum IL-35 and DAS28-ESR in patients with active RA. IL-35 treatment enhanced the regulatory function, suppressing the levels of inflammatory cytokines such as IL-17 and IFN-γ, and the cellular growth of effector T cells stimulated by conjugation with CD2, CD3, and CD28. [Conclusion] Our data suggest that IL-35 and Treg might have multiple therapeutic targets.

W34-3

Expression of a newly identified IL-1 family cytokine IL-38 in autoimmune diseases

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Conflict of interest: Yes

Objectives: We have recently demonstrated that a newly identified IL-1 family cytokine IL-38 is strongly expressed in synovia of RA patients and acts as an inhibitor of the pathogenesis of autoantibody-induced arthritis in mice (*Takenaka and Kaieda et al. Biochemistry and Biophysics Reports 2015 in press*). However, the role of IL-38 in autoimmune diseases is still unclear. **Methods:**We newly established anti-human IL-38 mAb, which can be used for immunohistochemistry and sandwich ELISA.The serum levels of IL-38 in 137 RA, 26 OA, 37 SLE , 5 adult-onset Still's disease patients and 56 healthy donors were examined by ELISA. **Results:** The serum levels of IL-38 were 5.7±0.4ng/ml, 2.8±0.8ng/ml and 2.8±0.7 ng/ml in RA, OA patients and healthy donors,respectively. Twenty one of 137 RA (15.3%) patients, one of 26 OA patients (3.9%), and 5 of 56 controls (8.9 %) were elevated above the limit of detection of our IL-38 ELISA system (9.375 ng/mL). Furthermore, 7 of 37 SLE (18.9%) and none of 5 adult-onset Still's disease patients were elevated above the limit of detection. **Conclusion:** The serum levels of IL-38 were elevated in a certain population, at least, RA and SLE patients. Further analysis should be needed to analyze functional roles of IL-38 in autoimmune disease.

W34-4

NPK1 regulates the inflammation amplifier via NFkB p65 phosphorylation

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Conflict of interest: None

Background We reported cellular machinery (termed the inflammation amplifier) that induces excessive productions of chemokines and IL-6 caused by the simultaneous activation of NFkb and STAT3 in non-immune cells. We have performed a genome-wide shRNA screenings and identified over 1000 genes as positive regulators of the amplifier. Here we characterized one of the positive regulators, NPK1. **Methods** NPK1 was knocked down by RNA interference in fibroblastic cells. Expressions of the inflammation amplifier target genes including chemokines and IL-6 were measured by qPCR and ELISA. WB and confocal microscopy were used to investigate the activation status of NFkB. We also assessed epigenetic status of the amplifier target genes by ChIP analysis. **Results and conclusion** The inflammation amplifier was abrogated in NPK-deficient cells. Although nuclear translocation of NFkB p65 was normal, Its binding to chemokine and IL-6 promoters was impaired in NPK-deficient cells. Recruitment of p300 was also reduced. We found that a residue of NFkB p65 was not phosphorylated in NPK-deficient cells, which was important for the association between NFkB p65 and p300. We conclude that NPK1 is involved in the particular site of NF-kB p65 phosphorylation, which can be a novel target for treatment of RA.

W34-5

The profiles of cytokines/chemokines in the cerebrospinal fluids (CSF) of patients with central nervous system (CNS) involvement of Sjogren's syndrome (SS) and Bechet's disease (BD)

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Conflict of interest: None

[Object] We have reported that the productions of IL-6, IL-8, IP-10, MCP-1 and G-CSF are increased in the CSF of neuropsychiatric SLE (NPSLE). To investigate whether the concentrations of IL-6, IL-8, IP-10, MCP-1 and G-CSF are increased in the CSF of patients with CNS involvement of SS and BD. [Methods] In 7 SS patients with CNS involvement and 6 BD patients with CNS involvement, 3 SS patients without CNS involvement, 6 BD patients without CNS involvement and 11 normal controls the concentrations of IL-6, IL-8, IP-10, MCP-1 and G-CSF in the CSF samples were measured by Bio-Plex Pro Assays. The mean+3SD concentrations of each cytokine/chemokine in 11 normal controls were defined as the normal upper limit. [Results] The concentrations of CSF IL-6, IL-8, IP-10, MCP-1 and G-CSF were not increased in both SS patients without CNS involvement and BD patients without CNS involvement. The concentrations of IL-6, IL-8, IP-10, MCP-1 and G-CSF were increased in SS patients with CNS involvement as well as NPSLE. Whereas in BD patients with CNS involvement, the concentrations of CSF IL-6, IP-10 and G-CSF were increased but not those of CSF IL-8 and MCP-1. [Conclusion] The different profiles of these cytokines/chemokines might indicate the different mechanism in the pathogenesis of SS and BD.

W34-6

Increased level of plasma VEGF : a diagnostic biomarker of RS3PE

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Conflict of interest: None

【Object】RS3PE can be classified with a VEGF associated disorder. RS3PE is a rare disease, but it is easy to make a diagnosis based on knowledge and a treatment. There is no report of the considering measurement of plasma VEGF in practical clinics. 【Methods】 I present case1)RF positive, ACPA negative RS3PEand case2)RS3PE associated with lung cancer, RF and ACPA both positive. 【Results】Case1) 86-year-old, female. I have diagnosed as RS3PE, and administered the PSL10mg/day. the medical data (CRP14.5, ESR136/, RF32, ACPA4.2, VEGF137 > 38.3). Case2) 72-year-old, female. I diagnosed it from the inspection value (CRP13.6, RF71, ACPA9.7, VEGF146, sputum cytology classV, CYFRA8.2, ALP345) as RS3PE due to lung squamous cell carcinoma. 【Conclusions】 For the case1), The edema and the hip joint pain have disappeared, the amount of PSL has been decreased. For the case2), PSL has been increased to 20mg/a day by the terminal lung cancer. It was possible to diagnose it as RS3PE by the VEGF measurement. cases.1) and 2) were seropositive. VEGF shows high price or more, and is forecast the bad prognosis in case2) is after a long term of the steroid is administered. The rise of VEGF plays useful and important role of diagnosing RS3PE, such as the different a method of the treatment of EORA, diagnosis about tumor.

W35-1

Clinical benefit of initial 1-year treatment with certolizumab pegol in MTX-naïve patients with early rheumatoid arthritis; 2nd years' outcome in C-OPERA study

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Conflict of interest: Yes

Objectives: To investigate clinical benefit of initial 1-year (yr) therapy with certolizumab pegol (CZP) during 2-yr therapy with MTX. **Methods**: MTX-naïve early RA patients (pts) with poor prognostic factors were eligible to enter C-OPERA. Pts were randomized to CZP+MTX (n=159) or placebo (PBO)+MTX (n=157) with optimized dose of oral MTX. After completing 52-week (wk) double-blind period, CZP (n=108) or PBO (n=71) was discontinued and MTX therapy was continued up to Wk104. Pts who flared (DAS (ESR) ≥3.2 for ≥4 wks) could receive rescue treatment with CZP. **Results**: Total CZP+MTX→MTX group showed less radiographic progression at Wk104 (linear extrapolation) with higher non-radiographic progression rate compared with PBO+MTX→MTX (84.2% vs 67.5%, p<0.001). Although clinical remission rates of CZP+MTX→MTX group decreased after CZP discontinuation, higher rates compared with PBO+MTX→MTX were maintained up to Wk104 (LOCF). Pts retreated with CZP due to flare after CZP discontinuation (n=28) showed rapid clinical improvement after CZP restart. Incidence of overall adverse events was similar between groups. **Conclusions**: Initial 1-yr CZP therapy brings clinical benefit to 2-yr therapy with MTX including inhibition of joint damage in MTX-naïve early RA pts with poor prognostic factors.

W35-2

In adalimumab(ADA) treatment, Remission induction and treatment continuation at 104 weeks in 185 patients

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Conflict of interest: None

Objective Clinical usefulness and treatment continuation following 104 wks of ADA in RA patients were investigated. ***Methods*** Subjects were 185 analyzable patients introduced to ADA at the author's institution from May 2009 to October 2013. Mean age was 54 years, mean duration of illness 6.9 years. 62 patients had a duration of illness below 2 years (<2) and 123 at least 2 years (≥2), 132 were Bio Naive (N), 53 were Switch (S), 151 received MTX ≥10 mg/wk (≥10) and 28 MTX<10 mg/wk (<10). There was no significant difference in baseline disease activity.

Results Overall DAS28 (CRP) remission rate showed clinical remission in 44% of patients from 4 wks, 80% from 52 wks and maintained it until 104 wks. Changes in DAS 28 (CRP) remission rates of 4, 12, 24, 52, 80, 104 wks for the <2 and ≥2 were similar to those seen in the N and S, but differed from those in the ≥10 and < 10. Overall HAQ remission rate at 104 wks was 81%; treatment continuation rate was 76%. MTX concomitant treatment response rate was 80%. ***Conclusion*** Remission was induced early with ADA in about 44% of patients, 80% of patients at 52 wks and maintained it until 104 wks. ADA plus an adequate dose of MTX in early-stage RA and Bio Naïve patients is the best approach to maximally exploit the ADA potential.

W35-3

Analysis of bio-free condition of adalimumab (ADA) and early introduction of ADA in patients with rheumatoid arthritis (RA)

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Conflict of interest: Yes

Purpose: To analyze the bio- free condition of ADA and the effect of early introduction of ADA in RA patients. Methods: We used ADA in 131 patients. Study 1: 22 patients discontinued ADA. We analyzed 14 patients who were followed up more than 24W after discontinuation. Study 2: 23 patients started ADA within 3 M from the introduction of MTX. 2 patients stopped ADA due to inefficacy. We analyzed 14 patients who were followed up more than 52 W. Results: Study 1. Patients were 54.6±10.5 YO, disease duration 3.2±2.7Y, Bio-naïve:13, switch: 1, PSL was increased in 1 patient. csDMARDs were added in 8 patients (4 patients before and 4 patients after discontinuation). DAS28-CRP did not change until 24 W and no patient re-started biologic DMARDs. Study 2. 45.0±14.9YO, 1.5±2.7Y, 6 patients used MTX alone as csDMARDs and 5 patients among them started new csDMARDs. DAS28-CRP decreased from 4.9±1.1 to 1.8±0.6 ($p<0.0001$), 9 patients achieved complete remission (64.3%), and 3 patients (21.4%) achieved bio-free condition without relapse. Conclusion: ADA made bio-free condition in 16.8% of the patients without relapse. Early introduction of ADA for bio-free condition might be a good choice in terms of medical cost. csDMARDs is thought to be important for bio-free condition.

W35-4

Bio free remission in early rheumatoid arthritis THE RAINBOW STUDY (first report)

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Conflict of interest: None

[Objective] Early RA patients who discontinued biologics (bio) for rheumatoid arthritis after achieving clinical remission were enrolled, and the rate of bio-free remission was assessed 1 year after discontinuation of bio. [Methods] Early RA patients were treated with either Infliximab (IFX; n=25)or Tocilizumab (TCZ; n=53), and if patients were fulfilled our criteria of remission (DAS28ESR<2.6, and the dose of prednisolone≦5mg/day) for over at least 6 months, they discontinued bio. If they were still fulfilled the remission criteria one year after discontinuation of bio, we define them as bio-free remission. [Result] Forty three RA patients could be assessed 1 year after baseline. Thirty patients could discontinue bio fulfilling remission criteria for 6 months within 1 year. Then 10 of 13 patients achieved bio-free remission after 1 year discontinuation. [Conclusion] This is our first report of THE RAINBOW STUDY, study of bio free remission in early rheumatoid arthritis. Our result suggested that early intervention of bio might raise the possibility for bio free remission.

W35-5

Duration of arthritis in individual joints of rheumatoid arthritis patients in the past predicts local relapse in the same joints at systemic flare from biologic-free remission

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Conflict of interest: None

Aim. To study the relationship between the previous signs of arthritis in individual joints of rheumatoid arthritis (RA) patients and their propensity to relapse after discontinuation of biologic treatment due to sustained remission.Methods. Clinical data regarding swelling and tenderness of individual joints of consecutive 30 patients with RA who relapsed after withdrawal of biologic therapy due to sustained remission defined by simplified disease activity index ≤ 3.3 for at least 6 months were analyzed. Results. The relapse rate of the joints with persistent signs of arthritis until one year after the onset of biologic therapy was 31.7%, which was significantly higher than those without them. The frequency of the joints in which arthritis arisen de novo at relapse was 2.2%. Higher relapse rate were observed in the joints with the signs of arthritis for prior one year from the time of discontinuation of biologic therapy compared to those only for 6 months. Conclusion. The joints with the signs of arthritis in the past predominately developed arthritis at relapse from biologic-free remission. Disappearance of signs of arthritis more than 1 year before discontinuation of biologic therapy associated with less local relapse of arthritis in individual joints.

W35-6

Clinical manifestation and cytokine profile in RA patients with deep remission after tapering biological DMARDs

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Conflict of interest: None

【Purpose】Biologic DMRD (bDMARD) is quite effective therapy for intractable RA, however heavy budget for medical care is serious problem in Japan. From this viewpoint, the decrease of medical budget is serious problem in Japan. From this viewpoint, the decrease of medical budget is critical. Then the tapering of biological DMARD is essential agenda for our society【Methods】The remission group without bDMARD consisting of 10 RA patients was compared with the control group of 10 same background such as age, sex, class, stage, DAS-28 (ESR), total Sharp Score and complications RA patients with bDMARD from viewpoint of clinical manifestation and cytokine profile【Results】The remission group had significantly higher grasp power, lower titer of anti-CCP antibody, higher level of IL-10, and lower level of IL-22.【Conclusion】At this moment, no reliable predicting marker to suggest the possibility of tapering bDMARD without recurrence. The above finding might be a clue of the new marker for stopping the bDMARD therapy to intractable RA patients.

W36-1

Factors Related to Death during Treatment with bDMARDS in Patients with RA

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Conflict of interest: None

We in this study tried to extract factors related to death during treatment with bDMARDS in one rural institution. Subjects were 405 patients (m/f = 93/313) with RA with a mean age of 61 years (range 18 - 85 years). Discriminant analysis was done to extract factors related to death incorporating 17 variables. The extent of ILD was graded into 4 grades by the chest CT findings. The bDMARDS administrated were as follows; ABT in 76 patients, ADA in 18, ETN in 168, GLM in 10, IFX in 42, TCZ in 102, and CZP in 9, respectively. The mean duration of administration was 13.8 months. MTX and PSL were used in 75 %(mean 7.6 mg/week) and 75 %(mean 5mg/day) of the patients, respectively. During observation period, 13 patients died and 7 deaths were judged to relate to bDMARDS. The direct causes of death were urosepsis in 1, bacterial spondylitis in 1, pneumonia in 1, and exacerbation of ILD in 4, respectively. Dscriminant analysis extracted 3 significant factors, age, ILD grade and use of SSZ/BUC. Steinbrocker's class tended to relate to death. Gender and the doses of prednisolone and MTX were not significant factors. We conclude that we should be careful for the these factors when bDMARDS are administrated.

W36-2

Efficacy and Safety of Abatacept in Rheumatoid Arthritis Patients over 75 Years Old or with Past History of Serious Infection

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Conflict of interest: None

[Purpose]In the treatment of elderly RA patients, we often encounter the adverse events such as infection, so it is important what drugs we should use for them. We used abatacept (ABT) for RA patients who was over 75 years old (YO) or who had the past history of serious infection. **[Methods]**Out of 82 patients treated with ABT at Niigata Rheumatic Center and Asahikawa Medical University from July 2010 to October 2015, clinical course and data of the patients who started ABT over 75 YO or who had the past history of serious infection were analyzed. The efficacy and safety of ABT was evaluated at 48 weeks. **[Results]**Twenty-two patients (6 males, 16 females), a mean age of 74.3 ± 11.2 YO and a mean disease duration of 10.1 ± 8.0 years were analyzed. Clinical parameters such as articular findings, serum marker, disease activity score, improved significantly. Fifty percent of the patients achieved remission or low disease activity score and 70% achieved them by SDAI. Adverse events occurred in 3 patients, two of them were pneumonia and another was bronchitis. Fourteen patients (63%) have continued ABT until now (October 2015). **[Conclusion]**We consider that ABT is an effective and relatively safe treatment for elderly RA patients, and it seems that the retention rate of ABT was good.

W36-3

Dropping cases by adverse events and insufficient effect of tocilizumab therapy for rheumatoid arthritis in the AORA registry

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Conflict of interest: None

[Objective] To investigate the dropping cases by adverse events and insufficient effect of tocilizumab (TCZ) therapy for rheumatoid arthritis (RA). [Methods] In 131 patients treated with TCZ (naïve group, 64 patients; switched group, 67 patients) in the 2015 AORA registry, the cause of dropout, and the course after TCZ therapy were investigated between the naïve (N) and switched (S) groups. [Results] 15 cases were dropped by adverse events or insufficient effect. The mean patient ages was 62 (range, 44-82) years, and the mean durations of administration was 12 (0-46) months. 4 cases were in the N groups, and 11 cases were in the S groups. All 11 cases were switched from anti TNF-alfa inhibitors. In the N groups, adverse events were all 4 cases (3 malignant tumor, and 1 herpes zoster). In the S groups, adverse events were 7 cases (2 infection, 2 anaphylactic shock, 1 malignant tumor, 1 facial nerve palsy, and 1 hyper serum CRP), and insufficient effect were 4 cases. 5 of all 15 cases were switched to another biologics; 4 of 5 cases were abatacept. 8 cases were treated without biologics, and 2 cases were died. [Conclusion] The dropping cases by adverse events and insufficient effect were more in the S groups.

W36-4

Keeping remission after discontinuation of biologics by adverse events in RA

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Conflict of interest: None

[Objectives]To investigate keeping remission after discontinuation of biologics (Bio) by adverse events in RA. [Methods] 21patients (2males and19 females,mean age 64.8 years old) amang 140 RA patients who were administrated Bio by September 2015 were analyzed. This is a retrospective study. [Results] MTX introduce all patients and the average dose of MTX are 4.5mg/w and the average dose of PSL are 3.2mg. Introducing of Bio are ETN for 12, TCZ for 4, GLM for 2, IFX for 2,and ADA for 2 patients. The reason of the discontinuation of Bio are lung disease for 5, high cost for 5, malignancy for 3, CNS disease for 2, Operation for 2, therapeutic failure for 2, pancytopenia for 1, severe diarrhea for 1, and leg failure for 1 patient. Keeping remission after discontinuation of Bio are 9 patients (42.9%). In keeping remission group in comparison with Non-keeping remission group 1)MTX for 1st DMARD are high (77.8% vs 41.7%) 2)Class are low (1.1 vs 1.9,) 3)DAS28ESR at discontinuation of Bio are low (2.22 vs 3.23) 4)keeping remission time are long (22.7 vs 3.7months,p=0.001) 5)A number of DMARD after discontinuation of Bio are few (1.23 vs 2.3) [Conclusion] Biologically-free remmision are acheiveable by MTX for 1st DMARD and low DAS28ESR at discontinuation of Bio.

W36-5

Clinical course of RA patients after the discontinuation of biological therapy due to adverse events

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Conflict of interest: None

[Objectives] Discontinuation of biological therapy due to adverse events (DAE) inhibits T2T practice. Clinical course of RA patients was examined after DAE.[Methods] Retention and DAE rate were calculated in 256 biological treatment cases, survival rate and reintroduction rate of biologics were calculated in 51 DAE cases, retention and DAE rate were calculated in the reintroduction cases by Kaplan-Meier estimates. [Results] Retention rate of biological treatment were 75/66% at 6/12 months. DAE rate were 9/14% at 6/12 months, and no difference were seen between the agents (P=0.84, Log-rank test). Survival rate were 90/88% at 6/12 months and reintroduction rate of biologics were 46/59/59% at 3/6/12 months in the DAE cases. Most of reintroduction was done within 6 months. Retention rate were 71/51% and DAE rate were 11/21% at 6/12 months, and they did not differ from those of entire biological therapy (P=0.51, 0.79, Log-rank test).[Conclusions] DAE occurred at a constant rate regardless of the kind of biologics. No biological therapy was introduced in the 40% of DAE cases, and T2T practice was difficult in these cases. Efficacy and safety were maintained in the reintroduction cases, the reintroduction seemed to be properly.

W36-6

Treatment to RA patients after discontinuation of biological agents due to adverse events

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Conflict of interest: None

【Purpose】 We investigated subsequent treatment after discontinuation of biological agents due to adverse events in RA patients in our hospital.【Subjects and Methods】 April 2012 or later, we use the biological products in 79 cases in our hospital, and 11 patients discontinued by adverse events. We investigated use drugs, type and outcome of adverse events, and disease activity in each case.【Results】 Adverse events canceled biologics were abatacept five cases, tocilizumab three cases, enbrel two cases, and certolizumab one case. Breakdown of adverse events were three cases of pneumocystis pneumonia, two cases of bacterial pneumonia, one case of prosthetic joint infection, renal abscess, lung cancer, malignant lymphoma, liver dysfunction, and skin rash. 5 cases were resumed biologics after discontinuation adverse events, and 3 cases resumed the same drug, and were all abatacept.【Conclusion】 Abatacept was considered a possible re-administered biologics after discontinuation adverse events.

W37-1

Clinical condition and treatment of the SAPHO syndrome

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Conflict of interest: None

【Object】The synovitis-acne-pustulosis-hyperostosis-oeteitis (SAPHO) syndrome has been known for a few decades though relevant treatment remains uncertain. We report clinical activity and novel treatment of the SAPHO syndrome.【Methods】69 patients with SAPHO syndrome treated in our clinic from January 2014 to October 2015 were analyzed. We collected clinical information from the medical records retrospectively. To treat the SAPHO syndrome, combinations of prednisolone, DMARDs, methotrexate, and immunosuppressants were provided. To evaluate the impact of these drugs, we applied modified FAS31 to pain assessment and PPPASI.【Results】There were 11 men and 58 women. The mean age at diagnosis was 49 years old. Cutaneous disorders preceded in 39 patients and oste oarticular disorders preceded in 23 patients. Cutaneous and osteoarticular disorders occurred simultaneously in 7 patients. Bone scintigraphy delinates increased uptake in the sternoclavicular region. After 3 months treatment there was symptomatic improvement. The mean score of FAS31 significantly decreased and cutaneous disorders improved in 62% of patients.【Conclusion】Combinations of prednisolone, DMARDs, methotrexate, and immunosuppressants were useful in SAPHO syndrome patients applying FAS31 and PPPASI for assessment.

W37-2

Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis (24-weeks treatment): A Randomized, Double-blind, Active- and Placebo-controlled Phase 3 Study (SPIRIT-P1)

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Conflict of interest: None

Objectives: To assess efficacy and safety of ixekizumab (IXE), an IgG4 monoclonal antibody to IL-17A, in psoriatic arthritis (PsA). **Methods:** Biologic DMARD-naïve active PsA patients (pts) (N=417, 12 Japanese) randomized to placebo (PBO; N=106), adalimumab 40 mg (ADA; active control, N=101) once every 2-weeks (Q2W), IXE 80 mg Q2W (N=103) or Q4W (N=107) after 160 mg initial dose. ACR20 (Wk24, primary endpoint), ACR50/70, 75% improvement in Psoriasis Area and Severity Index (PASI75), DAS28-CRP, HAQ-DI, and mTSS were analyzed using logistic regression (LR) or mixed-effects model for repeated measures (MMRM). **Results:** 382 pts (11 Japanese) completed Wk24. Significantly more pts in IXE groups achieved ACR20/50/70 and PASI75 than in PBO (Wk12/24, $p<0.001$, LR). DAS28-CRP and HAQ-DI improved (Wk12/24, $p<0.001$, MMRM), and structural damage (mTSS) inhibited (Wk16, $p\leq0.018$; Wk24, $p\leq0.004$, MMRM) in IXE groups compared with PBO. ADA efficacy results vs. PBO were significant and validated study design. Adverse events (AE) and serious AEs at Wk24 were higher in IXE and ADA than in PBO, but discontinuation due to AE was similar. No deaths occurred. **Conclusion:** IXE showed statistically significant efficacy in biologic DMARD-naïve active PsA. There were no unexpected safety findings in IXE groups.

W37-3

Evaluation of Liver Fibrosis by Real-time Tissue Elastography in Methotrexate-Treated patients with Rheumatoid Arthritis

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Conflict of interest: None

[Object] Real-time Tissue Elastography (RTE) allows noninvasive assessment of liver fibrosis. This study investigated the correlation between liver fibrosis index (LFI) assessed by RTE and the risk factor associated with liver fibrosis in MTX-treated RA patients. [METHODS] The correlation between LFI and variables of interest was examined. [RESULTS] 241 MTX-treated RA patients were enrolled. LFI value positively correlated with the maximum ALT level, an age, a body mass index (BMI), with negative correlation with eGFR. In MTX-started MTX naïve patients, LFI not correlated with the cumulative MTX dose, the period with MTX received, but negatively correlated with the period of maximum MTX dose point from MTX started and positively correlated with the serum ALT level at MTX started. [CONCLUSIONS] An age, a renal dysfunction, a high BMI, the serum ALT level at MTX started, the rapid escalation of MTX dose were the risk factor of liver fibrosis.

W37-4

The assessment of the safety and the efficacy of mycophenolate mofetil (MMF) treated in SLE patients in our hospital

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Conflict of interest: None

【Objective】Only a few reports said the efficacy and safety in Japanese SLE patients. We investigated them in the SLE patients in our hospital. 【Methods】We analyzed the SLE patients treated with MMF in our hospital since 2007. 【Results】We analyzed a total 23patients (2men, 21women, 16 lupus nephritis, 3 lupus enteritis, 2 CNS lupus, 1 hemophagocytic syndrome, 1 taclorimus (TAC) inducing glomerulonephritis). The Side effects were dizziness (2cases), hair loss (2cases), diarrhea (1case), nausea (1case),and pancytopenia (1case). All of the side effects was improved after decreasing or discontinuing MMF. The ratio of complete remission in lupus nephritis was 11/16 cases, partial remission was 4/16cases, no responder was 1/16 cases. There were 3 cases (exchanging azathioprine (AZA) for MMF), 1case (Mizoribine (MZB)→MMF), 1 case (cyclosporine A (CyA)→MMF), and any exacerbation of SLE was not confirmed. There were 7cases (MMF→AZA), 5cases (MMF→MZB), 1case (MMF→TAC), 1case (MMF→IVCY)and exacerbation of SLE was confirmed in 3cases (MMF→AZA), exacerbation of CNS lupus in 1case (MMF→MZB) 【conclusion】The response to MMF in SLE patients was good, and the side effect was improved after decreasing or discontinuing MMF. We showed the tendency to exacerbate SLE when exchanging MMF for others.

W37-5

Efficacy and safety of therapeutic angiogenesis in patients with intractable ulcers due to rheumatic disease

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Conflict of interest: None

[Objectives] To examine the efficacy and safety of autologous transplantation of bone-marrow-derived cells in patients with intractable ulcers due to rheumatic diseases. [Methods] Visual analog scale (VAS) as a self-assessment of pain and ulcer size were evaluated in patients who received the transplantation at our department from June 2004 to March 2015. [Results] A cumulative total of 22 cases with rheumatic diseases were included in the study. Mean age was 54.5 ± 12.0 years, and all were female. Both VAS and ulcer size were significantly reduced at 6 month after transplantation as compared to baseline (33.1 ± 29.7 vs 51.0 ± 34.5 mm, $P = 0.037$, and 0 (0-0.3) vs 0.5 (0.3-1.0) cm^2, $P = 0.008$, respectively). Ulcers were epithelialized within 6 month in 11 cases (50%). In 17 cases followed by 24 month, ulcer size was significantly improved from baseline (0 (0-0) vs 0.5 (0.3-1.0) cm^2, $P < 0.001$). Twelve cases (71%) were epithelialized within 24 month, with ulcer relapse in 3 cases (18%). One serious adverse event occurred within 6 month after transplantation, resulting in hospitalization for pulmonary embolism. [Conclusion] Therapeutic angiogenesis can be effective in pain reduction and ulcer healing in patients with intractable ulcers due to rheumatic disease.

W37-6

Corticosteroid-Free Trial of Tocilizumab Monotherapy for Adult Onset Still's Disease

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Conflict of interest: None

Objectives. To assess the efficacy and safety of tocilizumab (TCZ) monotherapy for the induction therapy of adult onset Still's disease (AOSD) in a prospective single-arm, cohort, pilot study. **Methods.** Eight AOSD patients (male 2, female 6) who had agreed with our prospective trial since April 2010 till May 2015 were enrolled. Patients received 8 mg/kg of intravenous TCZ fortnightly for the first two months (five courses), and monthly for the next 5 months. Efficacy was evaluated by serum markers, clinical symptoms and ratio of patients who required additional therapy, and safety was evaluated by adverse events for six month. **Results.** The mean age was 45.2. LOCF analysis revealed that WBC, CRP and serum ferritin level decreased significantly from 14075/μl to 7371/μl, from 12.2mg/dl to 0.32mg/dl and from 9176ng/ml to 3369ng/ml in 6 month respectively (each, $P<0.01$). The improvement rate of fever, arthralgia and eruption were 100%(n=8/8), 75.0%(n=6/8) and 71.4%(n=5/7). Only 2 patients required additional therapy (prednisolone). The reason of cessation consisted of lack of efficacy (25%, n=2) and adverse event (12.5%, n=1). An adverse event was UTI. There're no other significant adverse events. **Conclusion**. TCZ monotherapy may be an alternative treatment strategy for AOSD.

W38-1

Efficacy for prophylaxis against pneumocystis jiroveci pneumonia (PCP) and safety of dose-reduction trimethoprim-sulfamethoxazole (TMP/SMX) regimen

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Conflict of interest: None

OBJECTIVE: To compare low-dose TMP/SMX regimen with conventional-dose regimen from the perspective of efficacy for prophylaxis against PCP and safety. METHODS: Data from 112 patients in our department except cancer carrier who recieved prophylactic use of TMP/SMX for the first time, were retrospectively analyzed. The primary outcome was incidence of PCP and elevation of β-D Glucan with therapy intensification. The secondary outcome was incidence rate of all adverse event with discontinuation or dose reduction of TMP/SMX. RESULTS: 76 patients were administered on 7 g/week or over (mean: 7.3g/week) of TMP/SMX (CD), while 36 patients were administered on less than 7g/week (mean: 2.9 g/week) of TMP/SMX (LD). Only one patient of CD group was affected PCP, a significant difference was not observed in the primary endpoint (P=0.49). Also in the secondary outcome, a significant difference was not observed between CD and LD (27.6% vs 25.0% respectively, P=0.77) CONCLUSIONS: PCP prevention was established in all patients with low-dose TMP/SMX regimen.

W38-2

Association between sleep disorder and nocturnal hypertension in RA patient

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Conflict of interest: None

【background】We reported that actual total sleep time assessed by EEG was extremely short more than RA patients considered and nocturnal hypertension is associated with higher inflammation in RA patients 【object】The aim of this study was to examine association between nocturnal hypertension and sleep disorder in RA patients. 【method】We examined 24 RA patients (7 men and 17 women), 67 years of age. Nocturnal BP was assessed by 24 h ABPM. Total sleep time was assessed by EEG and questionnaire. Inflammation activities of RA were determined by DAS 28 (CRP). 【result】Each total sleep time in the EEG and the questionnaire were 340,330 min in remission, 262,360 min in low activity, 271,375 min in moderate, 266,414 min in high group. EEG/ questionnaire in total sleep time was 91% in dipper, 69% in non-dipper, 58% in

riser group. 【conclusion】Nocturnal hypertension is associated with sleep disorder in higher disease activity patients.

W38-3

Assessment of clinical outcomes and social backgrounds among 30 cases of late stage senior rheumatoid arthritis patients in an outpatient clinic: comparisons of 18 cases treated with BIO (ABT/ADM/TCZ/GLM/CTZ/tofacitinib=6/2/1/1/1/1 cases) and 12 cases without BIO

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Conflict of interest: None

[Objective] To examine the associations between various outcomes and the BIO treatment among rheumatoid arthritis (RA) patients. [Methods] Thirty late stage senior RA patients, who visited one clinic in Osaka city (8/01/2012-8/01/2015), were divided into two groups treated with BIO (n=12) and without BIO (n=18) to compare various clinical outcomes and social backgrounds. [Results] These two groups did not differ in the mean age. The statistically significant differences (all P<.05) were observed in (a) RA-stage (Bio group=2.8 vs Non-BIO group=1.9) and class (2.4 vs1.6);(b) the proportion of a single-medication treatment (17% vs 67%), (c) DAS (2.5 vs 2.1) and (d) HAQ (1.5 vs. 0.9). [Discussion] A statistically significant improvement in some outcomes (e.g., DAS and HAQ) was observed among the BIO-treated group, compared to the non-BIO group. Our findings suggest the importance of the coordination with region-center hospitals, physician's home visit for urgent cases, the consideration for social backgrounds and the comprehensive care including nurse care at homes.

W38-4

Clinical feature of Chlamydia-associated arthritis

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Conflict of interest: None

Data for Chlamydia (C.) -associated arthritis are sparse. The purpose of this study is to elucidate clinical feature of C. -associated arthritis. [Methods] Anti-C. pneumoniae IgM, IgG, IgA and anti-C. trachomatis IgM, IgG, IgA were measured by HITAZYME or anti-C. pneumoniae IgM was by AniLab-EIA. The cases with C. -associated arthritis were designated as anti-C. IgM-positive ones who had not any rheumatic disease such as RA, collagen diseases or OA. [Results] 1. We found 75 cases were positive for C. pneumoniae IgM among 77 with acute onset arthritis. The ratio of monoarthritis and polyarthritis was 1:74. Most complained multiple joint pains, especially at PIP. Among them, 32.4% showed joint swelling, occasionally followed by blood-flow signaling at joint US. Laboratory findings revealed the elevation of CRP 13%, positive for RF 12%, positive for ACPA 6.3%, the elevation of MMP-3 5%. Their joint pains disappeared after the administration of antibiotics at 74 among 75 cases. [Summary] C. pneumoniae-positive polyarthritis often showed clinical signs resembling RA, but disappeared after the treatment with antibiotics.

W38-5

Anti-Chlamydophila pneumoniae IgM-positive 4 cases, who were treated as seronegative RA

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Conflict of interest: None

We present 4 cases diagnosed as seronegative RA, also positive for anti-Chlamydophila pneumoniae IgM, and pursue the relationship between pathophysiology and Chlamydophila pneumoniae infection. Case1: 62-year-old-woman had pain of shoulders, elbows, hands and knees, swelling of shoulder, elbows and knee. CRP and MMP-3 were high. Her joint symptoms disappeared within 1 month after administration with MINO and MTX. Case2: 40-year-old-woman showed joint pain and swelling of right ankle. US demonstrated grade II-III blood-flow signal in right ankle. MMP-3 was 99.9. Her condition improved with MINO and SASP within 4 months. Case3: 73-year-old-woman complained joint pain and swelling of knees, fingers, elbow and ankles. MMP-3 was 549. Administration with MINO and MTX was effective. Case4: After common cold sign, 35-year-old-woman had an episode of pain of knees, neck, elbows, fingers and ankles, swelling of shoulder, elbow, fingers, knees and ankles. CRP was positive. Treatment with MINO and MTX was effective. All 4 cases fulfilled the diagnostic criteria of RA. However, they showed good response to treatment and might have had Chlamydophila-associated arthritis rather than RA.

W38-6

Comparison between the New and Old Criterion by American College of Rheumatology for the Classification of Fibromyalgia

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Conflict of interest: None

Comparison between the new and old criterion by American College of Rheumatology for the classification of fibromyalgia (FM) was performed in 61 patients with FM or doubtful FM (male 11, female 50, average age 54.0 yrs, average duration from onset 4.5 yrs). Tender points by 1990 criteria was 12.0 in average (min 0, max 18), and 42 out of 56 were diagnosed as FM. WPI score by 2010 criteria was 10.9 in average (min 2, max 18), and 38 out of 59 were diagnosed as FM. TP as well as WPI demonstrated significant differences in the positivity by their locus. WPI score plus SS score demonstrated positive correlation with TP (r=0.45). Since the diagnose does not always coincide, however, we should apply these criterion flexibly.

W39-1

Insulin selectively regulates TNFa-dependent cartilage degrading enzymes in osteoarthritic fibroblast-like synoviocytes

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Conflict of interest: None

[Object] Systemic factors like obesity or associated insulin resistance are recognized as risk factors for osteoarthritis (OA) development. In this paper we analyzed whether insulin can regulate cartilage degradeing enzymes from osteoarthritic fibroblast-like synoviocytes (FLSs). [Methods] FLSs were isolated from OA synovium obtained from patients who underwent total knee arthroplasty. We stimulated FLSs using TNFa and added insulin for 24 hours. Then we harvested FLSs to evaluate the gene expression of *MMP1, MMP13, ADAMTS4 and ADAMTS5* together with associated genes using real-time PCR. We also analyzed the protein release into culture medium using western blot. Statistical analysis was performed using ANOVA by GraphPad Prism software. A value of $p < 0.05$ was considered statistically significant. [Results] The gene expression of TNFa dependent *MMP1, MMP13, ADAMTS4, BMP2, IL-6* was suppressed by insulin ($p < 0.05$) while *ADAMTS5, TNFa and IL-1β* were not. Interestingly, MMP1 and MMP13 protein release were also suppressed by insulin. [Conclusion] Insulin selectively regulates TNFa dependent cartilage degrading enzymes. It is expected that insulin can be a new therapeutic target of OA by suppressing the cartilage degrading enzyme expression.

W39-2

Evaluation of Chondroprotective Effect by Rebamipide

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Conflict of interest: None

Introduction: Osteoarthritis (OA) is the most common joint disease, but few drugs are available to effectively prevent or treat cartilage degradation. In this study, we employed an *in vivo* and *in vitro* to examine the effects of rebamipide on articular cartilage degeneration. Materials and Methods: BALB/c strain mice were used and surgical induced OA model. Mice were injected into the knee, the dosage of rebamipide was 0 (A), 0.1mg/kg (B), 1mg/kg (C), and 10mg/kg (D). Specimens were evaluated using Mankin score. Chondrocytes were isolated from human OA cartilage. Cells were stimulated with recombinant human IL-1b (20 ng/ml), and then treated with or without rebamipide for 24h. The levels of mRNA expression of COL2A, IL-1b, TNF, MMP3, MMP13 were estimated using real-time PCR. Result: In Mankin score, average histological scores were significantly better in group C and group D than in group A. Strong immunoreactivity for Type II collagen was found in group C and group D. The mRNA expression of IL-1b, TNF, MMP3, MMP13 in chondrocytes was significantly down-regulated after treatment with rebamipide. And the mRNA expression of COL2A was significantly up-regulated after rebamipide treatment. Conclusions: This study suggested that rebamipide could prevent cartilage degeneration.

W39-3

Transthyretin and Amyloid Deposition in Articular Cartilage

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Conflict of interest: None

[Object] Amyloid deposits are prevalent in osteoarthritis (OA)-affected joints. Transthyretin (TTR) is one of a small number of human amyloid precursors found in OA cartilage. The goals of this study were to determine if the deposits had pathologic effects on cell and tissue function. **[Methods]** Amyloid deposition in normal and OA human knee cartilage was determined by Congo red staining. TTR in cartilage and synovial fluid was analyzed by immunohistochemistry and western blotting. The effects of recombinant amyloidogenic and non-amyloidogenic TTR variants were tested in human chondrocyte cultures. **[Results]** TTR, located predominantly at the cartilage surfaces, was detected in all OA and a majority of aged, but not young normal cartilage. In cultured chondrocytes, only an amyloidogenic TTR variant induced cell death and the expression of proinflammatory cytokines, and extracellular matrix degrading enzymes. The effects of amyloidogenic TTR on gene expression were mediated by Toll-like receptor-4 and p38 MAP kinase. **[Conclusions]** The findings are the first to suggest that TTR amyloid deposition contributes to cell and extracellular matrix damage in articular cartilage in human OA.

W39-4

PCL evaluation following CR TKA in OA Patients - Examination by MRI

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Conflict of interest: None

[Object] We can use the Oxidized Zirconium (OXINIUM) for femoral component in GENESIS II TKA.OXINIUM has the characteristic of producing fewer artifacts in an MRI scan. We evaluated the PCL by MRI scan over time. [Methods] The subjects were 46 knees of 35 patients with an average age at surgery of 73.6 years. ROM and JOA score were evaluated before and 24 months after surgery. The continuity of PCL, PCL angle, the width of PCL were evaluated 3 weeks and 24 months after surgery by MRI. [Results] MRIs could be taken over time of 41 knees in 31 patients. There was no significant difference in ROM before and after surgery. JOA score improved significantly after surgery from 57.9 to 84.0 ($P<0.001$). In the MRI evaluation, PCL could be confirmed in all cases, and tension was visualized at 90˚ flexion. PCL angle was 99.7˚ 3 weeks after surgery and 99.5˚ 24 months after surgery, with no significant difference. Although there were 3 cases in which the width of PCL increased 50% or more, these cases showed no relation to post-operative decrease in ROM and JOA score. [Conclusions] PCL could be confirmed in all cases without changes in the PCL angle. The PCL was swelling in some cases. There was no significant difference in ROM and JOA score whether the PCL was swelling or not.

W40-1

The new joint weighted scoring system which predicts the modified health assessment questionnaires scores in rheumatoid arthritis patients: a validation study using the National Database of Rheumatic Diseases by iR-net in Japan

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Conflict of interest: None

[Background] We reported the impact of each joint disease on the MHAQ by using 2011 NinJa (the National Database of Rheumatic Diseases by iR-net in Japan) data. We developed a joint weighted scoring system from the results of the odds ratio. An integer score was assigned to each identified bilateral and unilateral joint disease, respectively, as follows: shoulder, 4 and 2; elbow, 3 and 2; wrist, 2 and 2; hip, 0 and 3; knee, 3 and 2; ankle, 2 and 2; finger, 1 and 1. We acquired 3 points as the cut-off value of this system through statistical analysis (Mod Rheumatol, 2015, Epub ahead of print). [Objectives] To validate this scoring system by applying to NinJa in 2014. [Methods] A total of 13,459 subjects from NinJa in 2014 were analyzed. The presence or absence of disease in each joint (swelling and/or tenderness were considered as disease) and whether the disease was unilateral or bilateral were investigated. ROC curve analysis was performed to each patient with total score calculated according to the scoring system. [Results] ROC analysis' results were as follows: cut-off value, 3 points; AUC, 0.68; sensitivity, 53.4%; and specificity, 75.0%. [Conclusions] This socoring system was validated and suggested to be useful to predict of functional disability of RA patients.

W40-2

Association of mass of skeletal muscle with disease activity and daily activity for patients with RA

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Conflict of interest: None

Objectives: Although it is reported that reduction of skeletal muscle is more frequent in lower limb than upper limb, there are a few reports on RA patients. Therefore, we assessed association of mass of skeletal muscle with disease activity and daily activity for RA patients. Methods: Ninety three of RA outpatients were target for analysis to measure total mass of skeletal muscle (T mass), mass of those at upper limbs (U mass), and at lower limbs (L mass). Association of that with corresponding disease activity (DAS28-ESR) and daily activity (HAQ) were assessed. According to disease activity, patients were divided in two groups (LDA and HDA group) for comparison on T mass, U mass, and L mass. Results: There are significant associations of mass of skeletal muscle with disease activity ($rs = 0.23$, $p < 0.05$) and with HAQ ($rs = 0.38$, $p < 0.001$). As

compared to LDA group, all of skeletal muscle measurements are lower in HDA group and the difference is significant in U mass. Conclusion: The result indicates important perspective on skeletal muscle to control disease activity. Therefore, it is meaningful to facilitate rehabilitation for strengthening skeletal muscle for improving daily activity.

W40-3

Validation of the gait speed as outcome measure of physical function in patients with long-standing rheumatoid arthritis

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Conflict of interest: None

【Introduction】 Rheumatic arthritis causes joint destruction and limitation to activity of daily living. The aim of this study is to examine relationship between the gait speed and other outcome measure of physical function in patients. 【Methods】 Twenty five patients who were suffering from RA for more than 10 years and will be performed operation were included in this study. 10m gait speed, muscle strength, maximum circulation, pain, anxiety and depression, SF-36 were measured. The correlation of gait speeds with factors were analyzed by Pearson r rank test. A value of $P<0.05$ was considered statically significant. 【Results】 Gait speed in RA patients was 0.71±0.29 m/s. Age, ROM (hip flexion and extension, ankle plantarflex), muscle strength (hip abductor, knee extensor), maximum circulation of lower thigh, SF-36 (PF) were significantly correlated with gait speed. 【Conclusion】 Gait speeds, which can be measured easily in daily practice, was could be useful tool for evaluation of physical function.

W40-4

Possible predicting factors of the Barthel ADL index at the end of medical rehabilitation in patients with rheumatoid arthritis

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Conflict of interest: None

[Background] Accumulated evidence points that rehabilitation plays important role in treatment for RA patients. However, "rheumatoid frailty" may affect on the effect. [Methods] From October 2014 to September 2015, 49 consecutive RA patients received rehabilitation in our university hospital. The medical records were reviewed, and statistical analysis was performed to assess possible predicting factors of the Barthel index (BI), at the end of rehabilitation. [Results] There were 38 female and 11 male, and the mean age was 69.1 years old. Mean length of rehabilitation in the hospital was 37.9 days. Mean value of the BI at the end of rehabilitation was 76.4. Medication history of methotrexate (MTX) or biologics had a tendency to correlate with the BI, while medication history of steroid had a negative tendency. Patients with low ADL performance ($BI<20$) were frequently associated with infection (Urinary/respiratory), or heart failure. The BI in patients who underwent musculoskeletal surgery was signicantly higher than in patients without the surgery ($P<0.05$). [Conclusions] Medication history of MTX or biologics had positive, and the history of steroid had negative tendency to correlate the BI. Infection and heart failure may important risk factors for RA rehabilitation.

W40-5

Employment rate of rheumatic diseases patients in Japan

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Conflict of interest: None

The purpose of this study is to clarify the employment rate of rheumatic diseases patients in Japan, which can be the basic data of the promotion for balancing work and rheumatic diseases treatment. We used database of recipient certificates issued for specific disease treatment in 2012 and national population census in 2010. We calculated the percentage between 20-59 years old among rheumatic diseases patients, and the employment rate of them classified by both sex and age groups. The percentage between 20-59 years old among the patients of SLE, MCTD, Behcet's disease (BD), and Takayasu arteritis (TA) was more than 50%. Compared with the employment rate of general population in Japan (male 82%, female 64%, respectively), the rate of every rheumatic diseases patients was lower. The employment rate of BD (78%, 50%), SLE (74%, 41%), MCTD, scleroderma, and TA was relatively higher than that of dermatomyositis or polymyositis, and refractory vasculitis including microscopic polyangitis, Wegener granulomatosis, and malignant rheumatoid arthritis. In conclusion, rheumatic diseases were classified into two groups; that of relatively higher employment rate and that of lower one, which can influence the strategy of the promotion for balancing work and rheumatic diseases treatment.

W40-6

Study of music therapy for patients with rheumatoid arthritis by using Temporary Mood Scale and KOKORO Scale

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Conflict of interest: None

[Objectives] We previously reported that music therapy improves general health condition, pain, anxiety, and self-efficacy of patients with rheumatoid arthritis (RA). In this study we investigated in detail the effect of music therapy for the patients with RA by using Temporary Mood Scale (TMS) and KOKORO Scale (KS). **[Methods]** Music therapy was conducted by a music therapist, a pianist, hospital staffs, and students. Eight Japanese songs were sung with a piano accompaniment and 3 were played with chime bars by the participants. General health condition, pain, mood, relief and excitement were surveyed by self-rating questionnaire including 10cm VAS, face pain rating scale, TMS, and KS. **[Results]** Twenty patients with RA (19 females and 1 male) participated. mHAQ was 0.41±0.65. GH-VAS was changed from 2.9 to 2.4, FS from 6.3 to 4.6, tension in TMS from 6.3 to 4.9, depression from 6.5 to 5.5, anger from 5.2 to 3.7, confusion from 7.6 to 5.7, fatigue from 7.6 to 4.9, vigor from 8.0 to 8.5, relief in KS from 14.0 to 23.8, excitement from 15.1 to 21.03. All the scales other than vigor were improved significantly after music therapy. **[Conclusion]** Music therapy improves general health condition, pain, tension, depression, anger, confusion, and fatigue of patients with RA.

W41-1

Investigative research from consultation and registration study of anti-rheumatic drug at Japan Drug Information Institute in Pregnancy (JDIIP)

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Conflict of interest: None

[Object] By using the database of JDIIP, we analyzed the safety of anti-rheumatic agent use during pregnancy. [Methods] Patients who asked for consultation about anti-rheumatic agent (cohort C) during Nov 2005 to Nov 2015, and applied to registration study of pregnant (P) patients using anti-rheumatic disease (cohort R), since Jul 2012, were analyzed. [Results] A total of 466 patients were found eligible for this study.

By excluding patients who were using anti-rheumatic agent not for the rheumatoid arthritis, 344 (C: 262/10years, P 144, non-P 118, and R: 83/3years) patients went for further analysis. List of top 3 agents were MTX 151 (C: 128<P 54, non-P 74>, R: 23) patients, ETN 138 (C: 77<P 45, non-P 32>, R: 61) patients. SASP 78 (C: 63 <P 23, non-P 40>, R: 15) patients. Patients who were continuing agents later than last menstrual date were 70% in P patients in cohort C and 98% in patients in cohort R. In spite of the evidenced risk, MTX was used in 56% pregnant patients in cohort C, and 17% in cohort R. [Conclusions] Consultation method of our center is insufficient to accumulate the patients, and we need to promote the registration method. By analyzing the processes lead to the registration in previous patients, we are to improve the publicizing of this registration research.

W41-2

Drug treatment and problem to RA patient of a desire to bear children

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Conflict of interest: None

[Object]I examined various problems about them, moreover made a comparative review of number of desire to bear children and percentage of employment. [Method]I was investigated outpatients who developed RA under 40 years old. Target patients are 44 ± 18 years of age, 17.5 ± 13. 5 years of disease duration, 29.3 ± 6.3 years old age of maternal age and 6 members in each who gave birth one or gave birth two.Then three of them MTX single administration (referred to as MTX), five of them MTX+coDMARDS, one of them MTX+tsDMARS, three of them the others. [Result] both of them were impartial. But 3 cases, for reason of RA, pregnancy, I had the experience opposed. When I give birth, it was 47% to feel most anxiously by the answer to which I say "can i have normal child born in the future?" The person more cooperative in understanding to childbearing and child care, a real mother, there were most answers. [Conclusions] a patient is able to control of RA and a female patient of RA is possible to live similar one's daily life of public woman include desire to bear children, even though a side of effect of medicine or mental anguish.

W41-3

The study of pregnancy with systemic lupus erythematosus (SLE) at Tokyo Metropolitan Tama Medical Center.

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Conflict of interest: None

【Object】This study aimed to investigate the treatment and outcome of pregnancy with SLE and to make use for the future management. 【Methods】There were 6719 cases of high-risk pregnancy between March 2010 and September 2015 at our hospital. We investigated retrospectively 35 cases of pregnancy with SLE. 【Results】In pregnancy with SLE, for the disease activity was worsening, the additional treatment was done in 6 cases (17%). Two cases of them were newly developed and diagnosed during pregnancy, one case was the result of neonatal death. 11 cases (31%) were changed the treatment after pregnancy was found. 19 cases (54%) were not changed it until birth from desire for children. Preterm delivery occurred in 8 cases (23%), and abortion occurred in 1 case. Emergency caesarean section was performed in 9 cases (25%). 【Conclusion】In pregnancy with SLE, the risk of maternal-fetal complications, preterm delivery, and emergency cesarean section is higher than in healthy women. Moreover, patients who were developed and diagnosed during pregnancy might have high risk. Therefore, it is important to manage them carefully. In the future, patients treated with hydroxychloroquine will increase, we hope to improve outcomes by it.

W41-4

Clinical features of refractory obstetric anti-phospholipid syndrome and effectiveness of high-dose intravenous immunoglobulin therapy: a case series

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Conflict of interest: None

OBJECTIVE: To investigated the clinical features and effectiveness of high-dose intravenous immunoglobulin (IVIG) therapy in our case series of refractory obstetric anti-phospholipid syndrome (OAPS) patients. METHODS: We retrospectively analyzed patients with OAPS who visited our hospital from 2010 to 2014. Patients with a history of successful pregnancy on standard treatment (LDA or LDA plus heparin) were defined as the responsive group and those who did not have successful pregnancy outcomes on standard therapy were defined as the refractory group. The groups were compared using the chi-squared test. We also evaluated the effectiveness of IVIG therapy in the refractory group. Results: Among 27 OAPS patients, 7 (26%) were in the responsive group, 14 (52%) were in the refractory group. The refractory group had a significantly higher proportion of patients with a history of thrombosis, lupus anticoagulant (dilute Russell's viper venom time) positivity, and anti-phosphatidylserine/prothrombin antibodies. IVIG therapy was used during the next pregnancy in 9 patients in the refractory group. Six (67%) patients gave birth to full-term babies without adverse outcomes. CONCLUSION: Our study showed the clinical features of refractory OAPS and the effectiveness of IVIG for these cases.

W41-5

Maternal care for patients with rheumatoid disease in our hospital

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Conflict of interest: None

<Background> Not only treatment but also pregnancy and delivery are important for young women complicated with rheumatic disease. Many of patients who want to be pregnant are afraid of disease and medication. In our hospital, we reported outpatient clinic for maternal care for patients with rheumatoid disease in our hospital. <Method> We investigated the patients those who visited our outpatient clinic about their age, disease, reason of visit, pregnancy, and delivery of maternal rheumatoid disease. <Result> The mean age of the patients was 35.3±4.3 years old. Most common disease in our outpatient clinic was RA, followed by SLE and SjS. The most common reason of visit was hope of pregnancy. The patients who want to have first child were 31 people whose age was 34.7±4.8 years old. Six women in these patients got a pregnancy, and all of them delivered. <Discussion> Although ministry of Health, Labor and Welfare in Japan reports the mean age of mother at the time of the first child birth with 30.4 years old in 2013, the age of patients in our hospital was higher. Managements for disease, medication and hesitation of consultation for pregnancy were considered. <Conclusion> Maternal care for patients with rheumatoid disease in our hospital were reported.

W41-6

Questionnaire survey for patients at the maternity outpatient in our department

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Conflict of interest: None

[Purpose] Connective tissue disease often affects young women, and

the disease activity may get worse during pregnancy or after delivery. We support them in cooperation with obstetrics and gynecology department. We researched their satisfaction level and attitude by questionnaire. [Methods] Sixty-one patients were researched at the maternity outpatient in our department from August to September 2015. Their backgrounds, consultation motives, satisfaction of medical treatment contents, knowledge for the medication, hope and opinions were researched. [Results] The patients were 61 women (SLE: 27, RA: 14, others: 20). The average age was 34.2 ±4.8 years old. SLE patients wanted to have top priority "stability of own illness" on the occasion of the pregnancy (75.0%), and the others wanted to have "pregnant and giving birth"(70.6%). [Conclusions] It is common that patients with connective tissue disease hope for pregnancy. The role of the outpatient is very important concerning not only adjustment of medication but also mental support.

W42-1

A Secukinumab Phase III Global Clinical Trial in Patients with Psoriatic Arthritis (FUTURE1): Efficacy of Joint Structural Damage and Safety

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Conflict of interest: Yes

Objective To investigate the effect of Secukinumab (SEC), a human anti-IL-17A monoclonal antibody, on symptoms of psoriatic arthritis (PsA) and joint structural damage. **Methods** The phase III study (FUTURE1) was conducted in patients (pts) with PsA. A total of 606 pts were randomized either into the SEC 10mg/kg i.v. followed by 75 mg s.c. (SEC 10-75 IV/SC), 150 mg s.c. (SEC 10-150 IV/SC), or placebo (PBO) group in a ratio of 1:1:1. PBO group were re-randomized to SEC 75 mg or 150 mg s.c. at Wk 16 (non-responders) or Wk 24 (responders). **Results** ACR 20 response at Wk 24, primary endpoint, in the SEC 10-150 IV/SC, SEC 10-75 IV/SC, and PBO groups were 50.5%, 50.0% and 17.3%, respectively ($p < 0.0001$). Mean change from baseline to wk 24 were 0.08 and 0.57 for SEC pool group (SEC 10-75 and -150 IV/SC) and PBO group ($p < 0.05$). A prespecified analysis of PBO-pts stratified by prior anti-TNF therapy, mean changes in vdH-mTSS from Wk 24 to Wk 52 were -0.12 and 0.27 for anti-TNF-naïve and anti-TNF-IR groups, respectively. No new or unexpected safety signals were observed. **Conclusion** SEC demonstrated significant and sustained improvements in the signs and symptoms of PsA, and inhibited radiographic disease progression. SEC was well tolerated; safety findings were consistent with previous reports.

W42-2

Psoriatic arthritis presenting with rapidly progressive atlanto-axial subluxation

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Conflict of interest: None

Atlanto-axial subluxation (AAS) is associated with psoriatic arthritis (PsA), but the clinical course is unknown. We describe a 64-year-old male PsA patient who developed rapidly progressive AAS as demonstrated on cervical X-rays. The patient had a 7-year history of psoriasis and a 1-year history of PsA. Although infliximab and adalimumab therapy was initiated, it had to be discontinued due to eosinophilic pneumonia. Three months after admission, he exhibited a worsened gait disturbance together with right hemiparesis. A comparison of recent and previous cervical X-rays revealed that the atlanto-axial distance had extended from 3.0 mm to 8.1 mm over 2 months. An occipito-cervical fusion was performed and secukinumab was administered. Although he was in a wheelchair at the time of discharge, he was able to walk again with the use of rehabilitation equipment. Considering that AAS can occur abruptly, patients with psoriatic arthritis should undergo careful clinical and radiologic investigation.

W42-3

Clinical experience in 16 patients with pustulotic arthro-osteitis associated with palmoplantar pustulosis

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Conflict of interest: None

[Object] We report 16 patients with pustulotic arthro-osteitis associated with palmoplantar pustulosis. [Methods] Medical records of the patients were investigated retrospectively. [Results] The mean age of the patients was 61.4 years (range, 37 to 73 years). All patients were female. Seven patients (43.8%) developed palmoplantar pustulosis before the onset of arthritis/osteitis, and 4 patients (16.5%) developed palmoplantar pustulosis after the onset of arthritis/osteitis. Five patients (31.3%) developed palmoplantar pustulosis and arthritis/osteitis simultaneously. Thirteen patients (81.3%) had a smoking history and eight patients (50%) could not stop smoking. Three patients (18.8%) had a past history of breast cancer, and 1 patient (6.3%) developed lung cancer. Eight patients (50%) had allergy to metal, 11 patients (68.8%) had dental problems. Rheumatoid factor was positive in 4 patients (25%), and anti-cyclic citrullinated peptide antibody was positive in 3 patients (18.8%). Active spondylitis was observed in three patients (18.8%). [Conclusions] Although 81.3% of the patients had a smoking history, it should be noted that 4 of the 16 patients (25%) were associated with malignancy.

W42-4

The case of developing the HTLV-1 associated arthropathy after remission of the adult T cell leukemia

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Conflict of interest: None

HTLV-1 is well known to induce the adult T-cell leukemia (ATL). In addition, chronic polyarthritis involved with HTLV-1 (HAAP) had been also reported. Although HAAP has been generally considered to be developed in the HTLV-1 carrier, we do the case report of developing the HAAP after the ATL remission. The case was 81 age woman diagnosed with ATL acute type before 20 months and got remission by the CHOP and the anti-CCR4 antibodies therapy. From a month before, she had polyarthritis with no joint destructions in X-ray images. In the joint fluid, there were large atypical lymphocytes with cutting nuclear and they were polyclonal in the HTLV-1 DNA testing. Synovitis was mild macroscopically, but synovium had the atypical lymphocytes and plasmacytes. Thus, we diagnosed with HAAP and its symptoms improved promptly after the treatment by prednisolone and salazosulfapyridine. Although the pathogenic mechanism of HAAP is unknown, it is considered to be different to the pathogenesis of the ATL because there was no monoclonal expansion of infected cells. In this case, it is suggested that the pathogenic condition of the ATL had been changed to the HAAP after remission of it. We hypothesized that might be occurred by the treatment of anti-CCR4 antibodies.

W42-5

A study on the symptoms of HPV vaccine-related neurological immune abnormality syndrome (HANS)

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Conflict of interest: None

Background: Some of the side reaction by the HPV vaccine, will continue to progress while stratified exhibit a variety of symptoms cases has become a social problem seen.Pathology of recent HANS is reported to be the hypothalamic lesions. Purpose: to examine symptoms after HPV vaccination was investigated whether the symptom can be explained by lesions around the hypothalamus. METHOD: March to 9 cases 17 cases that was experienced in our department until April 2015 2014, it is directed to a 13.7 ± 1.6 years old average age, consider and symptoms from post-vaccination, the transition of the symptoms, and exercise each system failure (A), sensory system failure (B), autonomic, endocrine disorders (C), it was classified discussed four cognitive-affective disorders (D). Result: from after the first vaccination until the time of symptom appearance is 14.5 ± 14.5 months. Symptoms that appeared to diagnosis, headache (100%) general malaise (94%), was the limbs of pain (76%). A 71%, 94% B, C 94%, was 100% D. Conclusion:These autonomic, endocrine, cognitive, sensory, movement, is considered the main lesion is present in the hypothalamus that are integrated to control the immune. HANS is necessary to be considered as a new syndrome

W42-6

A pilot study of prophylaxis for glucocorticoid induced diabetes mellitus by linagliptin

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Conflict of interest: None

[Objectives]To evaluate efficacy of prophylaxis for development of glucocorticoid induced diabetes mellitus (GC-DM) by linagliptin. [Methods] Enrolled patients without DM were scheduled administration of 20mg/day or more of prednisone and had at least either one of following risk factor for GC-DM: eGFR =< 60ml/min/1.73m2; 65 years or older; HbA1c > 6.0 %. Patients who received steroid pulse therapy were excluded. The primary outcome was incidence proportion of development of GC-DM (fasting blood glucose level >= 126 mg/dL and/or casual blood glucose level >= 200mg/dL) within 1 month. In addition, we evaluated safety and concomitant use of other oral antidiabetics. [Results] Of 6 patients (3 males and 3 females) enrolled from December 2014 to October 2015, mean (±SD) baseline characteristics were follows: age, 74±5 years; body mass index (BMI), 19±2kg/m2; Hb, 9.5±0.4g/dL; HbA1c, 5.5±0.7%; eGFR, 72±33mL/min/1.73m2; CRP, 6.3±5.5mg/dL. Four patients (67%) developed GC-DM. Concomitant other oral antidiabetics was used in only 1 patient and no patient was need for insulin treatment. Hypoglycemic event was occurred in 1 patient. [Conclusion]Linagliptin was difficult to prevent the development of GC-DM but may allow the treatment of GC-DM without the insulin.

W43-1

The difference in treatment of RA between physician and orthopaedic surgeon. -analysis of NinJa database 2010/2014-

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Conflict of interest: None

Objective, patients: To bring out the difference of treatment and results between doctors, 3,734 patients with RA collected from NinJa 2010 and 2014 database were divided to three groups according to their head doctor (s): physician (68.7%), orthopaedic surgeon (24%) and both (7.3%). In this study we had compared two patient groups treated with physician (P) and orthopaedic surgeon (O) by themselves. **Results:** At 2010 (P/O) average age and disease duration: 60.9/63.2 y.o. and 11.2/16.4 ys, stage: 2.5/3.0, class: 1.8/2.1 and ratio of female: 82.4/85.4. Average data (2010→2014) were as follows; CRP: 0.59→0.48/0.88→0.62, DAS28-CRP: 2.54→2.27/2.88→2.56, mHAQ: 2.54→2.27/2.88→2.56 and no. of artificial joints: 0.14→0.21/0.61→0.75. Treatment at 2014 (%) were as follows; MTX+ 65.6/63.2, steroid+ 45.5/37.5 and bio + 21.6/35.0. Ratio of DAS28 remission (%): 48.2→59.6/34.9 →45.4, M or H disease activity: 37.6→27.5, 51.7→40.0. **Discussion:** Physicians treated RA patients with more PSL, while patients with orthopaedic surgeons were with longer disease duration, more complicated with physical ability and experienced more operations and biologic treatment. Hence the latter might be more progressed and severe states of RA, both patients had marked similar progress in the five years.

W43-2

The clinical course of the patients with elderly-onset rheumatoid arthritis (EORA)

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Conflict of interest: None

[Object]: Recently, together with the growing proportion of elderly population, the elderly-onset of RA (EORA) is progressing. We reported in 2014 that, the patients with newly developed and early RA who visited our hospital from 2009 to 2014, the mean onset age was remarkably high in EORA group and the swollen joint count (SJC) at the initial visit was higher. Now we investigated those patients' clinical courses of one year after introducing treatment. [Methods] On those patients whose disease duration≦2 years and who were followed at least one year and one newly enrolled patient (total 57 cases), we examined the chronological change of CRP, ESR, SJC and joint destruction, treatment procedures and infectious events. Results:The usage of steroid and the percentage of the patients whose joint destruction progressed was high. [Conclusion] It was suggested that, in our EORA patients, considerable number of the patients were not treated by DMARDs enough to overcome their disease activity and the individualized medicine based on the proper evaluation of each patients' organ function including immune function may be important.

W43-3

Study of clinical usefulness of HAQ(Health Assessment Questionnaire) for eldery Rheumatoid Arthritis patients

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Conflict of interest: None

In rheumatoid arthritis (RA) treatment, HAQ (Health Assessment Questionnaire) is the main measurement of joint function, but some questions in HAQ are unrealistic in daily life of elderly RA patients. We investigate whether it's the movement that each question of HAQ performed really or not in everyday life, and consider including every patient background. A total of 29 RA patients (5 men, 24 women, average age 69.3 years old) who treated with our hospital and Osaka Medical College were analized. We selected 21 movements in HAQ and made a questionnaire for them to extract the unrealistic movements in daily life for elderly RA patients. And the results for the two groups, group A (≧65 y.o) and group B (≧75 y.o) were analyzed separately.In conclusion, four movements in HAQ are not perfomed for RA patients in daily life frequently and another two movements are the same for elderly patients. It is predicted that by 2030, Japan's aging rate will rise to 31.8%, indicating that one out of three Japanese will be a senior citizen aged 65 or older, and that the figure will top the 40% mark to reach 40.5% in 2055. To achieve effective treatment for elderly RA patients, we should make the new measurement of joint function that can be useful for them in future.

W43-4

Problems in care which nurse performs for outpatient with rheumatoid arthritis

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Conflict of interest: None

[Object] The satisfaction survey results for outpatients with RA performed every year in our hospital, showed that treatment satisfaction increased, but the question for the life was not broken off. Therefore, we conducted a questionnaire survey of their awareness to clarify issues on RA treatment. [Methods] A survey was performed among 26 nurses working in the outpatient section, to determine their level of interest and reasons. Then, we interviewed nurses about anxiety and complications experienced. [Results] Regarding interest level in RA treatment, 34.6% nurses chose “interested” and 46.2 chose “interested a little”. The reasons were the majority of the patients had many opportunities.19.2% nurses chose “neither”. None of them chose “no interest”. According to the oral investigation, nurses did not know how to deal with patients who changed their condition. [Conclusions] To increase awareness, we created drug pamphlets and held a study meeting regularly. But, they could not apply knowledge provided, because of lack of communication between nurses and nurse patient interval. We will hold a more practical study session including a case study to ensure friendly environment that would improve communication such that many nurses can correspond and interact with patients.

W43-5

Medical Social worker (MSW) intervention on RA patients treated by biologics at perspective of their social background ~ Sweet Cohort~

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Conflict of interest: None

Objectives: Social background of RA patients largely influences their decision when biologics is first introduced. Our aim is to access role of MSW intervention on medical cost. Methods: Among 1,519 RA patients who visited our facility between April 2009 and Sep 2015, 627 patients treated with biologics. 186 patients intervened by MSW are target for analysis and divided into 3 groups. 1) Patients on biologic treatment 2) Patients scheduled for biologics 3) undecided patients Results: Analysis on medical cost revealed that ratios of 30% co-payment are 69.5%, 74.2%, and 84 % respectively, where Group 3 showed significantly higher ratio than the others. Ratios of 10% co-payment are 21.9%, 17.1%, and 2.8%, where group 3 showed significantly lower ratio than the others. 53.6% of 30% co-payment patients in all the groups are led to have biologics through intervention of MSW, resulting in more patients led to remission. Discussion: MSW intervention is effectively provided for patients to start biologics. MSW needs continuously to acquire medical and social knowledge for further improve MSW intervention leading improving benefit in RA patients as we recalled.

W43-6

Effect of the inpatient RA education for the biologics therapy

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Conflict of interest: None

Object: To complete effective long-term therapies for RA, patients’ voluntary enrollment in their therapy is required. However, the patient’s education by the medical staff is unsatisfactory, and the patient’s knowledge for RA including biologics therapy is limited. We compared the patient’s understanding levels for RA and biologics therapy before and after the short-term inpatient RA education (IRE) using a self-completed questionnaire. Methods: We performed 15 self-completed questionnaires to patients about RA and 5 items for biologics to 45 RA patients at Hazu medical center hospital, and compared the data of before and after IRE. Results: The levels of the patient’s understanding for RA were unsatisfactory without improvement after IRE. However, the patient’s understanding for the biologics therapy dramatically improved. Conclusions: Improvement of the patient’s understanding for RA by IRE is limited. However, some favorable changes for the biologics therapy were observed after IRE. This short-term IRE is expected as a tool for improvement of patient’s understanding for the RA biologics therapy.

W44-1

Clinical Analysis of Relapsing Polychondritis

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Conflict of interest: None

[Objectives] We extract the clinical features, FDG-PET findings, treatment regimen and investigate the clinical characteristics of RP patients. [Methods] We enrolled the five patients (M/F: 1/4) with RP diagnosed and treated in our facility between 2005 and 2015. We extract the subjects as follow; initial symptom, laboratory tests, radiographic features, initial intervention and the efficacy of treatment. [Results] The mean age at diagnosis of RP was 56.8 years old (range; 47-79). Laringotracheal involvement was detected in 3 cases, auricular chondritis in 2 cases, eye involvement in 2 cases and arthritis in 2 cases. All cases have Laringotracheal involvement or auricular chondritis.The intervention was conducted with glucocorticoid (GC) treatment in all RP patients. 3 cases were taken methylprednisolone-pulse. However three patients were refractory treatment. One case treated with methotrexate combined with GC and another 2 cases cyclophosphamide. The follow-up PET/CT examinations were performed in 2 cases. They showed that ^{18}F-FDG-uptake was significantly decreased or disappeared. [Conclusion] FDG-PET/CT is valuable for early diagnosis of RP as well as monitoring response to treatment.

W44-2

An association study between cutaneous and extracutaneous complications in patients with relapsing polychondritis; an epidemiological study

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Conflict of interest: None

[Objectives] Cutaneous complications in relapsing polychondritis (RP) were suggested to have an association with myelodysplastic syndrome (MDS). The aim of this study is to assess the relationship between cutaneous and extracutaneous complications in Japanese patients with RP. [Methods] We conducted a multi-institutional survey in 2009 (239 RP patients, male/female: 1.1:1, mean age of onset: 53, the mortality rate: 9.2%) and reanalyzed the data. [Results] 33 cases (14%) developed cutaneous manifestations. The average age at onset of the RP subgroup was 54 years and the male to female ratio was 1:1.1. MDS (5 cases) and Behcet’s disease (BD, 5 cases) were two major RP extracutaneous complications in the subgroup. Two and one patients with MDS suffered from

Sweet's syndrome and erythema nodosum-like lesions, respectively. All 5 patients and 1 patient with BD suffered from oral aphthosis and genital ulcer, respectively. One RP patient with MDS has died and the survival rate of RP with MDS was 80% during the mean follow-up period of 2.8 years. Death rate of RP patients with cutaneous complication was 15%, slightly higher than that of whole Japanese RP patients in this survey. [Conclusions] MDS in Japanese RP patients was suggested to be divided into the low-risk group of MDS IPSS.

W44-3

Clinical features of sarcoidosis patients with arthritis

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Conflict of interest: None

[Background] Sarcoidosis is a systemic inflammatory disorder. We clarified the clinical features of sarcoidosis patients with arthritis. [Objective] We investigated 174 patients (female 93; male 81) who were diagnosed with sarcoidosis who were treated for sarcoidosis in our clinic from 2011 to 2015. 11 patients (6.3%) had arthritis. [Results] The mean age at diagnosis of sarcoidosis was 53.6 years in the 11 patients with arthritis and the mean age at diagnosis of arthritis was 55.5 years. Patients with arthritis were predominantly female (81.8%). Pulmonary involvement was seen in 90.9% of patients with arthritis and 57.7% of patients without arthritis. The rate of uveitis was significantly higher in patients with arthritis than in those without arthritis (72.7% vs. 21.5%). 63.5% of patients with arthritis were positive for rheumatoid factor, and 45.5% were positive for anti-cyclic citrullinated peptide antibody. Regarding treatments for arthritis, 45.5% were treated with prednisolone (mean dosage, 4.6mg/day), and 45.5% by methotrexate (mean dosage, 8mg/week). [Conclusions] Female sarcoidosis patients with pulmonary involvement and/or uveitis tended to have arthritis. Low-dose steroid and methotrexate were effective in relieving arthritis in sarcoidosis patients.

W44-4

The complications of RS3PE syndrome

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Conflict of interest: None

[Objectives] To clarify the complications in RS3PE syndrome.[Methods] The total of 47cases, who were diagnosed as having RS3PE syndrome, were subjected to be analyzed the complications retrospectively. [Results] Average age was 78.4±7.5 years old. All RS3PE syndrome patients had a good response to prednisolone. But 34 patients (72.3%) received 5mg/day or more doses of prednisolone. These patients were complicated with osteoporosis and infections during 1 year treatment. [Conclusion] We suggested that RS3PE syndrome was complicated with osteoporosis and infections during the clinical course.

W44-5

Sequential Ultrasonographic Observation In Relapse of Polymyalgia Rheumatica

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Conflict of interest: None

PURPOSE: To evaluate the efficacy of ultrasonography in prediction of relapse of polymyalgia rheumatica (PMR). METHODS: Thirteen patients, who underwent US before and at least once after administration of PSL, were enrolled. Visual analogue scale (VAS) for shoulder pain, erythrocyte sedimentation rate and C-reactive protein, and physical findings were evaluated. RESULTS: The average dose of PSL was 14.0±3.2mg, and average interval between administration and second US was 104±120 days. The relapse was seen in four patients and, and it was difficult to discontinue PSL in one patient. In these five patients, number of places of fluid collection in first US was significantly larger than the others. There was no significant difference in age, sex and value of C-reactive protein. In second US, fluid collection was detected In six patients, and recurrence was seen in four of them. CONCLUSIONS: It was suggested that US findings may predict the relapse of PMR.

W44-6

Clinical analyses of 70 cases of polymyalgia rheumatica including 6 cases with tocilizumab

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Conflict of interest: None

Polymyalgia rheumatica (PMR), a recurrent rheumatic disease, responds to low dose therapy of prednisolone (PSL). It is difficult to reduce PSL dose in many cases. In refractory cases, oral immunosuppressant such as methotrexate (MTX) are administered concurrently, but often broken off them due to adverse effects. This time we report, with some speculations, 6 effective cases treated with tocilizumab (TCZ) and then reduced PSL dose. Seventy cases of PMR in our clinic from April 2007 are clinically analyzed. The mean age of onset is 69.6, the ratio of males to females is 1:1.7. All patients got PSL therapy, maximally 20mg (mean 14.3mg) per day. Twenty seven cases (39%) had a relapse, and 14 cases (20%) got cured during mean period of 23.6 months. In refractory cases, immunosuppressants such as MTX and azathioprine were administered concurrently, and 6 cases were treated with TCZ. PSL dose could easily reduce in all cases with TCZ. Two patients got cancer in the course despite the screening exams. In our 70 cases, 14 patients got cured and TCZ ameliorated 6 refractory cases.

W45-1

Prevalence and Clinical Characteristics of Patients with Psoriatic Arthritis

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Conflict of interest: None

[Objectives] The previously reported prevalence of psoriatic arthritis (PsA) among Japanese patients with psoriasis is less than that of Westerners. This study aims to investigate the prevalence and clinical manifestations of PsA in Japan.[Methods] This was a multicenter, non-interventional, retrospective cross-sectional study. Data from all patients with psoriasis examined between 2003 and 2014 at three tertiary care centers were included. We investigated the prevalence of PsA, surveyed the clinical manifestations, and determined whether the Assessment of Spondyloarthritis International Society (ASAS) classification criteria and the Classification for Psoriatic Arthritis criteria (CASPER) were met.[Results] Of the 3021 patients with psoriasis included, 431 had PsA (pooled preva-

lence, 14.3%; maximum, 20.4%; 258 male; mean age at diagnosis, 53years). No large differences between our results and previous reports from Western countries were observed in either clinical manifestations or treatment. Positivity of CASPAR criteria was 89.7% and 98.2% and 63.0% in ASAS criteria (peripheral and axial joint involved type).[Conclusion] The prevalence of PsA in patients with psoriasis in Japan was similar to that observed in Western countries, and is higher than previously reported in Asia.

W45-2

The assessment of axial involvement in Psoriatic arthritis

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Conflict of interest: Yes

【Objective】To assess the evaluate of imaging and the disease activity of axial involvement in psoriatic arthritis (PsA).【Methods】Enrolled thirty-one patients (age; 57 years, duration of PsA;11 years)with PsA were evaluated by X-ray and MRI of lumbar spine or sacroiliac joints (SIJ) were composed. MRI and X-ray were compared with clinical examinations including BASDAI, ASDAS, BASFI and BASMI.【Results】Forty percent were sacroilitis by X-ray according to the New York criteria. In the SIJ (n=25) of MRI, which enabled to assess the activity, 20% were active lesions, but there were no sacloilitis in X-rays of more than half of that. Radiological changes of lumbar were 74%. mSASSS of lumbar was mean 6 scores. In MRI (n=14) of lumbar spine, 50% were active lesions and 4 cases of this had no findings of sacroilitis in X-rays. BASDAI and ASDAS was higher in cases with active lesion than without that (no statistical significant). BASMI was correlated with mSASSS (Schober's test (P=0.021), lumbar side flexion (p=0.0001), cervical rotation (p=0.016)). There were no correlation between BASFI and mSASSS (p=0.54).【Conclusion】In axial involvement in PsA, it is important to assessment of imaging and the disease activity, because of abnormality of imaging without symptoms.

W45-3

Assessment of peripheral involvements in psoriatic arthritis

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Conflict of interest: Yes

Objectives: Psoriatic arthritis (PsA) manifests clinically in several ways and composite measures of disease activity in PsA have not been established. To verify which the existing composite measures, including the Composite Psoriatic arthritis Disease Activity Index (CPDAI), Disease Activity for Psoriatic Arthritis (DAPSA), and psoriatic arthritis disease activity score (PASDAS), are adapted for clinical examination. Methods: Using 160 clinical data from 81 patients with PsA (mean age: 56, mean PsA duration: 10 years), we compared with CPDASI, DASPSA and PASDAS and assesse to correlate between those and other parameters or ultrasound composites scores. Results: There was correlation between DAPSA and PSDAS (r=0.66). Significant correlation was seen between DAPSA and DAS-ESR (r=0.68), DAS-CRP (r=0.77), more strongly CDAI or SDAI (both, r=0.8). On the other hand, calcification of tendons in ultrasound composites scores were tendency to correlate with DASPA (p=0.08). Conclusions: As ultrasound composites scores were not reflected in the existing composite measures, new one tool is required in future.

W45-4

The radiological assessment of axial involvement in Japanese patients with psoriatic arthritis

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Conflict of interest: None

The quantitative measurement of axial involvement in psoriatic arthritis (PsA) have not been established. Currently, the radiological evaluation has made by mSASSS that is the scoring system for ankylosing spondylitis.PASRI is newly proposed method for PsA. The comparison of both methods has not been performed in Japanese patients with PsA. Objective: To comparison the performance of mSASSS and PASRI in Japanese patients with PsA. Method: Spinal radiographs of 22 patients with PsA were evaluated by mSASSS and PASRI. Result: The mean age/ disease duration at radiographic evaluation was 55.3/ 11.5 years, respectively. Both mSASSS and PASRI scores were higher in men than women, and the patients with sacroiliitis had higher score than patients without sacroiliitis. The significant correlation between mSASSS and PASRI was detected (r= 0.989). Next, we performed comparison of scores at baseline with those at five years later in part of the patients. The mean scores were increased 25.7 to 31.3 in mSASSS and 26.2 to 30.3 in PASRI, suggesting that no significant difference between mSASSS and PASRI. Conclusion: Both mSASSS and PASRI were useful for evaluation of axial involvement in PsA.

W45-5

Clinical characteristics of Japanese patients with reactive arthritis induced by intravesical BCG therapy for bladder cancer: a retrospective 19 years' two-center study

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Conflict of interest: None

Objective: To evaluate clinical characteristics and incidence of Japanese patients with ReA induced by intravesical BCG therapy (iBCG) for bladder cancer (BC). **Methods:** The clinical findings of Japanese patients who received iBCG (n=487 (182 and 305 in Kochi University Hospital (KUH) and Kurashiki Medical Center (KMC))) for BC from 1997 to 2015 were retrospectively assessed. **Results:** Of the patients received iBCG, 40/182 (22%) and 36/305 (12%), 51/182 (28%) and 51/305 (17%), and 83/182 (46%) and 81/305 (27%) in KUH and KMC presented fever, hematuria and painful urination, respectively. ReA was revealed in 4/182 (2.2%) and 6/305 (2.0%), uveitis in 3/182 (1.6%) and 1/305 (0.3%), and conjunctivitis in 15/182 (8.2%) and 15/305 (4.9%) in KUH and KMC, respectively. Total ReA was revealed in 10/487 (2.1%), and showed asymmetric polyenthesitis pattern and 25% HLA-B27 positivity. **Conclusion:** The incidence of ReA induced by iBCG in Japanese was 2.1% and might be more than in the Western countries. Positive HLA-B27 was revealed in 25% of ReA in our study, suggesting lower frequency than in the Western. Therefore, besides HLA phenotype, a cross reaction between a mycobacterium epitope and an antigen of joint cartilage might be suggested in the pathogenesis of ReA induced by iBCG in Japan.

W45-6

Sacroiliac arthritis coincident with gout: report of two cases

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Conflict of interest: None

[Background] Gout can present sacroiliac arthritis. We report two cases of sacroiliac arthritis by gout. [Case 1] A 40-year-old woman came to our hospital because of arthralgia. She had polyarthritis including DIP joints and was diagnosed as gout because urate crystals were detected in synovial fluid. She also had back pain at rest and tenderness of entheses. Both CT and MRI imaging showed sacroiliac arthritis. Dual energy CT, which can visualize urate crystals, showed urate deposition on sacroiliac joints. We diagnosed by exclusion that sacroiliac arthritis was caused by gout. Normalization of serum uric acid and prednisolone 10mg improved both peripheral and sacroiliac arthritis. [Case 2] A man was diagnosed as gout at 29-yo because of urate crystals in synovial fluid. Back pain at rest occurred at 36-yo and MRI scan showed sacroiliac arthritis. After that, he had repeated back pain coincident with gout attack for 9 years. He had limitation of lumbar spine and chest expansion, so the cause of sacroiliac arthritis might not be gout but be ankylosing spondylitis. [Conclusion] Gout can induce sacroiliac arthritis. Dual energy CT is useful especially for detection of urate deposition on joints whose puncture is difficult.

W46-1

Attitude surveys of pediatric and non-pediatric rheumatologists of transition

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Conflict of interest: None

[Purpose]Attitude surveys of pediatric and non- pediatric rheumatologists of transition were performed. [Method]Twenty-eight operation commissioners of Pediatric Rheumatology Association of Japan and 37 non-pediatric rheumatologists belonging to Institute of Rheumatology, Tokyo Women's Medical University were enrolled in the surveys. Experiences of adult patients with childhood-onset rheumatic diseases, ideal medical care to visit in adult age, and factors to make difficulty with transition to adult care were examined. [Results]One-third of pediatric rheumatologists still see grown-up patients whereas 62% of non-pediatric rheumatologist has experiences with childhood-onset patients. Transition to non-pediatric institute was supported by large majority of both pediatric and non-pediatric rheumatologists. Incomplete management support of personal independency to visit adult care and sharing knowledge and skills of pediatric rheumatology with non-pediatric rheumatologists. [Conclusion] The key elements for an effective transition are development education program to make children manage their illness independently and sharing further knowledge of pediatric rheumatology within non-pediatric rheumatology.

W46-2

Application of Gaslini Diagnostic Score in Japanese Children with Periodic Fever

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Conflict of interest: None

Objective: Utility of Gaslini Diagnostic Score, a differential diagnostic score in hereditary periodic fever syndrome from periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA)syndrome was investigated with Japanese children.Methods: 32 children (20 boys and 12 girls, age at onset: 34.8±19.4months) with periodic fever fulfilled Thomas diagnostic criteria were enrolled in this study. Clinical manifestations and polyomorphisms of responsible genes, MEFV, TNFRSF1A, and MVK, were examined.Results: The patients developed aphthous stomatitis (46.9%), stomach ache (34.3%), diarrhea (15.6%), and pectoralgia (9.4%). Thirteen (40.6%) had family history of periodic fever. High score of the diagnostic score over1.32 was seen in only 3 patients. However, 2 of the 3 had MEFV E148Q hetero, a quite common polypmorphism in healthy Japanese. Thirteen of 29 with low score less than 1.32 were polymorphisms negative. Other 16 patients had MEFV polymorphisms. Conclusion:The Diagnostic Score applied in Japanese children revealed low sensitivity (0%) and specificity (56.3%) excluding E148Q heteros. Clinical features are indispensable for interpretation of MEFV polymorphisms, further examination with more individuals in high risk group is necessary.

W46-3

Infusion reactions to tocilizumab in systemic juvenile idiopathic arthritis

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Conflict of interest: None

【Object】 We retrospectively examined the characteristics of patients who developed infusion reaction (IR) during the treatment with tocilizumab (TCZ) for systemic juvenile idiopathic arthritis (sJIA). 【Methods】 sJIA patients given TCZ at our hospital between July 2004 and October 2015 were classified into those who developed IR by the third TCZ administration (IR group) and those who did not (non-IR group). We compared the two groups in terms of clinical symptoms, blood tests, and cytokine profiles. 【Results】 In total, 38 patients received TCZ, 5 of whom developed IR. Patients in the IR group were significantly younger, shorter, and weighed less than those in the non-IR group. C-reactive protein (CRP) levels were undetectable after the initial TCZ administration in all cases, but became detectable by the third administration in 4 and 1 case (s) in the IR and non-IR groups, respectively ($p<0.001$). 【Conclusions】 Patients who developed IR were younger and TCZ was rapidly eliminated in these patients. These factors may have led to an increased risk of anti-TCZ antibody production, thereby contributing to an elevated IR frequency. When the CRP level was completely normalized after TCZ administration but became detectable again, the possibility of IR should be considered.

W46-4

Simple Estimation of area under the curve 0 to 12h of mycophenolic acid (MPA-$AUC_{0\text{-}12h}$) with childhood-onset autoimmune disese

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Conflict of interest: None

【Background and Objectives】Recently,mycophenolate mofetil (MMF) has been used for the treatment of childhood-onset autoimmune disease. Mycopenolic acid (MPA) is an active metabolite of MMF. The area under the curve 0 to 12h ($AUC_{0\text{-}12h}$) of MPA is considered to be effective pharmacokinetics parameter for therapeutic effect. However, frequent blood sampling is required to calculate $AUC_{0\text{-}12h.}$ This study is to investigate whether the limited sampling (each single MPA concentration, $AUC_{0\text{-}2h,}$ $AUC_{0\text{-}4h}$) would be useful to estimate the $AUC_{0\text{-}12h}$ in childhood-onset autoimmune disese.【Methods and Material】The 25 patients have been investigated the concentrations of MPA in recent 5 years. The mean age was 14.6 years. Seven serial blood samples were collected from each patient, and the AUC values were calculated. The statistical investigation was performed using Person's correlation coefficient to make comparisons between $AUC_{0\text{-}12h}$ and each MPA concentration, $AUC_{0\text{-}2h,}$ and $AUC_{0\text{-}4h.}$【Result】 There was not strong correlation between each single concentration and $AUC_{0\text{-}12}$ ($r^2<0.5$). $AUC_{0\text{-}12}$ was positively correlated with AUC0-2 ($r^2=0.677$) and $AUC_{0\text{-}4}$ ($r^2=0.918$).【conculusion】The simple AUC ($AUC_{0\text{-}2h}$ or $AUC_{0\text{-}4h}$) is useful for estimation of MPA-$AUC_{0\text{-}12h}$ by using in childhood-onset autoimmune disese.

W46-5

The use of EULAR Sjögren's Syndrome Disease Activity Index in pediatric onset primary Sjögren's syndrome

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Conflict of interest: None

Objectives: EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) has been used for the evaluation of a systemic disease activity about primary Sjögren's Syndrome (pSS). But there are few data about the ESSDAI of pediatric onset pSS. We investigated the ESSDAI of pediatric onset pSS at onset. **Methods:** 24 patients (6 male, 18 female, mean age of onset 10.3±3.1) with pediatric onset pSS who had visited our hospital were examined. **Results:** The mean ESSDAI score was 8.5±3.9. 3 cases scored more than 14 points, 15 cases ranged between 5 to 13 points, and 6 cases scored less than 5 points. There were more active patients (low~high activity level) in the constitutional domain (15 cases) and biological domain (17 cases). In this investigation, there was no patient with active disease in internal organ lesions (lung, renal, peripheral nervous and central nervous system). **Conclusions:** The proportion of patients with active disease above 5 points evidenced high ratios (75%, 18 cases). Pediatric onset pSS patients have few dry symptoms, but more systemic symptoms. So it is possible that ESSDAI can evaluate the disease activity more correctly than other methods of evaluation for dry symptoms.

W46-6

Serum IL-18 levels as a marker for disease activity in systemic juvenile idiopathic arthritis during Tocilizumab therapy

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Conflict of interest: None

Objectives Tocilizumab (TCZ) can mask some clinical features and laboratory findings including CRP in patients with systemic juvenile idiopathic arthritis (s-JIA). The aim of this study is to investigate the clinical significance of serum IL-18 levels as a marker for disease activity and for predicting the prognosis in patients with s-JIA during TCZ therapy. Methods We serially measured serum IL-18 levels in 14 patients with s-JIA during TCZ therapy and compared them with the disease activity and their prognosis. Results Serum IL-18 levels in 8 out of 9 patients without relapse decreased to the levels <1000 pg/ml in inactive phase. In contrast, serum IL-18 levels in all 5 patients with relapse during weaning of steroid sustained elevated >1000 pg/ml or elevated again to the levels >1000pg/ml after serum IL-18 levels normalized in inactive phase. Conclusions Serum IL-18 levels are useful marker for assessing the disease activity and predicting the prognosis in patients with s-JIA during TCZ therapy.

W47-1

Abnormal Expression of innate immunity-related genes in peripheral mononuclear cells from patients with IgG4-related disease

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Conflict of interest: None

To search pathogenesis-related genes of IgG4-related disease (IgG4-RD), we examined DNA microarray analysis of peripheral mononuclear cells from 27 patients with IgG4-RD registered with IgG4 related disease study group by the Ministry of Health, Labor and Welfare Japan and 13 healthy individuals. We found that 21 genes were decreased more than 3 times in IgG4-RD compared with healthy controls and that 30 genes were fluctuated more than 3 times before and after steroid treatment. Further, we examined the expression of innate immunity-related genes such as Charcot--Leyden crystal protein (CLC), membrane-spanning 4-domain subfamily A member 3 (MS4A3), defensin alpha 3 and 4 (DEFA3, DEFA4) and interleukin-8 receptors (IL8RA, IL8RB) using RT-PCR assay. Expression of all genes was significantly decreased in IgG4-RD compared with a normal group. Expression of DEFA3, DEFA4 and MS4A3 were significantly increased after steroid treatment. In contrast, expression of IL8RA, IL8RB and CLC didn't changed by steroid treatment. It is likely that the former 3 genes are related to the condition of IgG4-RD. On the other hand, there is a possibility that the later 3 genes may participate in the cause of IgG4-RD.

W47-2

Investigation of factors related to development of renal cortical atrophy after corticosteroid therapy in IgG4-related kidney disease

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Conflict of interest: None

[Objectives]This study was conducted to clarify the factors related to renal atrophy after corticosteroid (CS) therapy in IgG4-related kidney disease (IgG4-RKD). **[Methods]**We retrospectively evaluated clinical features including laboratory data, CT findings before and after CS therapy in 23 IgG4-RKD patients. **[Results]**Seventeen patients were men, and six were women (average age 62.0 years). Average follow-up period was 54.9 months. At diagnosis, their average serum IgG4 level was 1069 mg/dL, and 7 patients showed hypocomplementemia. The average eGFR was 65.6 mL/min/1.73m^2. Multiple low-density lesions (LDLs) on contrast-enhanced CT were observed in all patients. All patients were treated with prednisolone (PSL) at an average initial dose of 35.7 mg/day and showed improvement of LDLs. At least a part of LDLs resulted in partial renal cortical atrophy in 14 patients (Group A), whereas complete recovery without a residual cortical scar was achieved in 9 patients (Group B). Pre-treatment eGFR in Group A was significantly lower than that in Group B (56.9 vs 79.0, P=0.023). None of the other factors significantly differed between the two groups. **[Conclusions]** Our data suggests that pre-treatment renal insufficiency may relate to renal atrophy after CS therapy in IgG4-RKD.

W47-3

Immunophenotyping of lymphocytes in the peripheral blood and salivary gland tissues in patients with IgG4-RD

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Conflict of interest: None

[Objectives] The immunological hallmark of IgG4-related diseases (IgG4-RD) is the Th2-dominant immune response, but the pathogenesis involved remains still enigmatic. To elucidate this issue, our current study focuses on the immunophenotyping of lymphocytes from patients with IgG4-RD. [Methods] Mononuclear cells were isolated from the peripher-

al blood (PB) and salivary gland tissues of patients who met the comprehensive IgG4-RD diagnostic criteria and were subject to flow cytometric analysis. [Results] In the PB $CD4^+CD45RA^-CXCR5^+$ follicular helper T (Tfh) cells significantly increased in number, and the proportion of Tfh2 subsets was particularly prominent. In the tissues CD4/8 ratio markedly increased, suggesting massive infiltration of CD4+ T cells. In addition, $CD45RA^-CCR7^-$ effector memory T cells increased in the tissues, in which $CXCR5^+CCR6^-CXCR3^-$ Tfh2 cells were noted. On the other hand, plasmablasts increased in number in the PB, which was ameliorated by therapeutic intervention. The proportion of plasmablasts was also remarkable in the tissues, along with the predominance of naïve B cells. [Conclusions] Together, these results suggest that infiltrating naïve B cells were induced to differentiate into IgG4-producing plasmablasts by effctor memory T cells.

W47-4

The relationship between serum cholinesterase, number of organ involvement and fibrotic markers in Japanese patients with IgG4-related disease

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Conflict of interest: None

【**Objective**】To evaluate the relationship between cholinesterase (ChE), number of organ involvement (NOI), serum fibrotic markers and outcome in IgG4-related disease (IgG4RD). 【**Methods**】The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of patients with IgG4RD (n=20) were assessed. Several laboratory data of IgG4RD with multiple involvements (IM) (n=10), IgG4RD with limited involvement (IL) (n=10), ANCA-associated vasculitis (AAV) (n=10) and Sjogren syndrome (SjS) (n=10) were compared. Furthermore, we studied the relationship between NOI, several fibrotic markers and outcome in IgG4RD group. 【**Results**】Serum ChE levels were significantly lower in IM group than IL, AAV and SjS groups. In total IgG4RD cases, ChE levels inversely correlated with NOI and fibrotic score, and fibrotic score positively correlated with NOI. Finally, Dkk-1, one of Wnt inhibitors, levels in IM were significantly lower than IL and healthy subjects. Low level of Dkk-1 before and after treatment tended to predict the progression of organ atrophy. 【**Conclusion**】The ELF score and serum Dkk-1 level might be a clinically useful indicators of fibrosis and the extent of IgG4RD. Notably, continuous lower level of Dkk-1 related to organ atrophy and serum ChE levels could predict these phenomena.

W47-5

Analysis of serum IgG4 level and association with IgG4 related disease in the general population

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Conflict of interest: None

[Background] It is not well known about the IgG4 level and relationship with the disease in the general population. [Purpose] We measured IgG4 in the general population in Noto, Ishikawa Prefecture and examined the presence of the potential IgG4 related disease (IgG4-RD). [Method] People in Noto area participating in the collaboration study of three Universities (Chiba/Kanazawa/Nagasaki) during 2014-2015 were employed. Serum IgG4 was measured by nephelometry and secondary survey was done about cases more than 135 mg/dl of IgG4. We examined the relationship of parameters such as a lifestyle and allergy with IgG4 level. [Result] 481 people (223 men, woman 258, average age was 64.5 years old) had examinations. The average IgG4 level was 45.3 mg/dl (3-254 mg/dl). 17 people more than 135 mg/dl of IgG4 level were recognized. 4 of them took secondary survey and none of them had IgG4-RD. Serum IgG, IgE, and diastolic blood pressure were extracted for a multivariate analysis as a factor related with the IgG4 level. [Conclusion] The proportion of serum IgG4 beyond 135mg/dL was 3.6% in general population. Thus, the specificity of serum IgG4 concentration seems low. Serum IgG4 level was related with an IgE level, suggesting the association between IgG4 elevation and allergic disease.

W47-6

A case of paraneoplastic Mikulicz's disease associated with gastrointestinal stromal tumor

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Conflict of interest: Yes

A 55-year-old male noticed the bilateral swelling of his submandibular glands in Apr. 20XX. In Aug, he consulted an otorhinolaryngologist. The elevation of serum IgG4 was pointed out, but no medication was recommended. After 2years, the bilateral swelling of his lachrymal glands also appeared, then, he was referred to our hospital. CT examination revealed the bilateral swelling of his lachrymal, parotid and submandibular glands. The histological examination of submandibular gland demonstrated the lymphoplasmacytic infiltration by IgG4+/IgG+ plasma cells > 70% and 18-23 IgG4+ plasma cells /HPF, and he was diagnosed with IgG4 related disease. During the search for the organ involvement of IgG4-RD, a rectal tumor was found and diagnosed as gastrointestinal tumor (GIST) histologically. After the neoadjuvant therapy with imatinib, the resection of the rectal tumor was carried out. After the resection, the swelling of his lachrymal, parotid and submandibular glands disappeared. While the malignant tumor should be excluded for the diagnosis of IgG4-RD, there is rarely a report about the paraneoplastic IgG4-RD. The coexistence of malignancy should be ruled out when IgG4-RD is diagnosed.

W48-1

Usefulness of FDG-PET/CT Imaging in Diagnosing and Monitoring Treatment Response in IgG4-related Disease

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Conflict of interest: None

(Objective) We investigated the usefulness of FDG PET/CT for diagnosis and monitoring treatment effect of IgG4-related disease (IgG4-RD). (Method) This study included 31 patients followed up at our facility between 2008 and 2015. All patients underwent baseline FDG-PET/CT. The diagnosis for IgG4-RD was based on comprehensive diagnostic criteria for IgG4-RD. We retrospectively studied the relation of serum IgG4 level, soluble IL-2R level, pattern of FDG uptake, maximum standardized uptake value (SUVmax) and each clinical course. (Result) The mean age was 67 years. The mean serum IgG4 level was 620 mg/dl. We diagnosed with IgG4-RD as follows: definite: 17, possible: 13, probable: 1. In 12 of 66 lesions found by FDG-PET/CT, there were abnormal FDG uptake without abnormal radiologic findings. In 6 of 31 cases, the biopsy site could not be identified except in FDG-PET/CT. After 2 weeks, 4 to 12 weeks at the initial steroid dose, FDG-PET/CT was performed in 2 cases. Significant reduction of FDG uptake was shown 2 weeks after treatment. Soluble IL-2R also decreased more than IgG4 level 2 weeks later. (Conclusion) FDG-PET/CT is useful in selecting a biopsy site for the pathological examination. FDG uptake and soluble IL-2R were markedly decreased with only 2 weeks of steroid therapy.

W48-2

Prevalence of IgG4-related disease: a single-institute study

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Conflict of interest: None

[Background/Purpose] The epidemiology of IgG4-related disease (IgG4-RD) is poorly described. The aim of this study was to examine the prevalence of IgG4-RD. [Methods] We retrospectively examined the number of patients newly diagnosed as having IgG4-RD in all departments of Nagaoka Red Cross Hospital between 2011 and 2014. We also examined the number of patients newly diagnosed as having systemic lupus erythematosus (SLE), sarcoidosis and microscopic polyangiitis (MPA) during the same period, in comparison with the IgG4-RD patients. [Results] Between January 2011 and December 2014, 34 patients (18 men and 16 women) were newly diagnosed as having IgG4-RD at our hospital. The department first visited by the patients was otolaryngology in 35% of cases, urology in 26% and gastroenterology in 18%. The affected organs observed at diagnosis were the salivary glands in 47% of cases and the pancreas in 35%; retroperitoneal fibrosis/periaortitis was evident in 32%. The number of patients newly diagnosed as having IgG4-RD during the 4-year period was about 70% that of SLE patients and double that of patients with sarcoidosis and MPA.[Conclusion] It is not rare to encounter IgG4-RD in a general hospital, especially in departments of otolaryngology, urology and gastroenterology.

W48-3

Analysis of 85 patients with IgG4-related disease and malignancy

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Conflict of interest: None

[Purpose] The purpose of this study is to analyze the clinical features of patients (pts) with IgG4-related disease (IgG4-RD) and malignancy. [Methods] Between 2004 and 2015, we retrospectively evaluated 85 pts with IgG4-RD in our hospital. We analyzed the prevalence of malignancy and the factors related to it in pts with malignancy. We compared mean age, gender, laboratory data, affected organs and therapy between the malignancy and non-malignancy groups.[Results] There were 54 and 31 male and female pts, respectively with a mean age of 65.0 years. Malignancies developed in 17 pts (20%), before the diagnosis of IgG4-RD in 10 pts (59%, mean 4.6 years earlier), and after in 7 pts (41%, mean 1.7 years later). Colon and prostate cancers were seen in three pts each, and gastric, lung and renal cancers and malignant lymphoma (ML) in two pts. ML developed after the onset of IgG4-RD in both pts. No significant differences were seen in mean age, gender, laboratory data, affected organs and the prevalence of corticosteroid therapy or the mean dose of prednisolone.[Conclusion] Malignancies developed at a relatively high frequency. However, no specific characteristics were identified, making periodic screening for malignancy of particular importance.

W48-4

Clinical analyses of the 10 retroperitoneal fibrosis patients

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Conflict of interest: None

[Object] Retroperitoneal fibrosis is characterized by the presence of inflammatory and fibrous retroperitoneal tissue. Despite that retroperitoneal fibrosis has the similar clinical manifestations and histologic characteristics, the pathogenesis and epidemiology seem to vary. [Methods] We surveyed the clinical characteristics of the 10 retroperitoneal fibrosis patients (9 male patients and 1 female patient) having visited our hospital. [Results] The average occurrence of the disease is at the age of 70.7. 3 patients complained mainly of backache while others seemed to be asymptomatic. 8 of 10 patients were idiopathic and most of them were IgG4-related disease. Biopsy was performed in 6 cases (4 lip biopsies and 2 biopsies of retroperitoneal fibrosis) and 4 cases satisfied the criteria of IgG4-related disease (IgG4/IgG ratio>40%). The laboratory findings showed high IgG4 level (>135mg/dl) in 9 cases. [Conclusions] Retroperitoneal fibrosis was treated successfully with glucocorticoid in all of them and no recurrence is found until now. Only limited reports about retroperitoneal fibrosis were found and we will show our cases.

W48-5

Clinical features of IgG4-related disease: a single- center survey

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Conflict of interest: None

Objective: This study was conducted to evaluate the clinical course of IgG4-RD. Methods: A total 29 patients according to the comprehensive IgG4-RD diagnostic criteria since 2009 in Our hospital. Clinical manifestations and courses were retrospectively reviewed. Results: Male:Female ratio was 2:1. The mean age was 65.1 years old (range 52-79). The most common organ involvement was submandibular gland (34.5%) followed autoimmune pancreatitis (24.1%) and retroperitoneal fibrosis (20.7%). Serum IgG4 were elevated to >135mg/dl in all patients, the mean concentrations were 782.5±986.8mg/dl. 25 patients were treated with corticosteroid and the initial doses were 35.4±5.9mg/dl (prednisolone). The relapse was observed in 4 patients (16.0%). There were 13 malignancies (prostate 3, colon 2, lung 2) during the follow up period. Patients with malignancies had more organ involvements than those without malignancies. Conclusion: The associations of malignancies in IgG4-RD are relatively high, and further large-scale analysis will be needed.

W48-6

IgG4-related disease: a retrospective study of 51 cases in Kurashiki Central Hospital

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Conflict of interest: None

[Object] IgG4-RD is a chronic, systemic, multiorgan inflammatory disorder.We report the clinical and laboratory characteristics of 51 patients with immunoglobulin G4-related disease (IgG4-RD). [Methods] The patients were admitted to, or were out-patients in Kurashiki Central Hospital, between January 2011 and October 2015 according to the criteria for IgG4-RD. Clinical presentations, imaging studies, serum IgG4 examinations were performed in all patients. [Results] The fifty one patients (male-to-female ratio 13:4) enrolled in this study had an average age at onset of disease of 69.1 years and IgG4 level at 806.9±6.2 mg/dl. Most patients presented with multiple organ involvement, salivary gland, lung, pancreas,biliary tract,retroperitoneum, aorta, and kidney. Six patients' serum IgG4 was in reference interval, and all of them had retroperitoneum. Seven cases (13.7%) had recurrence, at serum IgG4 2056 mg / dl on average. It is higher compared with the non-recurrence group (533.7mg / dl). [Conclusions] Patients who have high serum IgG4 level tend to have renal and salivary involvements, and are vulnerable to relapse.

W49-1

Relation between glucocorticoid regimen and relapse rate of IgG4-related disease - A multicenter study of 168 cases

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Conflict of interest: None

【Object】Glucocorticoids (GCs) are effective in the treatment of IgG4-related disease (IgG4-RD), however relapse is often observed. The adequacy of standard regimen for IgG4-RD (Initial dose: prednisolone (PSL) 0.6 mg/kg/day) has not been sufficiently validated. We conducted a retrospective multicenter study. 【Methods】From 13 institutions belonging to the Research Committee of IgG4-RD, Japan Agency for Medical Research and Development, we collected and analyzed clinical information of 168 IgG4-RD cases definitely diagnosed by the comprehensive diagnostic criteria for IgG4-RD (2011) or clinical diagnostic criteria for autoimmune pancreatitis (2011). 【Results】Whereas the relapse rates of the cases treated with PSL 0.40-0.69 mg/kg/day were flatly 22%, the relapse rates of those treated with a low dose (≦0.39 mg/kg/day) or a high dose (≧0.70 mg/kg/day) GCs ranged 43-50%. The relapse rate of the cases treated with slow GC tapering (< PSL 0.4 mg/day) was 25%, significantly lower than 52% in the cases treated with fast GC tapering (≧0.4 mg/day) (p = 0.024). 【Conclusions】The relapse rates were comparably low, when treated with the initial GC doses ranging 0.40-0.69 mg/kg/day. To avoid relapse, slow tapering of GC (< PSL 0.4 mg/day) is considered significant.

W49-2

A multicenter phase II prospective clinical trial of glucocorticoid treatment for patients with untreated IgG4-related disease

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Conflict of interest: None

Objectives; Although glucocorticoid is effective for patients with IgG4-related disease (IgG4-RD), the treatment has not yet been standardized, then a prospective phase II clinical trial was performed. Patients and methods; This study enrolled patients who fulfilled the definite IgG4-RD by using the comprehensive diagnostic criteria. Prednisolone was administered at the initial dose of 0.6mg /kg body weight. Every 2 weeks, the dose was reduced by 10%. The subsequent maintenance dose and need for prednisolone were determined by each physician. The primary endpoint was the complete remission (CR) rate at 1 year, and secondary endpoints included overall response rate (ORR), the maintenance dose, the relapse and adverse events. Results; Totally 61 cases from 12 institutes were enrolled. After clinicopathological review, 3 cases denied, and 13 were defined as probable, one possible, and 44 definite. In 44 definite cases showed that the CR rate was 65.9%, and ORR 90.9%. The main adverse events were glucose intolerance (41%), infection (18%). 6 cases (15%) were relapsed. Conclusion; Even in Japan where there are many IgG4-RD experts, there were many misdiagnoses. Therefore, a central clinicopathological review of diagnosis is very important, if a clinical study is planned.

W49-3

Clinical characteristics of the cases of IgG4-related disease with drug-free remission and analysis of the drug-free remission predictors

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Conflict of interest: None

Objective: Glucocorticoid is effective for the induction of IgG4-related disease (IgG4-RD). Almost cases need maintenance treatment, but glucocorticoid can be discontinued in some cases. We cannot predict whether glucocorticoid will be discontinued before the treatments at this point. This time, we retrospectively analyzed the clinical characteristics of both drug-free remission group (A group) and continuing maintenance treatment (B group). **Method**: The subjective were 93 cases with IgG4-related dacryoadenitis and sialadenitis, treated with glucocorticoid for over a year. Clinical factors before the treatments were compared in both groups. Next, the expressions of IgG, IgG4, CD68, IL-32, and TNFα were analyzed in the submandibular gland specimens from the both group. **Results**: Four cases could achieve drug-free remission. The initial dose of glucocorticoid in A group was significantly lower than that in B group ($p<0.05$). The histopathological analysis revealed the expressions of IgG4 and IL-32 in the submandibular gland specimen from A group were significantly lower than those from B group. **Conclusion**: Low expression of IgG4 and IL-32 in the involved organs may be able to predict drug-free remission in IgG4-RD.

W49-4

Increased expression of CCL18 and CCR8 in affected tissues of patients with IgG4-related disease

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Conflict of interest: None

<Objective> To clarify the protein expression of CCL18 and CCR8 (the receptor for CCL18), and expressing cells of these chemokine and chemokine receptor in affected tissues of patients with IgG4-related disease (IgG4-RD). <Methods> 1) The protein expressions of CCL18 in labial salivary glands (LSGs) were compared between IgG4-RD (N=3), Sjögren's syndrome (SS) (N=4), and healthy controls (HC) (N=5) by immunofluorescence (IF) staining. 2) CCL18 expressions on macrophages (CD68), dendritic cells (DCs) (CD11c), B cells (CD20), and plasmacytes (CD138) in LSGs of IgG4-RD (N=3) were examined by double IF staining. 3) The protein expressions of CCR8 and expressing cells (T cells, B cells, and plasmacytes) were examined by double IF staining in lacrimal glands of IgG4-RD (N=1).**<Results>** 1) CCL18 was highly expressed in LSGs of IgG4-RD, whereas not in SS and HC. 2) Many macrophages, DCs, B cells, and plasmacytes expressed CCL18 in LSGs of IgG4-RD. The frequencies of CCL18 expression on these cells were comparable. 3) Many T cells, some plasmacytes, and a few B cells expressed CCR8 in lacrimal glands of IgG4-RD. <Conclusion> These findings suggested that CCL18-CCR8 signaling was up-regulated in affected tissues, and this axis might contribute to the pathogenesis of patients with IgG4-RD.

W49-5

Clinical features and relapse predictors of IgG4-related disease

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Conflict of interest: None

BACKGROUND: Although remission induction of immunoglobulin G4-related disease (IgG4-RD) is easily achieved by steroid monotherapy, relapse is often observed along with steroid dose tapering. We conducted a retrospective study to clarify the risk factors of relapse of IgG4-RD. **METHODS:** We included patients who were referred to our hospital from January 2006 to July 2015. We defined relapse of IgG4-RD as an emergence or exacerbation of symptoms and/or radiological findings suggestive of IgG4-RD. **RESULTS:** 30 patients were included in this study; 10 cases of Mikulicz disease (MD), and 20 cases of IgG4-RD with systemic organ involvement. None of MD cases relapsed. Among 20 cases of IgG4-RD with systemic organ involvement, 6 cases (30 %) experienced relapse. The mean initial prednisolone dose was 0.71±0.21 mg/kg (S.D.). No statistical differences in baseline serum C-reactive protein, IgG, IgG4 values and IgG4/IgG ratio between relapsed and non-relapsed groups. The ratio of change in serum IgG4 to change in serum IgG after one month of treatment was relatively lower in relapsed group than in non-relapsed group (33.8 % vs. 52.0 %). **CONCLUSIONS:** The ratio of change in serum IgG4 to change in serum IgG after one month of

treatment may be beneficial in predicting future relapse of IgG4-RD.

W49-6

Analysis for relapse of IgG4-related disease after corticosteroid therapy

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Conflict of interest: None

<Objectives>To clarify the clinical features of patients with IgG4-related disease (IgG4-RD) who experienced relapse after steroid therapy. <Methods>We examined patients with definite IgG4-RD by comprehensive diagnostic criteria 2011, who had started to be treated with steroid between July 2008 and March 2015, and had been treated for more than 6 months. We investigated 1) relapse rate, 2) comparison of clinical features and treatment between relapsed and non-relapsed cases, and 3) clinical course of relapsed cases, retrospectively. <Results>25 patients (64.3±10.9 years old, 14 males/11 females) were examined. 1) Four patients experienced the relapse (relapse rate 16.0%). 2) The relapsed patients were significantly younger (53.2±6.4 vs 66.4±10.3 years old, $p<0.05$), and started to be treated significantly earlier from disease onset (4.5±2.2 vs 16.7±15.3 months, $p<0.05$) than non-relapsed patients. Gender, serum IgG4, affected organs, initial steroid dose, and duration of therapy were similar between groups. 3) Relapses occurred 26.5±14.2 months later from initiation of therapy, at mean PSL dose of 6.5±3.9 mg/day, and in one of the initially affected organs. <Conclusion>Relapses occurred in 16% of patients after steroids therapy, especially in younger and earlier treated cases.

W50-1

Mizoribine-tacrolimus combination therapy provides acceptable relapse and persistence rates for patients with active lupus nephritis

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Conflict of interest: None

Objective: To evaluate the relapse and persistence rates of mizoribine-tacrolimus combination therapy for lupus nephritis (LN). **Methods:** Thirty LN patients were treated with the combination therapy and then retrospectively evaluated. Following induction therapy, maintenance treatment was continued with the combined drug regimen. If possible, prednisolone and two immunosuppressants were tapered to 5 mg/day and one immunosuppressant, respectively. Relapse was defined as treatment escalation above 20 mg/day of prednisolone, with or without additional immunosuppressant. The relapse and persistence rates at periods of up to 5 years were investigated. **Results**: A complete remission (CR) was observed in all cases (100%) and at various time points. Two relapse cases (6.7%) were observed in the third year. With the exception of one case, where the patient was retreated with cyclophosphamide, 29 patients (96.7%) continued the original treatment plan. Twenty six patients (86.7%) were classified as achieving a CR at the last visit as a result of the combination therapy. Discontinuation due to severe adverse events was not observed. **Conclusion**: This study demonstrates the long-term efficacy and safety of mizoribine-tacrolimus combination induction and maintenance therapy for LN.

W50-2

Risk factors of developing idiopathic osteonecrosis in systemic lupus erythematosus

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Conflict of interest: None

[Object] Systemic lupus erythematosus (SLE) patients are prone to develop idiopathic osteonecrosis (ION) compared to other connective tissue disease patients or healthy subjects, the reason however remains to be elucidated. We aimed to identify risk factors of developing ION in SLE patients. [Methods] A single center retrospective study comprising 74 consecutive SLE patients who underwent magnetic resonance imaging of hip joints from January 2000 to March 2015. [Results] All 74 patients were given glucocorticoids. ION of the femoral head occurred in 33 patients. Male ($p = 0.009$), malar rush ($p = 0.019$), antiphospholipid antibodies ($p = 0.015$), high dose of prednisolone (59.7±5.2mg vs 45.9±13.8mg, $p<0.001$) and intravenous cyclophosphamide ($p = 0.046$) were identified as risk factors at univariate analysis. Male and high dose of prednisolone were independent variables at multivariate analysis. Conversely, SLE disease activity index and pulsed methylprednisolone were not identified as risk factors. [Conclusions] Male, malar rash, antiphospholipid antibodies, high dose of prednisolone and intravenous cyclophosphamide may be risk factors of developing ION in SLE patients.

W50-3

A retrospective study of 118 pregnancies complicated with systemic lupus erythematosus (SLE)

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Conflict of interest: None

[Object] Our aim was to investigate the actual situations of pregnancies in patients with SLE, and to elucidate related factors with maternal and neonatal outcomes. **[Methods]** We carried out questionnaire surveys to pregnant women with SLE who were seen at our clinic. **[Results]** A total of 118 pregnancies in 77 women were identified. The average age was 30.5 years old. Mean disease duration was 8.3 years. 9 pregnancies were associated to be the onsets of SLE. In the outcomes of pregnancies, 69% achieved live born infants, 53.6% were low birth weight infants, and none were post-mature deliveries. 25 pregnancies suffered from pregnancy-induced hypertension (PIH). 54 pregnancies had histories of lupus nephritis, and 10 had antiphospholipid syndrome. Flares occurred in 14.7% of the pregnancies diagnosed as SLE before pregnancy. The details of flare symptoms were fever, eruption, arthritis, proteinuria, thrombocytopenia, hemolytic anemia, leukopenia, complement decrease, elevated anti-dsDNA antibody. We did a univariate analysis of the base line date and found that the use of immunosuppressant did not associated with flares. **[Conclusions]** We presented situations of pregnancy in patients with SLE. Immunosuppressant may not become the risk of fetus.

W50-4

The control of interferon and transcriptional regulator can lead amelioration of clinical and immunological conditions in lupus prone mice being treated with JAK inhibitor

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Conflict of interest: None

Objective: We reported that JAK/STAT pathway-mediated regulation of interferon (IFN) related genes may have an important role in the disease activity of SLE. Therefore, the application possibility of tofacitinib (TOFA) was investigated for the new therapeutic strategy of SLE.**Method**: TOFA had been administered to lupus model mice, NZB/NZW-F1. We evaluated and analyzed the clinical/pathological/immunological condition of mice and the gene expression from SLE mice $CD4^+$ and patients $CD3^+$ T cells.**Result**: Anti-DNA antibody and proteinuria were decreased in TOFA administered groups. Glomerular nephritis was also ameliorated. In $CD4^+$ T cell analysis, naïve cells increased and effector/memory cells significantly decreased in TOFA groups. After TOFA administration, the expression of type I IFN related gene *IFIT3* was significantly suppressed in both $CD4^+$ from lupus prone mice and $CD3^+$ T cells from SLE patients after treatment. Additionally, IFN and transcriptional regulator gene expressions were decreased in TOFA treated mouse kidneys.**Conclusion**: We concluded that the control of IFN and transcriptional regulator can lead amelioration of clinical and immunological conditions in lupus prone mice being treated with TOFA. TOFA may contribute to the development of a new therapy against SLE.

W50-5

Longer suppression of anti dsDNA antibody by sequential therapy with bortezomib and cyclophosphamide in lupus model mouse

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Conflict of interest: None

Object: Recently, a proteasome inhibitor bortezomib (Bz) was reported to be effective in lupus model mouse. However, since plasma cells and anti-dsDNA antibody titers were increased again after cessation of Bz-treatment, some maintenance therapy after Bz might be required for longer remission. In this study, we explored the effect of cyclophosphamide after Bz treatment in lupus model mouse. Methods: MRL/lpr mice (14wk) were treated with (1) PBS, (2) Bz (750ug/kg, twice in a week), (3) Cyc (1mg/body, once in two weeks) and analyzed for anti-dsDNA antibody, glomerulonephritis and plasma cell number at 24wk. In another experiments, drugs were switched from Bz to PBS, from Bz to Cyc at 22wk and the titers of anti-dsDNA antibody were measured. Results: Both treatments with Bz and Cyc significantly decreased the number of spleen cells, glomerulonephritis index. Bz significantly decreased plasma cells and anti-dsDNA antibody titer, while Cyc did not. After the cessation of Bz, Cyc kept anti dsDNA titer significantly lower than PBS. Conclusions: Sequential therapy with Bz and Cyc could maintain longer remission in lupus. Such a novel therapeutic strategy may contribute to the development of more effective therapy with proteasome inhibitors.

W50-6

The first randomized control trial to evaluate the effectiveness of boltezomib as a treatment for refractory Systemic lupus erythematosus

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Conflict of interest: Yes

[Object]Bortezomib (Bz) is a proteasome inhibitor targeting plasma cells. Here, we evaluated the efficacy and safety of Bz versus placebo for the treatment of reflactory SLE. [Methods]14 patients in whom the dose of predonine could not be reduced to ≤ 10 mg/day despite the immunosuppressive therapy. Bz, 1.3 mg/m^2, or placebo was administered twice weekly, 8 times in total. [Results] Among the 14 patients, 8 and 6 were assigned to the Bz group and the placebo group, respectively; 4 of the 8 in the Bz group and 2 of the 6 in the placebo group discontinued the trial. The reason for discontinuation was inability to continue the trial due to adverse reactions in all of the 4 in the Bz group, and insufficient effects in both of the 2 in the placebo group. The percent change of the anti-ds-DNA antibody titer at treatment 24 was 4.24% in the Bz group and -1.96% in the placebo group, which did not support the efficacy of Bz.On the other hand, the SRI at Week 12 was 75% in the Bz group and 40% in the placebo group. [Conclusions]Bz therapy for SLE is associated with many adverse reactions. It is necessary to establish the protocol aiming at the prevention of adverse reactions. On the other hand, we observed improvement of clinical findings, regardless of the anti-dsDNA antibody titer,

W51-1

Impact of anti-erythropoietin recetor antibodies in lupus nephritis

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Conflict of interest: None

Purpose: To examine the clinical significance of autoantibodies to the erythropoietin receptor (EPOR) in patients with biopsy-proven lupus nephritis (LN). **Methods**: Forty-six SLE patients with LN who had undergone kidneyl biopsy during 1993-2014 were enrolled in this study. Anti-EPOR antibodies in sera from these patients were measured using enzyme-linked immunosorbent assay. **Results**: Anti-EPOR antibodies were detected in 19 (41%) of the 46 SLE patients. Anti-EPOR antibody-positive group was low in hemoglobin concentrations and the number of reticulocytes. In addition, anti-EPOR antibodies positively correlated with scores of SLEDAI and BILAG. In patients with International Society of Nephrology/Renal Pathology Society 2003 Class IV LN, the titer of anti-EPOR antibodies were correlated with the percentage of cellular crescents in glomeruli. In addition, -30% change in estimated glomerular filtration rate was more frequently observed in patients with anti-EPOR antibodies than in patients without, and serum levels of the antibodies were significant risk factors for progression of kidney dysfunction. **Conclusion**: These results suggests that anti-EPOR antibodies might be involved in the progression of LN, and the levels of anti-EPOR antibodies may be a predictor for kidney dysfunction.

W51-2

Clinical significance of anti-C1q Abs in patients with SLE

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Conflict of interest: None

The aim of this study was to compare the prevalence and levels of anti-C1q Abs in the sera of patients with SLE. The study involved 137 patients with SLE and 180 patients with other collagen diseases and 30 healthy controls. Anti-C1q Abs were investigated using ELISA system. The prevalence of IgG class anti-C1q Abs was significantly higher in SLE patients than in those of other diseases. The positive rate of anti-C1q Abs in SLE was 35%. IgM class anti-C1q Abs was also significantly higher in SLE than control. To conclude, the results of our study show that the measurement of anti-C1q Abs may be a helpful tool in the assessment of patients with SLE.

W51-3

The regulatory role of Allergin-1 in autoantibody production

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Conflict of interest: Yes

【**Objectives**】 Allergy inhibitory receptor-1 (Allergin-1) is known as an immune suppressive molecule. The purpose of this study is to clarify the role of Allergin-1 in autoantibody production. 【**Methods**】 1) WT and Allergin-1 deficient (Allergin-1$^{-/-}$) mice were treated with dead cells derived from thymocytes. At 2, 4, 6, 8, 10 and 12 weeks after dead cells injection, the titer of anti-dsDNA and anti-Histonre antibodies in serum was measured by ELISA. 2) At 12 weeks after dead cells injection, IgG and C3 deposition on glomerulus were analyzed by immunofluorescent staining. 3) Peritoneal macrophages from WT and Allergin-1$^{-/-}$ mice were stimulated by LPS. The production of IL-6 and TNF-α in culture supernatant was measured by ELISA. 【**Results**】 1) The titer of Anti-dsDNA and anti-Histone antibodies were significantly higher in Allergin-1$^{-/-}$ mice 8 and 12 weeks after dead cells injection. 2) In Allergin-1$^{-/-}$ mice, IgG deposition tended to be increased. 3) The production of TNF-α from macrophages was significantly increased in Allergin-1$^{-/-}$ mice compared with WT mice, whereas IL-6 was not. 【**Conclusion**】 Allergin-1 might play a regulatory role in autoantibody production through the suppression of cytokines from macrophages.

W51-4

Analysis of immune cell subsets in peripheral blood mononuclear cells (PBMCs) from patients with systemic lupus erythematosus

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Conflict of interest: Yes

【Objectives】SLE is a systemic autoimmune disease. Although the roles of auto-reactive B cells and regulatory T cells in its pathogenesis have already been suggested, the precise etiology remains unknown. We explore the etiology of SLE through FACS of various immune cell subsets followed by NGS analysis. 【Methods】24 SLE patients and 16 healthy controls were picked up. Each immune cell subset in PBMCs was identified by multicolor flow cytometry and sorted for NGS analysis. 【Results】In SLE patients, CD19+ B cells in lymphocytes decreased. In T cell subsets, CD4+ T cells decreased, and CD8+ T cells increased. Naïve T cells in T cell subsets also decreased. Both follicular helper T cells (Tfh) and Th1 cells decreased, while Th2 cells increased. CD4+CD25- regulatory T cells showed no significant differences. Plasma blasts increased in B cell subsets. In DC subsets, mDCs decreased, and pDCs showed no significant difference. In monocyte subsets, CD16+ monocytes increased. 【Conclusion】 The ratio of each subset in peripheral blood might reflect the immune responses occurred in affected organs considering the former reports of local increase of DCs and Tfh cells associated with disease activity. We discuss pathological significance of each immune cell with some data from NGS analysis.

W51-5

Analysis of the relationship between CD26^{+} T cell subsets and the pathophysiology of systemic lupus erythematosus

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Conflict of interest: None

[Objectives] T cell costimulatory molecule CD26 is up-regulated following T cell activation, and the increased number of CD26^{+} T cells has been detected in patients with autoimmune diseases including RA. Since the role of CD26 in the pathogenesis of SLE still remains to be elucidated, our objective is to examine the expression and function of CD26 in T cells of SLE patients.[Methods] Human CD4^{+} or CD8^{+} T cells were purified from PBMCs of 50 SLE patients or 30 healthy adult volunteers. The phenotypes of CD26 positive or negative subsets and the response to CD26-mediated costimulation were extensively examined.[Results] CD4^{+}CD26^{nega} T cells were markedly increased in SLE patients, and these cells were shown to be cytotoxic effector cells with high expression of both perforin and granzyme B. In addition, CD4^{+} T cells from active SLE patients produced much less amount of IL-10 following CD26 costimulation compared with healthy controls. Both CD4^{+} and CD8^{+} T cells from SLE patients treated with tacrolimus or cyclosporine exhibited very low responsiveness to CD26-mediated costimulation. [Conclusion] Our data strongly suggest that CD4^{+}CD26^{nega} cytotoxic T cells are increased in SLE patients while IL-10 production through CD26-dependent pathway might be dysregulated.

W51-6

Association of *HLA-G* polymorphisms with systemic lupus erythematosus

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Conflict of interest: None

[Background] HLA-G, a non-classical HLA class I, plays a role in regulation of immune responses. Recent studies suggested possible involvement of HLA-G in autoimmune diseases. In systemic lupus erythematosus (SLE), association of *HLA-G* 3' untranslated region (UTR) polymorphisms, 14bp indel (rs371194629) and a SNP rs1063320, with susceptibility to SLE has been examined in several populations with conflicting results. In this study, we investigated whether *HLA-G* polymorphisms are associated with SLE in a Japanese population. [Method] 14bp indel and rs1063320 were tested for their association with SLE in 843 SLE patients and 778 healthy controls by a case-control study. [Result] 14bp ins was increased in SLE (dominant model: P=0.022, odds ratio [OR] 1.26). The association was prominent in early-onset SLE (age of onset <20 years) (allele model: <20 vs. control, P=0.0048, OR 1.47, <20 vs. ≥20, P=0.035, OR 1.34). With respect to rs1063320, G allele was increased in SLE with anti-Sm (anti-Sm positive vs control, P=0.0056, OR 1.87) and anti-RNP antibodies (anti-RNP positive vs control, P=0.011, OR 1.79) under the recessive model, although no significant association with overall SLE was detected. [Conclusion] These observations suggested association of *HLA-G* with SLE susceptibility.

W52-1

Discordance in global assessments between patient and evaluator in patients with rheumatoid arthritis associations with anxiety and depression: cross-sectional analysis in a large observational cohort in Japan

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Conflict of interest: None

[Objectives] To clarify the factors affected the discordance between the patient global assessment (PGA) and evaluator global assessment (EGA), we investigated the patients with rheumatoid arthritis (RA) in Ninja database. [Methods] We analyzed RA patients who completed the Hospital Anxiety and Depression Scale (HADS). To predict the discrepancy between the PGA and EGA, univariate and multivariate models were used to evaluate the effect of clinical parameters including swollen joint count on 28-joint assessment (SJC), tender joint count on 28-joint assessment (TJC), Steinbrocker's clinical stage and class, HAQ-DI, ESR, the presence / absence of concomitant drugs (corticosteroid, MTX and biological DMARD). [Results] Data from 7,680 patients were included in this study. Increased HAQ-DI, TJC and HADS score (anxiety and depression) led to a discrepancy toward worse PGA, while increased numbers of SJC and elevated ESR led to a discrepancy toward worse EGA. [Conclusions] Our data indicated that psychological distress as well as HAQ-DI and TJC showed more discrepancy between PGA and EGA, which led to worse PGA.

W52-2

Clinical characteristics of elderly onset of rheumatoid arthritis over 80 years old in *NinJa* 2014 database

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Conflict of interest: None

【Objectives】The onset age of rheumatoid arthritis (RA) became elder, recently. We elucidated the characteristics of elderly onset of RA over 80 years old in *NinJa* 2014. 【Methods】15023 of the RA patients were registered in *NinJa* 2014. The patients were grouped for every 5 years in the onset age of RA, to compare between each group. 【Results】 The number of patients in groups of the onset age from 65 to 69 (Group 65-69) was 1325, 916 in Group 70-74, 538 in Group 75-79, 189 in Group 80-84, and 56 in Group 85-90. The ratio of Stage I in Steinbrcker stage classification was 30.4% in Group 65-69, 30.0% in Group 70-74, 40.0% in Group 75-79, 36.4% in Group 80-84, and 28.0% in Group 85-90. Each group was divided by disease duration, and one group was within 2 years, and the other was from 2 years to less than 5 years. The ratio of Stage I in each group were 64.8% and 49.7% in Group 75-79, 65.8% and 24.7% in Group 80-84, and 40.0% and 0% in Group 85-90, respectively. Glucocorticoid was more often medicated, and MTX and b-DMARDs were less done to Group 80-84 and Group 85-90 than to the others. The average of mHAQ and DAS28-ESR were higher in these two groups. 【Conclusion】 These results showed possibly that the destruction of bone progressed more rapidly in elder onset RA over 80 years.

W52-3

The dietary habit of RA patients and its clinical significance

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Conflict of interest: None

【Object】There has been several reports that food intake influences the pathogenesis of RA. The study of the dietary habit in RA patients is essential in order to clarify the clinical impact of food intake on disease activity. 【Methods】In KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance) cohort, we took a survey of dietary habit in 2015. The relation between dietary habit and disease status was examined. We compared the result of KURAMA cohort with that of Nagahama cohort (healthy people). 【Results】KURAMA cohort included 294 RA patients (mean age 63 years old, female:male 4:1, mean disease duration 11 years, mean DAS28-ESR 2.7). In KURAMA cohort, the intake frequency of vegetables had statistically significant negative correlation with DAS28-CRP, SDAI, mHAQ, patient VAS, and MMP-3. The intake frequency of frozen foods had positive correlation with SDAI, ESR, doctor VAS, and MMP-3. In comparison between KURAMA and Nagahama cohort, RA patients ate milk, fruits, sweets and ham more frequently than healthy people, and miso soup and tsukemono less frequently. 【Conclusions】There appeared to be correlations between disease activity and the intake frequency of vegetables or frozen foods. The eating habit partially differs between RA patients and healthy people.

W52-4

Early arthritis cohort study for prediction of rheumatoid arthritis in healthy islanders

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Conflict of interest: None

Background: It is important to diagnose early for early RA. Aim: We have attempted screening healthy population for early arthritis to measure ACPA in serum. Methods: Since 2014, we have tried to screen healthy islanders for RA in "A City", Nagasaki Prefecture. Screening for the early RA, ACPA measuring, questionnaires about arthralgia with fingers/wrists, family history with rheumatic diseases were done, 2 out of 3 were defined the high-risk subjects for RA. High-risk subjects were recommended to visit the rheumatologist in "A City" for further exams. After 2015, only ACPA positive subjects were included in high-risk group. Results: We had obtained informed consents from 2252 subjects, % female was 64.3 %, range of age was 29 - 93y.o., and ACPA positivity was 1.9 %. Fifty-eight subjects were required for further exams. Only 26 subjects (44.0 %) visited the rheumatologist in "A city", and final diagnoses

were as 6 RA, 6 UA, 6 OA, 2 SpA, 7 others. There were 16 subjects with both of ACPA positive and finger/wrist arthralgia, only 10 subjects done further exams, final diagnoses were 4 RA, 5 UA, 1 SpA. Current and past smoking rate was 31.0 %. Conclusions: ACPA positivity was 1.9 % in healthy islanders. Long-term follow-up is necessary to clarify the course of early arthritis.

W52-5

The clinical roles of anti-SS-A autoantibody and rheumatoid factor in systemic sclerosis

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Conflict of interest: None

[Objectives] To clarify the clinical roles of anti-SS-A antibody and rheumatoid factor (RF) in systemic sclerosis (SSc). [Methods] SSc patients who were registered in Y-CURD, the integrated database of medical records of patients at our department and its affiliated hospitals, were divided into groups on the basis of anti-SS-A and/or RF positivity. [Results] Among 485 patients with SSc registered in Y-CURD, 101 were anti-SS-A-positive and 272 were anti-SS-A-negative, while 112 were unknown. Eighty-one were RF-positive and 147 were RF-negative. Both the anti-SS-A-positive group and RF-positive group showed higher frequency of comorbid rheumatoid arthritis (RA) as compared to the negative groups. After the patients with comorbid RA were excluded, anti-SS-A antibody was significantly associated with low age of onset and high frequency of sicca syndrome. RF was significantly related to low 10-year survival rate, high frequencies of sicca syndrome and widespread scleroderma. The group with both anti-SS-A antibody and RF and the group with solo anti-SS-A antibody showed higher frequency of reflux esophagitis and pulmonary fibrosis, respectively. [Conclusion] To categorize SSc on the basis of anti-SS-A and RF may be effective in prediction of appearance of symptoms and prognosis.

W52-6

A study of pustulotic arthro-osteitis (PAO) among almoplantar pustulosis(PPP)

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Conflict of interest: None

(Objectives) Our study's aim was to evaluate PAO prevalence and characteristics in PPP patients in our hospital. (Methods) An observational study was conducted in Nissay Hospital, Osaka, Japan.From Nov.2011 to May 2015, eightytwo consecutive PPP patients were evaluated by a rheumatologist. Laboratory and radiological tests were performed. Demographic and clinical data were collected. (Results)There were thirty-three cases (40.2%) of PAO among 82 cases of PPP. The study included PAO patients, age 58.0±10.7, PAO presenting age 52.7±11.4, gender 5 males,28 females, BMI 23.4±2.6. Smoking rates was 69.0%. 64%(16/25cases: 8 cases Uninspected) patients had a chronic tonsillitis. The mean values of laboratory tests as follows: Rheumatoid factor 3.5±3.9mg/dl (all negative), ACPA 0.6U/ml (all negative), ASO 57.1±65.0IU/ml, CRP 0.44±0.62 mg/dl, MMP-3 33.5±14.8 ng/ml. Clinical assessments were DAS28 (CRP4) 2.65±0.59, VAS (patient pain) 52.2±16.9mm, BASDAI 5.69±1.97, mHAQ 0.38±0.19. Treatment drugs were sulfasalazine (13cases), minocycline (14cases), NSAIDs (21cases), biotin (5cases),bisphosphonates (4cases). (Conclusions) PAO was identified in 40.2% of patients with PPP. Chronic tonsillitis was found in half of the PAO

W53-1

Safety and effectiveness of adalimumab in Japanese ankylosing spondylitis (AS) patients: intermediate results of all-case postmarketing surveillance

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Conflict of interest: None

Objective: To investigate adalimumab (ADA) safety and efficacy in ankylosing spondylitis (AS) by interim analysis (IA) of (all-case) special drug use surveillance. **Methods:** Safety and efficacy data were tabulated for 131 of all ADA-treated AS patients (Oct 2010 - Mar 2013). IA included all patients with inadequately controlled AS, observed from start of 24-week ADA treatment. Evaluated items were onset of adverse events and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). **Results:** Of the 127 patients in the safety analysis, adverse drug reactions (ADR) occurred in 35 (27.6%) and serious ADR in 5 (3.9%). Main ADR (>1.5%) were infectious/parasitic and gastrointestinal. Noted items were non-serious infectious disease in 10 (7.9%) and serious malignancy in one (0.8%) patient. We assessed BASDAI 50 response rate in all patients in the efficacy analysis at weeks 12 (29/58, 50%) and 24 (25/50, 50%), and in new patients at weeks 12 (23/49, 46.9%) and 24 (19/41, 46.3%), with significant ($p<0.01$) change from ADA treatment start. **Conclusion:** We saw no safety trends suggesting deviation from overseas safety profiles. For efficacy, there was a significant ($p<0.01$) change in BASDAI 50 response rate from treatment start to weeks 12 and 24.

W53-2

Influence of previous biological treatment on treatment outcome of certolizumab pegol

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Conflict of interest: None

[Objectives] The present study was undertaken to investigate the influence of previous biological treatment on treatment outcome of certolizumab pegol (CZP) in RA patients. [Methods] This study included 80 RA patients treated with CZP whose clinical data could be followed for 52 weeks in Tsurumai Biologics Communication Registry. DAS28-ESR, SDAI and continuation rate after 52 weeks were compared between biological naïve group (n=52) and switch group (n=28), and in switch group, between previous only TNF antagonists group (n=16) and previous non-TNF antagonists group (n=12). [Results] In background, MTX combination rate was significantly higher in naive group. (84.6% vs 53.6%, $p<0.05$) Both DAS28-ESR and SDAI were significantly lower in naive group from the fourth week on. The continuation rate was significantly higher in naive group. (78.8% vs 46.4%, log-rank test=0.001) In switch group, the continuation rate was significantly higher in only TNF group than non-TNF group. (62.5% vs 25%, log-rank test=0.032) [Conclusions] Biological naïve patients have good treatment outcome of CZP. In biological switch goroup, CZP has more efficacy in patients who were previously treated with only TNF antagonists than patients previously treated

with non-TNF antagonists.

W53-3

Clinical efficacy of certolizumab pegol therapy in patients with active rheumatoid arthritis ~A MULTICENTER STUDY~

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Conflict of interest: None

[Objectives] To evaluate the clinical efficacy of Certolizumab pegol (CZP) in patients with RA. [Methods] Patients with a diagnosis of RA according to the 2010 ACR/EULAR criteria who had been prescribed CZP from TBCR between April 2013 and October 2014 were enrolled. The final study cohort of 80 patients. We reviewed the methods about the improvement of DAS-ESR and the rate of remission patients at Week52 by LOCF method. [Results] The group of patients included 15 males and 65 females. The mean age was 60.1±14.2 years old; the disease duration was 9.7±9.3 years and the patients of receiving methotrexate was 59 cases (74%). Clinical findings related to RA were as follows: mean tender and swollen joint count, 5.7±4.9 and 5.4±4.2; patient's and physician's global assessment of disease activity, 51.7±26.5 mm and 44.7±23.2 mm; CRP, 1.9±2.2 mg/dL; ESR, 48.9±34.0 mm/h. The DAS-ESR improved from 5.01±1.31 at baseline to 3.70±1.35, 3.47±1.43, 3.47±1.46 and 3.41±1.45 at Week 4, 12, 24 and 52 (all $p<0.001$) significantly. At Week 4, 12, 24 and 52 the rate of patients who achieved remission were each 22.7%, 28.9%, 30.0% and 31.3% in DAS-ESR criteria. [Conclusion] This study suggested that the new TNF-antagonist therapy of CZP was effective in patients with active RA.

W53-4

Tendency to choose TNF inhibitors in biologic agent therapy of rheumatoid arthritis from Tsurumai biologic communication registry

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Conflict of interest: None

[Object]We investigated the tendency to choose TNF inhibitors from patients' baseline characteristics using TBCR. [Methods]There were 289 cases who started TNF inhibitors from 2012.The median age [Q1, Q3] was 59 years [46, 68]. RA duration was 4 years [1, 11]. MTX dose was 8mg [6, 12]. DAS28 (CRP) was 4.1 [3.2, 4.9]. We compared the proportion of TNF inhibitors between the group under Q1 and above Q1 or between the group under Q3 and above Q3.[Results] With regard to age, the proportion of ETN and ADA in the group under 46years was significantly higher than in the group above 46years. With regard to RA duration, the proportion of ADA and ETN in the group under 1year was higher and that of GOL in the group above 11years was higher. With regard to MTX dose, the proportion of ETN and GOL in the group under 6mg was higher and that of ADA in the group above 12mg was higher. With regard to DAS28, the proportion of ETN and ADA in the group under 3.2 was higher.[Conclusions] ETN and ADA were chosen for patients who had younger age, shorter RA duration and lower disease activity. While ETN was chosen for patients who had lower MTX dose, ADA was chosen for those of higher MTX dose. GOL was chosen for patients who had longer RA duration and lower MTX dose.

W53-5

Efficacy of Infliximab for suppressing radiographic progression of cervical lesions in patients with rheumatoid arthritis comparison with methotrexate therapy ; two years of follow-up ~a Multicenter Registry Study ~

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Conflict of interest: None

[Objectives] To evaluate the efficacy of Infliximab (IFX) for suppressing the radiographic progression of RA cervical lesions comparison with methotrexate (MTX) for 2 years. [Methods] We used IFX and MTX for treating each 88 and 40 Japanese patients with active RA for at least 2 years. For evaluation of cervical lesions, ADI, SAC, and the Ranawat value were measured by plain lateral radiographs in the flexion position, at initiation and Year 1,2. [Results] In the patients receiving IFX (n=88) and MTX (n = 40), the mean age was 53.9±12.9 vs 62.5±10.7 years old ($p<0.001$); disease duration was 10.7±9.2 vs 9.3±10.0 years ($p=0.127$); the mean dose of MTX was 7.8±2.1 vs 7.3±2.4mg/w ($p=0.414$). The respective changes in cervical lesion parameters after 1 year were as follows: ADI: 0.22±0.44mm vs 0.25±0.44mm ($p=0.591$); SAC: -0.16±0.40mm vs -0.18±0.39mm ($p=0.716$) and Ranawat value: -0.15±0.36mm vs -0.13±0.34mm ($p=0.733$). The respective changes in cervical lesion parameters after 2 years were as follows: ADI: 0.35±0.59mm vs 0.53±0.72mm ($p=0.193$); SAC: -0.27±0.61mm vs -0.48±0.64mm ($p=0.038$) and Ranawat value: -0.26±0.47mm vs -0.35±0.58mm ($p=0.486$). [Conclusion] This study suggested that IFX treatment can be used to suppress the progression of RA cervical lesions.

W53-6

Short- and long-term effectiveness of certolizumab pegol

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Conflict of interest: None

Objective: To evaluate the short- and long-term effectiveness of certolizumab pegol (CZP). **Methods:** We retrospectively evaluated 12 patients treated with CZP between July 2013 and May 2015 at our hospital. Short-term effectiveness was assessed by the maximum improvement in disease. Long-term effectiveness was assessed by both the level of disease at the latest visit during CZP treatment and the persistence rate. The clinical power of CZP was also estimated from pre- and post-treatment with CZP. **Results**: Eight patients (67%) achieved clinical remission (CR) with seven of these patients (88%) achieving CR within two months after beginning treatment. Six of the patients (50%) maintained CR at the latest visit; 9 of the 12 patients (75%) continued CZP treatment. Of the six patients (infliximab, 4; golimumab, 2) who switched to CZP treatment, three (50%) and two patients (33%) achieved CR as short- and long-term outcomes, respectively. For the patients that switched to CZP from other biologics (golimumab, 1; adalimumab, 1; tocilizumab, 1), one patient previously treated with tocilizumab (IL-6 receptor antibody) achieved CR. **Conclusion**: CZP treatment provided superior short- and long-term outcomes. We propose that the approved dosage regimen of CZP is effective in neutralizing TNF-α.

W54-1

The clinical efficacy of Tofacitinib in patients with rheumatoid arthritis who exposed biological era or not

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Conflict of interest: None

(Subject) 38 RA patients who received TOFACITINIB (TOF) treatment for at least 24weeks in the facilites of TBCR., average age 58.5 ± 9.7 years, disease duration 14.1 ± 10. 0 years. Efficacy was evaluated by DAS28 CRP at the start point and 24 weeks thereafter. The efficacy (remission rate) and outcome across the bio naive group of eight patients, one biologic agent use group of 12 patients and two or more biologic agents use group of 18 patients was compared. Reason for discontinuation was noted in patients who stopped treatment. (Result) At start of treatment; HDA26 cases, MDA 5 cases, LDA 2 cases and 4 cases of remission. At 24weeks; HDA 5cases, MDA 6 cases, LDA 4 cases, remission 15 cases, 3 discontinuations due to adverse events, 3 discontinuations due to lack of response, one case of change of hospital and one case of missing data. Across the groups, at 24weeks; 7 of the 8 patients in the naive group achieved remission, with no discontinuation; 4 of the 12 patients in one biologic agent use group achieved remission, one discontinuation due to AE, and two discontinuations due to lack of response; 3 of the 18 patients in the two or more biologic agent use group achieved remission, two discontinuations due to AE, and one discontinuation due to lack of response.

W54-2

A rheumatoid arthritis patient who died due to Listeria meningitis during tofacitinib treatment

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Conflict of interest: None

【Background】 Tofacitinib (TOF) is a tsDMARD which blocks Janus kinese family and cytokine signals. Serious adverse events, especially serious infection, are needed to be paid attention to during TOF treatment in RA patients. 【Case】 The case is 71 years old woman. Her past history was tricuspid valve regurgitation. Onset of RA was in 1996. We had treated by several csDMARDs. In 2006, we started Methotrexate (MTX) 6mg/week. However, in 2010, we added Infliximab to MTX because of ineffectiveness. Nevertheless, due to ineffectiveness and adverse drug reactions, we changed to Etanercept and MTX. The effect was not enough, so we changed to TOF and MTX 12mg/week in October 2014. After changing, symptoms improved. In July 2015, she came to ER due to fever and disturbance of consciousness. Meningitis was suspected. Her consciousness was JCS II-10. Listeria monocytogenes grew in spinal fluid and we administered ABPC. The 2nd day, her consciousness became JCS III-300, and the 9th day, she died. 【Discussion】 This case satisfied Japanese PMS guideline of TOF. In observation, WBC didn't decrease. Nevertheless, she suddenly appeared disturbance of consciousness, and died due to Listeria meningitis

W54-3

Baricitinib, Methotrexate, or Baricitinib Plus Methotrexate in Patients with Early Rheumatoid Arthritis Who Had Received No or Limited Treatment with DMARDs: Results of a Global Randomized, Double-blind Phase 3 Study Including Japanese Patients

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Conflict of interest: Yes

Objective: To evaluate efficacy/safety of baricitinib (bari) in DMARD-naïve patients (pts) with active RA. **Method:**588 pts (Japan:104) with no or limited exposure to DMARDs were randomized to methotrexate (MTX), bari 4 mg QD or bari 4 mg QD+MTX. **Result:** ACR20, 50 and 70 responses at Wk 24 (NRI) were achieved by 61.9%, 43.3%, 21.4% of pts with MTX (Japan:69.4%, 55.6%, 30.6%), 76.7%, 59.7%, 42.1% with bari (Japan:72.4%, 55.2%, 51.7%), and 78.1%, 63.3%, 39.5% with bari+MTX (Japan:71.8%, 53.8%, 48.7%), respectively (each p≤.01 vs. MTX for overall), with more rapid onset in bari and bari+MTX than MTX. Compared to MTX, improvements in signs symptoms, physical function, and PROs were significantly larger with bari or bari+MTX. At Wks 24&52, compared to MTX, progression of radiographic structural joint damage was significantly reduced with bari+MTX and numerically lower with bari. During Wk 52, rates of TEAEs in the MTX, bari, and bari+MTX groups were 71.9%, 71.1%, 77.7% overall, and 83.3%, 96.6%, 92.3% for Japan, respectively. Herpes zoster was seen in all groups; most occurred in Japan. **Conclusion:**Compared to MTX in DMARD-naive pts with RA, once daily oral baricitinib used alone or in combination with MTX improved disease activity, physical function, PROs, and radiographic progression.

W54-4

Baricitinib Versus Placebo or Adalimumab in Patients with Active Rheumatoid Arthritis (RA) and an Inadequate Response to Background Methotrexate Therapy: Results of a Global Randomized, Double-blind, Placebo- and Active-Controlled, Phase 3 Study Including Japanese Patients

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Conflict of interest: Yes

Objective: To evaluate efficacy/safety of baricitinib (bari) in RA patients with an inadequate response to methotrexate (MTX). **Method:**1305 pts (Japan:249) with active RA despite stable background MTX were randomized to placebo (PBO), bari 4 mg QD or adalimumab (ADA) 40 mg biweekly. **Result:**For the primary endpoint, ACR20 response at Wk 12 was achieved by 40.2% of patient with PBO (Japan:34.4%) and 69.6% with bari (Japan:66.7%) (p≤.001). At Wk 12, statistically significant improvements in disease activity measurements including ACR20/50/70 and PROs were seen for bari vs. PBO, many as early as Wk 1. Compared to ADA, bari was superior in ACR20 and DAS28-hsCRP improvements at Wk 12. At Wk 24, a statistically significant decrease in progression of mTSS was seen for bari vs PBO. During 24 Wks, rates of TEAEs were higher for bari (70.8%[Japan:84.9%]) and ADA (67.0%[Japan:79.4%]) compared to PBO (60.0%[Japan:68.8%]), SAE rates were similar for bari and lower for ADA compared to PBO. During 52 Wks,four deaths occurred prior to rescue/switch, two in bari and one each in ADA and PBO. **Conclusion:**In pts with active RA despite background MTX, once-daily oral bari improved disease activity compared to PBO and to ADA, and inhibited radiographic progression, with acceptable safety and tolerability.

W54-5

Comparative Investigation into Pharmacokinetic Equivalency between Biosimilar NI-071 and Remicade®, and Efficacy and Safety

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Conflict of interest: Yes

[Objectives] To investigate pharmacokinetic (PK) equivalency between Biosimilar NI-071 and Remicade® with healthy subjects. Additionally, to investigate efficacy and safety in RA patients. [Methods] 96 healthy subjects were administered a single dose of 3 mg/kg of NI-071 (hereafter, N group) or Remicade®(hereafter, R group), and AUC_t(0-8 weeks) for PK equivalency was verified. 242 RA patients were given repeated doses, and comparative investigation of their efficacy and safety was performed. [Results] In the pharmacokinetic testing, the 90% CI for the ratio of AUC_t of the N group versus the R group was within log (0.80) to log (1.25), and equivalency was verified. Furthermore, in Phase 3 clinical testing on RA patients, average values for DAS28-ESR variations at the 14th week from the 0 week were -2.13 for N group and -2.16 for R group, and the 95% CI of the difference is -0.280 to 0.328, and equivalency in efficacy was verified. In comparisons of efficacy and safety until the 54th week, the both groups were similar. [Conclusion] The Biosimilar NI-071 was verified to have equivalent PK to Remicade®, and even in RA patients, it was shown to possess efficacy and safety equivalency/same quality.

W54-6

The effects of BCAA supplementation on glucocorticoid (GC)-induced myopathy in patients with rheumatic disorders

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Conflict of interest: None

To test the effects of daily bolus supplementation of BCAA (12 g/d, 3 months) on GC-induced myopathy in patients with rheumatic disorders, we conducted a Phase I-II, open label, randomized, and parallel group clinical trial. Disease activities of the patients were well controlled and their GC dose was significantly reduced with or without BCAA. Bioelectrical Impedance Analysis (BIA) for segmental skeletal muscle mass and computed tomography (CT) analyses for cross sectional area of mid-thigh muscle reveled that, in both BCAA (-) and (+) groups, their limb muscle mass was significantly increased during this trial. BIA and muscle strength and functional tests revealed that BCAA supplementation significantly improved whole-body skeletal muscle mass, and skeletal muscle strength and function. Moreover, CT analysis unveiled that the effects of BCAA supplementation on recovering skeletal muscle mass was prominent in particular muscles. This trial is the first report that BCAA supplementation was safe, did not exacerbate disease activity, and could, at least in part, improve skeletal muscle mass, strength, and function in patients with rheumatic disorders treated with GC.

W55-1

Association between HTLV-1 infection and response to tumor necrosis factor inhibitor treatment in Rheumatoid arthritis: results from the Multicenter study

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Conflict of interest: None

Background/Purpose To investigate the association between HTLV-1 infection and response to tumor necrosis factor inhibitor treatment in Rheumatoid arthritis in an Endemic Area of HTLV-1. Methods Between November 2003 and December 2013, consecutive Bio-naïve rheumatoid arthritis patients were recruited from the Nagasaki university hospital, the Miyazaki university hospital and their affiliated hospitals retrospectively. Clinical disease activity as disease activity score (DAS) 28-ESR was examined at baseline and after introduction of the anti-TNF therapy at 6 months, and compared the differences with and without antibodies to HTLV-I. Result The study enrolled 564 RA patients with data available for DAS28-ESR evaluation. There were 52 cases of anti-HTLV-1 antibody positive, the prevalence was 9.2%. DAS28-ESR with and without anti-HTLV-1 antibody (5.18±1.37, 5.20±1.34 at baseline) were significantly decreased after 6 months of treatment (3.78±1.46, $p<0.01$, 3.38±1.32, $p<0.01$). The changes of (Δ values) DAS28-ESR was significantly lower in patients with anti-HTLV-1 antibody than without that. (1.41±1.40 versus 1.82±1.20, $p<0.01$). Conclusion The presence of antibodies to HTLV-I in RA patients might be associated with poor response to tumor necrosis factor inhibitor treatment.

W55-2

Prospective observational study on clinical usefulness of anti-hepatitis B virus (HBV) prophylaxis in hepatitis B surface (HBs) antigen-positive patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To investigate the prevalence of reactivation of hepatitis B virus with the immunosuppressive therapy for the patients with rheumatic diseases, we started multicenter, observational, prospective study by fifteen hospitals founded by Japanese Red Cross. [Methods] Patients with immunosuppressive therapy for rheumatic diseases showing positive HBs antigen (HBsAg) patients, or negative HBsAg and positive anti-HBs or anti-HBc antibody were registered. We extracted 47 HBsAg-positive RA patients who had successfully been followed-up for a year and performed a comparative study on background characteristics, liver function, and RA treatment. [Results] The number of subjects treated with antiviral prophylaxis increased from 32 at initial enrollment to 34 at follow-up. No significant changes in findings on liver function tests were noted between enrollment and follow-up in any subjects, and no clinical hepatitis development was observed in the 13 subjects who had not been using antiviral prophylaxis in the past year. [Conclusion] No clinical hepatitis development was seen in any HBsAg-positive RA patients during one-year monitoring. In the future, we hope to establish a method of identifying the risk of developing hepatitis and develop appropriate preventive measures.

W55-3

Risk factors for Pneumocystis jirovecii Pneumonia (PCP) in patients with rheumatoid arthritis (RA): A retrospective single center analysis

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Conflict of interest: None

[Background] Along with the use of Methotrexate (MTX) and Biologic DMARDs (Bio) for RA treatment, RA-PCP has been reported. We clarify risk factors of RA-PCP, and examine prophylaxis of Sulfamethoxazole/Trimetoprim (ST). [Methods] The 19 cases were diagnosed as RA-PCP. The diagnosis of PCP was performed based on both chest CT findings, and β-DG positive or PCR positive. The 2621 cases of RA patients not developing PCP without prophylaxis were selected as the control. [Result] PCP group showed the higher age (70.26 ± 11.82 vs. 64.22 ± 12.42 years old, $p<0.05$), the higher dosage of prednisolone (6.20 ± 4.06 vs. 2.39 ± 1.99 mg/day, $p<0.01$) or MTX (7.68 ± 3.67 vs. 5.18 ± 4.54 mg/week, $p<0.05$). The number of immunosuppressant was more in PCP group (1.26 ± 0.65 vs. 0.80 ± 0.59, $p<0.01$). By defining the risk score from the odds ratio of the items that were significant in the multivariate analysis (MTX ≧ 6 mg/week: 1 point, PSL ≧ 5 mg/day: 3 points, age ≧ 65 years old: 1 point, immunosuppressive agents ≧ 2: 1 point), the RA-PCP incidence of score with 0-2 points, 3-4 points, ≧ 5points were 0.1%, 2.1%, 5.8%. [Conclusion] Our risk score system might be useful to the prophylaxis for RA-PCP, and the cases with ≧ 5 points of risk score should consider the prophylaxis of ST.

W55-4

Strategy for the prevention of tuberculosis in patients under the treatment by bDMARDS in our department

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Conflict of interest: None

One of the points we should pay attention during the treatment by bDMARDS is prevention of TB. According to the reports in the early era of bDMARDS in which prevention of TB was not done, the OR of TB development was more than 10. We studied whether our strategy for the prevention of TB in patients under the treatment by bDMARDS is appropriate. Subjects were 235 patients with rheumatic diseases who were introduced with bDMARDS for the first time. The mean age was 61.5 years. When more than one of the following standards was found, patients were administrated with 70ophylactic dose of INH. Those standards were, 1. more than70 years of age, 2. TST moderately positive, 3. QFT positive or intermediate, 4. a history of TB, and 5. findings suggestive of old TB on CXR or CT. Prophylaxis by INH was done in 47%. In these patients, positive ratio of the standards listed above were 32%, 19%, 10%, 3% and 17%, respectively. The total duration of prophylaxis was 815 years. Using the statistics of Japan of the incidence of TB stratified by age, and assuming that the TB incidence is 10 times higher in bD-MASRDS users, development of 2.2 patients with TB was prospected, but no actual TB developments. We conclude that our strategy for the prevention of TB is so far working well.

W55-5

A prospective study of the inuence of biologic agents on the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with RA by *NinJa* cohort data for 12years

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Conflict of interest: None

[Objectives] To evaluate the incidence of biologic agents on the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with rheumatoid arthritis (RA) prospectively. [Methods] We calculated the standardized incidence ratio (SIR) of TB from the clinical data on National Database of Rheumatic Disease by iR-net in Japan (*NinJa*) prospectively from 45 facilities for 12 years. [Results] Among 95,421 RA patients registered from 2003 to 2014, 65 patients developed TB and the SIR of TB was 2.97 (95%CI:2.25-3.39). 9 patients (13.8%) were treated with biologic agents. The SIR of TB in RA patients treated with biologic agents was 2.76 (0.96-4.57), and the SIR of TB in patients treated without biologic agents was 3.05 (2.25-3.85).

W55-6

Clinical features of RA patients with confirmed/suspected nontuberculosis mycobacterium (NTM) under biologics

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Conflict of interest: None

Purpose: To clarify clinical features of RA patients (Pts) with confirmed/suspected NTM infection under biologics. **Methods:** Subjects were 390 RA cases with biologics. Pts were devided into 3 groups; 1) confirmed NTM; positive for both microbiological examination and chest abnormalities suggesting NTM, 2) suspected NTM:positive for the chest abnormalities,but not for microbiological tests, and 3) non-NTM; negative for the chest abnormalities. **Results**: At the starting biologics, confirmed-, suspected- and non-NTM Pts were 25, 3 and 362, respectively. Non-NTM Pts did not develop chest abnormalities suggesting NTM during biologcs. In the suspected NTM, 14 pts showed exacerbation of chest abnormalities and NTM was detected in 5. Total 8 Pts had NTM; 3 diagnosed before and 5 during biologics, and 7 of them started/ continued biologics. Five of the 7 patients were also treated with anti-NTM drugs. 6 Pts reciving biologic are in less than low disesase activity of RA without exacerbation of NTM. **Conclusion:** Patients with findings of brobchoectasia and multiple nodules have a high risk for NTM. When exacerbation of these lesions, investigation for NTM should be performed. With combination of anti-NTM therapy and careful watching, biologics can be used safly for RA patients with NTM.

W56-1

Previous history of biologics affects the tofacitinib efficacy in RA patients while previous number of biologics does not

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Conflict of interest: None

[Objectives] Tofacitinib (TOF) has been available for rheumatoid arthritis for more than 2 years. Although JCR guideline describes that we can use TOF in bio-naive patients, we usually use TOF in patients with one or multiple biologics failures. We studied the effect of previous history and number of biologics on TOF efficacy. [Methods] Participants were consecutive 37 RA patients treated with TOF registered in the TB-CR-Plus. We compared the percent decreasing of DAS28-CRP from baseline at 4, 12, and 24 weeks and TOF drug retention rate between bionaïve (N=8) and bio-switch (N=29) group, and also within bio-switch group by previous number of biologics (1, 2, and more than 3). [Results] The bio-naïve group demonstrated significantly greater percent decreasing of DAS28-CRP at all time points (e.g. -54.6 vs -27.2% at 24 weeks, $p<0.05$). There was no significant difference in drug retention rate between bio-naïve and switch. We found no difference in percent change of DAS28 or drug retention rate within bio-switch group. [Conclusion] The previous history of biologics treatment negatively affects the clinical efficacy of TOF but the previous number of biologics does not. We can

choose treatment option of using TOF both in the bio-naive and the multiple bio-failure patients.

W56-2

Risk Factors for Herpes Zoster in Japanese Rheumatoid Arthritis Patients treated with Tofacitinib; results from the global clinical development program

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Conflict of interest: Yes

Object: Assess the risk factors for herpes zoster (HZ) in Japanese patients (pts) with rheumatoid arthritis (RA). **Methods:** Analysis involved Japanese pts from the tofacitinib RA global clinical program. Crude incidence rates (IRs; pt with events/100 pt-years [95% CI]) for HZ were calculated. Univariate and multivariable analyses were used to evaluate potential risk factors for HZ. **Results:** 556 Japanese RA pts were enrolled in the trials (1705 pt-yrs' exposure). 120 tofacitinib-treated pts experienced 138 HZ events; overall IR was 8.01 (6.64, 9.57). In the crude analysis, numerically higher IRs (overlapping CIs), were observed for HZ in tofacitinib 10mg BID group (IR 9.94 [6.66, 14.28]) compared to 5mg BID group (IR 7.54[6.07, 9.26]). MTX use/dose, and glucocorticoid (GC) use/dose at baseline were not identified by univariate analyses as risk factors for HZ. Multivariable analysis identified age as a risk factor for HZ and pts with baseline GC >5mg/day may have higher HZ risk compared with those with no GCs at baseline. **Conclusion:** In this subpopulation, age and use of GC may be associated with HZ risk. This somewhat contrasts with global analysis where background DMARD use and GC may have a greater impact on HZ risk. Limitations include sample size and possible confounding factors.

W56-3

Interim Safety and Effectiveness Report from Postmarketing Surveillance of Tofacitinib in Japanese Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

Objectives: Postmarketing surveillance (PMS) has been conducted evaluating the safety and effectiveness of tofacitinib in Japan, following all patients (pts) with rheumatoid arthritis (RA) for 3 years. **Methods:** Interim analysis of pts from an ongoing study who were followed for 6 months (Sep 4, 2015 data cut). Adverse events (AEs) were coded using the MedDRA/J. **Results:** Pts background at baseline were as follows: female 79.1%, mean age 61.0 years, mean disease duration 11.7 years. Safety analysis followed 888 pts in the tofacitinib arm of which 649 pts (73.1%) completed the 6 month observation period. At least one AE was observed for 295 pts (33.2%). Most frequent was Herpes Zoster (HZ) (n=36, 4.1%). Serious AEs occurred in 75 pts (8.4%); most frequent were HZ (n=7, 0.8%), pneumonia (n=5, 0.6%) and interstitial lung disease (n=5, 0.6%). Infections (n=114, 12.8%) were serious in 37 pts (4.2%). Five cases (0.6%) of malignancy including lymphoproliferative disorder, uterine cancer, breast cancer, ovarian cancer and bladder cancer were reported. There were four deaths (0.5%). Latest available data will be presented at congress. **Conclusion:** PMS has not revealed any new or unexpected safety signals compared with the tofacitinib RA clinical development program.

W56-4

Malignancy in Tofacitinib-Treated Japanese Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). This analysis evaluated age- and sex- standardized incidence rates (ASRs) for malignancy (excluding NMSC) in Japanese RA (JRA) pts in the tofacitinib clinical program. **Methods:** Malignancy data were pooled from 2 Phase (P) 2, 1 P3 and 1 open-label long-term extension RA studies conducted in Japan (April 2014 data cut). Cumulative ASRs were calculated (6-month intervals). Crude IRs and SIR were calculated for tofacitinib clinical trials in Japan and Japan Medical Data Center (JMDC) RA sub-populations. General population data (Japan 2010) were used to calculate ASRs. **Results:** Of 556 tofacitinib treated JRA pts (1705 pt-yrs of exposure); 22 pts had malignancies. Overall, post tofacitinib exposure in JRA pts, cumulative ASR (95%CI) for malignancy (excluding NMSC) was 1.34 (0.46-2.21) patients with events/100 pt-yrs of exposure, and the SIR (95%CI) was 2.13 (1.33-3.22) which overlapped with the SIRs for several JMDC cohorts. **Conclusion:** SIRs for malignancies (excluding NMSC) in tofacitinib-treated JRA patients were comparable with JMDC RA sub-populations. Ongoing post-marketing surveillance will further evaluate malignancy among Japanese RA patients treated with tofacitinib.

W56-5

Early effect of tofacitinib on circulating RANKL and osteoprotegerin in rheumatoid arthritis

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Conflict of interest: None

Objectives: The selective Janus kinase (JAK) inhibitor tofacitinib has demonstrated efficacy for rheumatoid arthritis (RA), the mechanisms by which it influences structural joint damage are poorly understood. In this study, we investigated the effect of tofacitinib on serum soluble RANKL (sRANKL) and OPG in patients with RA. **Methods:** 14 patients with active RA who inadequate response to DMARDs were started on treatment with tofacitinib. Next, circulating levels of sRANKL and OPG, together with a parameter of inflammation, were examined at baseline, week 2, 4 and 12. **Results:** Base line levels of sRANKL were significantly correlated with the levels of CRP. After tafacitinib treatment, SDAI score, CRP and ESR was decreased significantly from the base line. Average of sRANKL level and sRANKL/OPG ratio at week2, 4 and 12 were decreased significantly from the baseline. On the other hand, average of OPG levels was not change during 12 weeks. Interestingly, the

decrease of the sRANKL level was greater by the patient with the high sRANKL level. **Conclusions:** Our results show that tofacitinib has improved RANKL levels and RANKL/OPG balance immediately in RA. This mechanism might be a control of RANKL induction via JAK pathway inhibition in activated CD4+ T cells and synovial fibroblast.

W56-6

Effectiveness of tofacitinib in clinical practice for RA patients: Results from Tsurumai Biologics Communication Registry plus Sudy (TBCR plus)

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Conflict of interest: Yes

Purpose: To investigate the effectiveness of tofacitinib (TOF) for Japanese RA patients in clinical practice**Patients and Methods:** 44 cases treated with TOF were registered in TBCR plus. We analyzed 29 patients with 24 weeks and more of observation period from initiation of TOF (excluded the patients who were enrolled in clinical trial). The effectiveness of TOF by dose of MTX was explored.**Results:** Median age and disease duration were 63 years and 26months. Proportion of Female, RF or anti-CCP positive were 88.9% and 86.2%. DAS28-CRP was significantly improved from 5.31 to 3.80. Drug retention rate for 24 weeks was 79.3%. There was no significant difference in baseline characteristics by weekly dose of MTX (Low: MTX ≤6mg/w, High: ≥8mg/w). We could not find significant differences in DAS28 and its category at 24 weeks between groups (LDA achievement rate; Low, 20%, High 37.5%). Dug retention rate at 24 weeks was 93.8% in Low group and 61.5% in High group.**Discussion and Conclusion:** We should not apply TOF to patients with safety issues for treatment with MTX. Based on drug retention rate, we selected the patients for treatment with TOF properly. We showed the effectiveness of TOF with low dose or without MTX. Further study should be needed for importance of MTX for TOF.

W57-1

Final report of Iguratimod post-marketing surveillance in patients with rheumatoid arthritis (52 weeks)

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Conflict of interest: Yes

[Objective] To investigate the safety and effectiveness of iguratimod (IGU), a post-marketing surveillance (52 weeks) was conducted in all patients with rheumatoid arthritis (RA) who were treated with IGU in Japan. We reported the interim results of this surveillance following up for the first 24weeks in JCR2015. The purpose of this presentation is to report the final results of the surveillance in the RA patients observed for 52 weeks.[Method] Of all patients treated with IGU between September 2012 and April 2013, 2,679 patients were evaluated for safety, and 1,619 patients for effectiveness.[Results] Adverse drug reactions (ADRs) and serious ADRs were reported in 1,020 patients (38.07%) and 122 patients (4.55%), respectively. The most frequent ADR was gastrointestinal disorders, and the most frequent serious ADR was infections. These data were similar to those of the 24 weeks analysis in this study. As for effectiveness, DAS28-4CRP decreased over time from baseline until 52weeks.The remission rate at 52 weeks was high in patients receiving MTX or biologics concomitantly.[Conclusion] No new important ADRs were found even in patients receiving long-term administration of IGU compared with 24 weeks treatment. These data indicated that IGU was effective for up to 52 weeks.

W57-2

Long term efficacy of iguratimod plus methotrexate in active rheumatoid arthritis patients with an inadequate response to high-dose methotorexate

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Conflict of interest: None

【Objectives】We investigated the efficacy of combination therapy with iguratimod (IGU) and high dose-methotrexate (HD-MTX) in active RA patients for 52 weeks. 【Methods】Twenty-three patients with RA who didn't get remission despite treatment with HD-MTX over 10mg/week for 3 months were treated with combination therapy of IGU. Primary endpoint was DAS28 (4/ESR) improvement, DAS28 (4/ESR) remission, and EULAR response at 52 week. 【Results】Patients data (mean±standard deviation) were age 50.0±12.2 years old, disease duration 9.5±6.0 years, stage 2.6±1.2, MTX dosages 12.4±2.1 mg/week, MTX use duration 6.9±3.5 years, etanercept use 22%(n=5), prednisolone use 82%(n=18), and prednisolone dosages 4.8±1.9 mg/day. IGU dosages at 25mg/day was 26%(n=6) and at 50mg/day was 65%(n=17). DAS28 (ESR) was statistically significantly improved at 4.36±0.65 to 2.76±0.79* at 52 week (*$P<0.01$ paired t-test*). High remission rate (0 week: low 9%, moderate 82%, high 9% vs 52 week: remission 48%, low 26%, moderate 26%) and good treatment response (EULAR response: good response 47.5%, moderate response 47.5%, and no response 5%) were achieved. 【Conclusion】Combination therapy with HD-MTX and IGU for long term was good treatment option in active RA with an inadequate response to HD-MTX.

W57-3

The optimal treatment of iguratimod in rheumatoid arthritis patients without concomitant methotrexate

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Conflict of interest: None

[Objectives]In this study, we investigated the efficacy and optimal treatment of iguratimod in RA patients without concomitant MTX.[Methods]Patients treated without MTX and taking iguratimod for longer than 52 weeks were included, from the Nagoya university-affiliated hospital. We retrospectively reviewed the clinical data.[Results]Fifty-eight patients were included in this study. Mean age was 72 years old and mean disease duration was 13.6 years. The reasons for inability to use MTX were adverse events of MTX and pulmonary complication. Mean DAS28-ESR was 5.1±1.2 at baseline, and 4.5±1.6 at 24 weeks ($p<0.05$). According to the logistic regression analysis, the factors which were significantly associated with the achievement of low disease activity (LDA) at 24 weeks were the DAS28-ESR at each time points and disease duration. DAS28-ESR at 12 weeks was most significantly associated with LDA at 24 weeks.[Conclusion]We found that iguratimod therapy is effective for RA patients without concomitant MTX and early clinical response up to 12 weeks after initiating iguratimod therapy without concomitant MTX, can predict the medium-term achievement of LDA in practice.

W57-4

Clinical efficacy of iguratimod therapy in patients with rheumatoid arthritis

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Conflict of interest: None

Objective. The clinical profile of iguratimod (IGU) has not been sufficiently clarified yet. Therefore, we investigated the efficacy of IGU for patients with rheumatoid arthritis (RA). *Methods*. Eighty-five RA patients (69 females) who received IGU were observed in this retrospective study. The mean age was 67 years, and the mean duration of disease was 11 years. As concomitant treatment, 35 patients received methotrexate (MTX: 8.7mg/week), 34 patients used prednisolone (PSL: 3.9mg/day). The improvement and efficacy were evaluated by the disease activity score (DAS) 28 which were monitored at baseline and 24 weeks. We also examined the efficacy of IGU with and without concomitant MTX. *Results*. Gender, disease duration, dose of concomitant PSL, DAS28, and MMP-3 did not significantly differ between patients with and without concomitant MTX at baseline. The mean DAS28 at baseline (4.3) significantly improved to 3.2 at 24 weeks ($p<0.01$). Good and moderate EULAR response observed in 48 cases (56%) at 24 weeks. DAS28 and the changes of DAS28 did not significantly differ between patients with and without concomitant MTX. *Conclusion*. Efficacy of IGU therapy was maintained to 24 weeks in RA patients. Our results suggested the efficacy of IGU in patients treated with MTX and without MTX.

W57-5

Efficacy of iguratimod for treating 133 rheumatoid arthritis (RA) patients

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Conflict of interest: None

Objectives: Iguratimod (IGU) is the newest disease-modifying antirheumatic drug (DMARD) received regulatory approval in 2012. The efficacy of IGU was investigated with 133 RA patients at the authors' hospital. **Methods:** Of the 133 RA patients who had been administered IGU at the authors' hospital since September 2012, the survey covered the 74 patients with whom analysis was possible. These consisted of 69 females and 5 males. The mean age was 59.1 years, and the mean disease duration was 5.2 years. Of the 74 patients, 54 (73%) were concomitantly administered methotrexate, and the mean methotrexate dose was 10.4 mg/week. Using DAS28CRP, the efficacy was evaluated, and the maintenance rate, safety, etc., were investigated. **Results:** Alleviation according to the DAS28CRP was shown from week 4 of IGU administration. At week 12, 55% of patients showed remission or low disease activity; and at week, 24 37% showed remission, and 18% showed low or no disease activity. The maintenance rate for these effects was 77%. **Conclusions:** The development of effects with IGU was at least as favorable as with other DMARDs, and it is an excellent drug with respect to efficacy and maintenance rate. It is expected that it will constitute an effective therapeutic agent for RA in future.

W57-6

Ultrasonographic evaluation of Iguratimod therapy in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the clinical efficacy of Iguratimod (IGU) therapy patients with rheumatoid arthritis (RA) using ultrasonography (US). [Methods] We used IGU treated 51 RA patients more than 24 weeks. We evaluated the improvement of gray scale (GS) and power doppler (PD) score from baseline to week 24. [Results] The patients included 15 males and 36 females. The mean age was 65.4±11.6 years; the mean disease duration was 9.1±11.0 years; and the number of MTX combination, other DMARD excluded combination, IGU monotherapy and Biologics combination were each 30, 9, 8 and 4 cases. Clinical findings related to RA were as follows: tender and swollen joint count, 4.2±2.9 and 3.2±2.2; patient's and physician's global assessment of disease activity, 39.7±23.3 and 39.7±18.9mm; CRP, 1.1±1.3 mg/dL; ESR, 31.4±18.6 mm/h; DAS-ESR, 4.37±0.85; DAS-CRP, 3.80±0.74; CDAI, 15.3±6.4 and SDAI,16.4±6.8. The mean GS score changed from 16.8±12.4 at baseline to 15.7±11.0 ($p=0.158$) and 14.5±9.8 ($p=0.043$) at week12 and 24. The mean PD score changed from 7.9±6.8 at baseline to 6.0±6.1 ($p=0.001$) and 5.3±5.5 ($p=0.006$) at week12 and 24. [Conclusion] The present study provides evidence supporting the IGU therapy improved not only the disease activity not also the inflammatory synovitis.

W58-1

Comparison of MTX-polyglutamates Concentration (MTX-PG) in erythrocytes, Safety and Efficacy in Patients with Rheumadoid Arthritis between single- and split- dosage regimens :SAME study

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Conflict of interest: None

[Background and Objective]Though MTX has been well-known anchor drug for RA, dose regimen varies. The splitting dosage of MTX was frequently prescribed in Japan, however, the difference between splitting and single dose regimens were not fully examined. We conducted a preliminary study to evaluate the safety, efficacy profile and MTX-PG in two groups. [Methods]Thirty-one patients who had been insufficiently controlled by MTX (8 mg/week) were randomly assigned to 2 groups. MTX dose was increased according to single and split-dose regimen respectively. Safety and efficacy parameters were monitored at baseline, 4, 8, 12 and 19 weeks. MTX-PGs were also detected by LC-MS/MS at same interval. [Results]There were no significant differences in the average of age, disease duration, and baseline DAS28-CRP between two groups. The split-dose group showed higher MTX-PG2 and slight lower MTX-PG4 than single-dose. There were no differences in the improvement of DAS28-CRP between two groups and weekly MTX dose. The elevation of AST and ALT was observed only in split-dose group. [Conclusion]Split-dose group showed different distribution and kinetics of MTX-PGs compared with single-dose. The efficacy did not show any difference between them. Liver toxicity was shown only in split-dose group.

W58-2

Factors Related to Non-use of MTX in Patients with RA

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Conflict of interest: None

MTX is administrated as the first line drug. However, MTX is not administrated for substantial part of the RA patients. We tried to extract factors related to non-use of MTX retrospectively, and also did a multiple regression analysis to make a formula to expect the dose of MTX in patients with MTX. Subjects were 434 patients with RA with the mean age of 66 years. The mean body weight was 55 kg, and the mean disease duration was 13.8 years, respectively. The stage and class were 177/129/58/70 and 164/183/69/4, respectively. We incorporated 16 variables to perform discriminant analysis to find factors related to non-use of MTX. The mean DAS28ESR was 4.75 before starting csDMARDS and that at the last observation was 2.83 irrespective of use or non-use of MTX. Discriminant analysis extracted 7 significant variables related to use or non-use of MTX. These were age, class, ILD grade, dose of PSL, use of SSZ and/or bucillamine, DAS28ESR and eGFR. The last 2 variables favor for use of MTX and others favor for non-use of MTX. Multiple regression analysis obtained a formula that predicts the dose of MTX in MTX-users. The significant variables were age, body weight, class, DAS29ESR, eGFR, and ILD grade. We conclude that it is suitable to decide to use or not use MTX.

W58-3

The Boolean4 remission rate and the annual hospitalization number for serious adverse events for high dose MTX monotherapy in Japanese patients with RA by NinJa 2014 cohort

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Conflict of interest: None

(PURPOSE) The purpose of this current study is to review serious adverse event by MTX dose dependent in patients with RA. (Material and Methods) In 15023 Japanese RA patients registered with NinJa2014, 4698patients medicated MTX monotherapy were divided 5 groups by MTX dose once a weekly.; 1-4mg/week n=661, 5-7mg/week n=1114,7.5-9mg/week n=1261, 9-12mg/week n=1353,respectively. We defined hospitalization for various infectious disease (including opportunistic infections), interstitial pulmonary disease, pancytopenia, malignant lymphoma as serious adverse event and research annual hospitalization in each groups. Final, we compare the event number for 5 groups by Odds ratio. (Results) The Boolean4 remission rate in each groups were 4mg groups 32.1%,6mg 29.3%, 8mg 29.3%, 1012mg 25.3%, 12mg 26.2%, respectively. Incidence of serious adverse event of the all NinJa 2014 cohort was 463patients (3.5%), and the OR with MTX each groups were 0.91, 0.83, 0.42, 0.35, respectively. (Conclusion)In our cohort, the annual hospitalization number for serious adverse events was not high, especially over 8mg/week of MTX dose. MTX monotherapy within 16mg/week in Japan is safe, but the efficacy was not getting better by dose depending.

W58-4

The impact of the combination therapy of conventional synthetic disease-modifying antirheumatic drug with anchor drug, MTX in the Japanese large cohort, NinJa(National Database of Rheumatic Diseases by iR-net in Japan)

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Conflict of interest: None

(Material and methods) In 15023 RA patients registered in Japanese large cohort of NinJa (National Database of Rheumatic Diseases by iR-net in Japan), 31.6% of the patients had been medicated MTX monotherapy, 16.4% had the combination therapy with MTX + bDMARD, 15.6% had combination therapy with MTX + csDMARD, and 18.1% monotherapy or combination therapy with csDMARD other than MTX.Extraction of combinations with Boolean remission rate higher than 20% from these therapies showed MTX+BUC+TAC, MTX+IGU, MTX+SSZ, MTX+SSZ+BUC, BUC+SSZ, MTX+BUC that had high efficacy. In addition, from the point of view of safety, the hospitalization rate of each combination was generally around 5%, which was not much different from the rate in the overall NinJa. (Discussion) On the whole, in NinJa2014, combination therapy with DMARD in which 2 or 3 drugs are selected from 4 drugs of SSZ, BUC, TAC, and mainly MTX, the anchor drug, has been actively performed also in Japan, and csDMARD, MTX, and SSZ evaluated as strongly recommended in Guidelines for the management of rheumatoid arthritis, Japan College of Rheumatology 2014 have already played the central roll. Iguratimod is increasing as new DMARD as combination drug in RA.

W58-5

Liver dysfunction in the patients with rheumatoid arthritis started to treat with MTX in combination with isoniazid for prevention of tuberculosis simultaneously

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Conflict of interest: None

OBJECTIVE: For patients with rheumatoid arthritis (RA) at high risk of tuberculosis, we start isoniazid (INH) before administration of MTX. However, we start MTX simultaneously with INH when the activity of RA is high. We investigated the characteristics of liver dysfunction in the patients taking MTX and INH in our hospital. **METHOD:** A retrospective study was conducted of patients with RA started to treat with MTX in combination with INH in comparison with those with MTX alone in our division between July 2012 and December 2014. **RESULT:** Out of 153 patients, 72 patients (47.1%) received administration of MTX alone, and 65 patients (42.5%) received administration of MTX simultaneously with INH. One month after the start of MTX, the number of the patients with liver dysfunction was three (4.2%) and five (7.7%), respectively (p=0.38). The average of AST/ALT was 33 (±3.0)/54 (±3.6) and 72.4 (±61.6)/100.8 (±45.8) IU/l, respectively (p=0.23/0.14). The number of the patients who stopped taking MTX because of liver dysfunction by MTX or INH was five (6.9%) and four (6.2%), respectively (p=0.85). **CONCLUSION:** There were no significant differences in the frequency and degree of liver dysfunction, and the proportion of withdrawal of MTX, between the patients taking MTX only and taking MTX with INH.

W58-6

The efficacy of daily supplement of 1mg of folic acid on the dose-dependent adverse reactions of methotrexate

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Conflict of interest: None

Background: Methotrexate (MTX) is a disease modifying antirheumatic drug used as a first line agent for treating rheumatoid arthritis (RA). Supplementation with folic acid (FA) during treatment with MTX is recommended in 2014 JCR guide line. Regardless of weekly supplementation of 5mg FA, there are patients who experience MTX dose dependent adverse events (AEs). Objectives: We assessed the benefits of daily supplementation with 1mg FA in MTX dose dependent AEs that occurred during weekly 5mg FA during treatment with MTX for RA. Methods: Consecutive patients with RA treated with MTX using weekly 5mg FA, were recruited when MTX dose dependent AEs were appeared. Serum liver enzyme levels, presence of nausea, stomatitis and depilation were evaluated before and after the change dosage of FA. Results: Twenty-six RA patients treated with MTX and weekly 5mg FA, were recruited. AEs were consisted with 8 abnormal serum liver enzyme levels, 15 nausea, 2 stomatitis and 1 depilation. After the change to daily supplementation of 1mg FA, 6 hepatic AEs were ameliorated and 2 were prevented to aggravate. All GI AEs, stomatitis and depilation were recovered. Conclusions: Daily supplementation of 1mg FA has efficacy to the MTX dose dependent AEs that occurred during weekly supplementation of 5mg FA.

W59-1

Memory CD4 T cells and memory B cells contribute to the pathogenesis in polymyositis and dermatomyositis

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Conflict of interest: None

Objectives: Polymyositis (PM) and dermatomyositis (DM) exhibit various manifestations. Revealing the lymphocyte contribution to the clinical features in PM/DM provides target-specific therapy. Since muscle pathology was not enough to clarify the etiology, peripheral blood mononuclear cell (PBMC) subsets were assessed to examine the immune state. Methods: PBMC subsets in 3 PM patients, 14 DM patients and 11 healthy controls (HC) were analyzed with flow cytometry. The subsets in the patients were compared before and after therapy. Results: Compared to HC, ratios of CD4/CD8 and central memory CD4 T cells/effector memory CD4 T cells (T_{CM}/T_{EM}) were elevated, while those of naïve CD8 T cells/lymphocytes and memory B cells/naïve B cells (mB/nB) were decreased in active PM/DM. Those changes in ratios of CD4/CD8 and mB/nB were found in patients without interstitial pneumonia (IP). A CD4/8 ratio was higher and ratios of mB/nB and follicular helper T cells/CD4 T cells were lower in patients with IP than those without IP. The T_{CM}/T_{EM} ratio fell and the mB/nB ratio became comparable to HC after therapy. Conclusions: These results suggest that T_{CM} proliferation and T_{EM} migration to lesions help CD8 T cells injure muscle tissues. Memory B cells play a role in PM/DM, especially in IP.

W59-2

Angiogenesis in fasciitis associated with dermatomyositis

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Conflict of interest: None

Objective: To examine whether angiogenesis is observed in fasciitis associated with dermatomyositis (DM), and which angiogenesis-related factors are expressed. **Methods:** We analyzed 12 patients including 6 with DM and 6 with polymiositis (PM), who underwent MRI and en bloc biopsy before treatment. Total vascular inflammation score (TVIS) and angiogenesis score (AS) were defined to evaluate the severity of fasciitis and the grade of angiogenesis in the fascia, respectively. Immunohistochemical staining was performed by using anti-VEGF, anti-IL-1β, anti-IL-6, and anti-TNF-α antibodies to evaluate the expression of angiogenesis-related factors in the fascia. **Results:** Significant fasciitis, defined as TVIS of ≥3, was detected in all DM patients, while not detected in any PM patients. TVIS and AS in the fascia were significantly greater in DM compared with PM. The numbers of VEGF, IL-1β and TNF-α positive cells were all significantly greater in the fascia of DM compared with PM. IL-6 positive cells in the fascia were barely present in DM and PM patients. **Conclusion:** Angiogenesis was observed in the fascia with severe inflammation among patients with DM. Our data suggest that VEGF, IL-1*β,* and TNF-*α* are involved in angiogenesis associated with DM fasciitis.

W59-3

Post-treatment short-term changes in needle electromyography among patients with polymyositis (PM) and dermatomyositis (DM) and their clinical usefulness

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Conflict of interest: None

[***Object***] We aimed to study post-treatment short-term changes in needle electromyography (EMG) among patients with PM/DM and their clinical usefulness. [***Methods***] Patients with PM/DM were administered for the treatment of muscle manifestations and received needle EMG before and after treatment. The data of findings of needle EMG, MMT, serum CK levels were retrospectively collected. The following findings of needle EMG were evaluated: fibrillation potential (Fib), positive sharp wave (Pos), low-amplitude motor unit potential (MUP) (Low), short-duration MUP (Short). [***Results***] Ultimately, 24 patients were included in the present study, and 17 and 10 patients received needle EMG at 4 and 8 weeks after treatment, respectively. Fib and Pos significantly improved at 4 weeks, and all of the needle EMG findings improved at 8 weeks ($p<0.05$). Although MMT scores and CK levels also significantly improved, their improvement did not significantly agree with the improvement of needle EMG findings except for Fib and Pos and CK levels at 8 weeks. [***Conclusion***] Electrical activity in muscle recorded at rest and during voluntary movement significantly improved at as early as 4 and 8 weeks after treatment, respectively. Needle EMG findings can serve as different outcome measure from MMT and CK in PM/DM.

W59-4

Clinical and pathological features of cancer-associated myositis (CAM) positive for antitranscriptional intermediary factor-1γ antibody (TIF-1γ ab)

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Conflict of interest: None

[Object] To clarify clinical and pathological features of CAM positive for anti-TIF-1γ ab. **[Methods]** This study enrolled 4 patients with CAM diagnosed between 2007 and 2015, whose tumor and skin tissue was available for pathological study. Using immunoprecipitation (IP) and IP-Western blot, we identified myositis-asssociated abs in the sera. We compared clinical features based on anti-TIF-1γ ab positivity and studied the expression of TIF-1γ in the tissue by immunostaining. [Results] Two patients were positive for anti-TIF-1γ ab (cholangiocarcinoma (CCC) and breast cancer) and the other two were negative (gastric cancer and ovarian cancer). Two positive patients were classical dermatomyositis (DM) with muscle weakness but without interstitial lung disease (ILD). In contrast, other two patients were clinically amyopathic DM with ILD. Two positive patients experienced recurrence during glucocorticoid (GC) treatment while other two patients did not. Pathological study showed the expression of TIF-1γ in the tissue regardless of antibody positivity. [Conclusions] Patients with CAM positive for anti-TIF-1γ ab were classical DM without ILD and refractory to GC. In addition, anti-TIF-1γ ab production might be induced by not only its antigen overexpression but also other mechanisms.

W59-5

Clinical characteristics, survival rate and swallowing outcomes of myositis patients with dysphagia; A retrospective multicenter study

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Conflict of interest: None

[objectivesTo determine clinical characteristics, survival rate, and swallowing outcomes of myositis patients with dysphagia.[methodsWe retrospectively analyzed 19 myositis patients with dysphagia and compared them with 200 myositis patients without dysphagia. [Results]In myositis patients with dysphagia, the median age was 62.9 years old and older than without dysphagia (P<0.001). Median upper MMT was 3.4, and lowerthan without dysphagia.Ten patients were malignancy associated myositis. Nine patients required dysphagia diet and nine patients required tube feeding and one patient required intravenous hyperalimentation. After treatment, sixteen patients with dysphagia improved swallowing function. Three patients could not improve and they were all malignancy associated myositis. Swallowing function improvement rate was gradually increased. Seven patients developed aspiration pneumonia. Cumulative survival rate was significantly lower in myositis with dysphagia compared to myositis without dysphagia (P<0.001). [Conclusion] Myositis patients with dysphagia had a highly prevalence of malignancy and cumulative survival rate was significantly lower than without dysphagia.Most of the myositis patients with dysphagia might improve their swallowing functions.

W59-6

Three cases of focal myositis of the calf following S1 radiculopathy

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Conflict of interest: None

[Objective] Here we report three cases of focal myositis of the triceps surae muscle induced by S1 radiculopathy. [Method] We retrospectively studied clinical features and examination findings of three patients diagnosed with leg focal myositis induced by S1 radiculopathy. [Result] The patients were 75 and 85-year-old men, and a 55-year-old woman, who have some kind of symptom about leg. The involved side was only left leg in the former but bilateral in the latter two. The serum creatine kinase level were 530, 1090, 1633 IU/l, respectively. MRI showed degenerations of vertebral bodies and/or intervertebral disk of L5/S1, and abnormal hyperintensity of the involved muscles on STIR sequence in all patients. Ultrasonography of muscle revealed that, the affected muscles of the second patient were atrophic, but in remaining two patient, the muscles were hypertrophic. Electromyogram findings of gastrocnemius muscles showed all neurogenic changes. The common pathological findings were group atrophy of gastrocnemius muscle fibers and infiltration of inflammatory cells. [Conclusion] It is necessary to remember this disease in the case of myopathy of calf. Furthermore, the muscle ultrasonography test is very useful for detect the affected regions because of the ease and non-invasiveness.

W60-1

Validation of Krebs von den Lungen-6 as a Biomarker of Interstitial Lung Disease with Polymyositis and Dermatomyositis

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Conflict of interest: None

[Object] KL-6 is widely used as serum biomarkers for ILD in PM/DM. However, their usefulness in patients with PM/DM is not fully established. We aimed to evaluate the usefulness of KL-6 as a biomarker of ILD with PM/DM, including that in the short time course after treatment. [Methods] A total of 42 patients with active PM/DM were included. ILD was diagnosed on HRCT. Clinical, radiological, and laboratory data were retrospectively collected from the medical records and statistically analyzed. [Results] Of the 42 study subjects, 30 patients had ILD. Although there was no significant difference in %VC (pre treatment) (p>0.05), serum KL-6 and SP-D levels were significantly higher (p<0.01) in patients with ILD. Levels of serum KL-6 and SP-D were significantly correlated with %VC and %DLCO (p<0.01). All the patients with ILD were received immunosuppressive therapy, and 12 patients showed some clinical and/or radiological improvement in 4 weeks. Levels of serum KL-6 were not significantly different between those at pre treatment and at 2 or 4 weeks post treatment (p>0.05). [Conclusion] Serum KL-6 is a useful biomarker for the diagnosis of ILD associated with PM/DM. However, the levels of serum KL-6 did not respond immediately by treatment even in the cases with clinical improvement.

W60-2

Analysis of serum KL-6 and SP-D before treatment in idiopathic inflammatory myositis (IIM) with interstitial lung disease (ILD), especially in clinically amyopathic dermatomyisitis (CADM)

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Conflict of interest: None

【Objectives】It was reported that a CADM patient with rapidly progressive ILD (RP-ILD) whose serum SP-D level was normal, previously (Chiba H, et al. Chiryogaku 2001;44:606-8.). We evaluated the correlation of anti-MDA antibody, which is often detected in CADM patients with RP-ILD, and serum KL-6 and SP-D level in the patients with IIM of our hospital. 【Method】We analyzed the clinical data of IIM patients performed induction therapy from January 2011 to September 2015 in our hospital. 【Results】All IIM patients were 51 cases; polymyositis (PM)/dermatomyositis (DM)/CADM were 15/18/16 cases, respectively. Patients who had ILD were 11 cases with PM, 12 cases with DM, 15 cases with CADM. Anti-MDA5 antibody positive patients were 15 cases. All of them were CADM patients, and except of one patient had ILD. Twenty-nine cases of 38 patients with ILD were evaluated serum KL-6 and SP-D before treatment. All nine patients with anti-MDA5 antibody among those 29 cases had high KL-6 but normal SP-D. The sensitivity and specificity of "high KL-6 but normal SP-D" to anti-MDA5 antibody-positivity in the patients with ILD were 100% and 65% respectively. 【Conclusion】The IIM patients with ILD who have "high KL-6 but normal SP-D" should be suspected as anti-MDA5 antibody-positive patients.

W60-3

Elevation of serum ferritin or KL-6 levels at baseline and increase of both these marker levels are poor prognostic factors in Clinically amyopathic dermatomyositis (CAMD)

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Conflict of interest: None

Objective: To identify poor prognostic factors in CADM that is frequently complicated with refractory interstitial pneumonia (IP). Methods: Subjects were consecutive 16 patients who admitted our department from 2009 to 2015. These patients were treated with a combination of high dose glucocorticoid, cyclosporine, and intravenous cyclophosphamide as a first line therapy. Results: Active IP was found in 13 of 16 cases. Anti-MDA Ab was positive in 13 cases, 12 of which have active IP. Death occurred in 7 cases; 6 died of respiratory failure by IP and 2 of bleeding (muscles a brain) and all of these patients had anti-MDA Ab. At the start of therapy, patients whose serum ferritin levels above 1000 ng/ml6 or those (n=5) or those with KL-6 levels above 1200 U/ml (n=4) were poor in prognosis; all of these patients deceased. Patients whose serum levels of both ferritin and KL-6 were increasing during intensive immunosuppressive therapy also showed poor prognosis, despite their levels at the beginning of the therapy. Conclusion: Elevation of serum ferritin or KL-6 levels at staring therapy and increase of both these markers-levels are poor prognostic factors in CADM.

W60-4

Prognostic analysis using chest high-resolution computed tomography in acute/subacute interstitial pneumonia with dermatomyositis patients

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Conflict of interest: None

Objectives. We investigated the prediction of outcomes of patients with dermatomyositis with acute/subacute interstitial pneumonia (DM-A/SIP) on the basis of chest high-resolution computed tomography (HRCT) images. Methods. In 20 patients with DM-A/SIP (7 deaths), the relationships between prognostic outcomes and chest HRCT findings or CT scoring on the first examination were retrospectively investigated. Results. No correlation was observed between chest HRCT findings and prognosis. However, the ground-glass opacity (GGO) scores of the right upper and middle lobes and left upper lobe were significantly higher in the death group than in the survivor group (P = 0.01, 0.001, and 0.02, respectively). A right middle lobe GGO score of ≥ 3 (GGO ≥ 25% of the lobe) was determined to be the best cut-off value for a poor prognosis (sensitiv-

ity: 86%, specificity: 86%), and the survival rate after 24 weeks was significantly lower in patients with a right middle lobe GGO score of ≥ 3 (survival rate: 0.0%) than in those with a score of < 3 (92.9%) (P < 0.0001). Conclusions. High GGO scores of the bilateral upper lobes and middle lobe on the first chest HRCT were an index of a poor outcome in DM-A/SIP patinets.

W60-5

Risk factors of exacerbation of polymyositis/dermatomyositis associated interstitial pneumonia (PM/DM-IP)

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Conflict of interest: None

Objective: To identify risk factors of the exacerbation of polymyositis/dermatomyositis associated interstitial pneumonia (PM/DM-IP). Methods: A total of 45 PM/DM-IP patients who were treated with predonisolone (PSL) and/or immunosuppressive agents as an induction therapy in our hospital from January 2002 to August 2015 were included in the analysis. The patients were classified into the exacerbation group and the non-exacerbation group and compared about characteristics and treatment. Results: The exacerbation group was 17 (37.8%) and the non-exacerbation group was 28 (62.2%). The mean age, sex, and the proportion of DM were not different between the two groups. As an induction, the dose of PSL was 0.87mg/kg and 0.89mg/kg, respectively (p=0.17), and the comcomitant use of immunosuppressants was 8 (47.1%) in the exacerbation group and 14 (50.0%) in the non-exacerbation group (p=0.85). With respect of maintenance therapy, the rate of immunosuppressant use with PSL was 8 (64.7%) in the exacerbation group and 26 (92.9%) in the non-exacerbation group (p=0.02). Conclusion: The concomitant use of immunosuppressants with PSL during the maintenance therapy is important to prevent the exacerbation.

W60-6

Seasonal influence on the onset of polymyositis/dermatomyositis with interstitial lung disease

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Conflict of interest: None

[Object] To investigate seasonal patterns in the onset of polymyositis (PM) and dermatomyositis (DM) with interstitial lung disease (ILD) in terms of myositis-specific antibodies. [Methods] From a multicenter cohort of PM/DM with ILD including 44 institutions, 409 patients (pts) with identified onset were extracted. The cohort consisted of pts with adult onset PM and DM (including clinically amyopathic DM and probable cases) who diagnosed after Jan 2010. ILD was confirmed by CT. Anti-MDA5 antibody was detected by enzyme-linked immunosorbent assay, and anti-aminoacyl-tRNA synthetase (ARS) antibody (Jo-1, PL-7, PL-12, EJ, OJ, and KS) was detected by immunoprecipitation. [Results] Anti-MDA5 antibody was detected in 179 pts (114 females); anti-ARS antibody in 129 pts (91 females); and negative for both in 101 pts (59 females). Mean age of onset was 55±12, 54±13, and 58±12 years old, respectively. The onset of PM/DM with ILD was evenly distributed throughout the seasons. In quarterly period of Apr-Jun, Jul-Sep, Oct-Dec, and Jan-Mar, the proportion of anti-MDA5 antibody positive cases were 32%, 45%, 50%, and 47%, respectively, which showed significant increase during autumn and winter (p=0.02). [Conclusions] The onset of anti-MDA5 antibody positive cases peaked in autumn and winter.

W61-1

Indocyanine green (ICG) -enhanced fluorescence optical imaging (FOI) in patients with active rheumatoid arthritis: a comparative study with ultrasound

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Conflict of interest: None

Objectives: This study is undertaken to explore the utility of ICG-enhanced FOI comparing with ultrasound in RA patients. Methods: Thirty three active RA patients (mean disease durations 7.8 years and DAS28 5.65) who were consecutively enrolled in this study. Both FOI and ultrasound were performed at 18 joints including bilateral 2nd -5th MCP, PIP joints and wrist joints. FOI assessments of Phase 1-3 (P1-3), composite image (CI) as well as GS score and PD score were semi-quantitatively classified from 0 to 3 as described. Results: Positive finding were found in 159, 283, 185, 196 and 195 out of 594 joints in P1, P2, P3, CI and PDUS, respectively. With PDUS ≥ grade 1 as reference, the sensitivities of FOI in whole joints were 65.6, 91.8, 68.2 and 71.8 % and specificities were 92.2, 73.9, 87.0 and 86.0 % in P1, P2, P3 and CI, respectively. The frequencies of positive findings and diagnostic performance was different by each joint. Among individual patients, each total FOI scores positively correlated with both GS (rs=0.57-0.85) and PD scores (rs=0.467-0.84) as well as with DAS28-ESR (rs=0.27-0.66) and CRP (rs=0.42-0.59). Conclusion: FOI is considered to detect joint inflammation of RA patients with high accuracy. However, the significance of each phase of FOI may be different.

W61-2

Relationship between diurnal variation of the symptoms and joint ultrasonography findings in rheumatoid arthritis

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Conflict of interest: None

[Objectives] In rheumatoid arthritis (RA), there may be a diurnal variation like morning stiffness. Although it has been frequently used in the diagnosis and management of RA, diurnal variation in the joint ultrasonography (US) findings has not been reported. Here joint US performed in the morning and afternoon, and compared with clinical symptoms. [Methods] Thirty-four patients with RA (average age; 62.44-year-old, male-female ratio; 1:1.83, disease duration; 6.91 years, DAS-CRP; 4.12) hospitalized for diagnosis or treatment strongly, from 2012 to 2015 were assessed. We evaluate tender joint count (TJC), swollen joint count (SJC), patient VAS (Pt-VAS) in the morning and afternoon (at AM 10:00 and PM 4:00). We also evaluate GS·PD for 4 stages (0-3) in 60 locations consisting of both finger, wrist, elbow, shoulder, knee joints and wrist joints' extensor thecal synovial membrane by joint US images for total GS·PD score (0-180). [Results] There are no significant difference in the joint US findings, tender and swollen joint count, Pt-VAS and morning stiffness between the morning and afternoon. There are no changes in clinical and laboratory findings by time. [Conclusion] There were no significant diurnal changes in the disease activity scores or US findings.

W61-3

Presence of ultrasound detected subclinical synovitis in midfoot and hindfoot among patients with rheumatoid arthritis

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Conflict of interest: Yes

Object; In patients with the rheumatoid arthritis (RA) achieved in clinical remission, subclinical synovitis often exists using ultrasound (US) in MTP joint. The purpose of this study is to clarify characteristics of US detected subclinical synovitis in midfoot and hindfoot.Methods; 253 RA patients (201 women, mean age 63.6ys, mean disease duration 11.9ys), who were registered in KURAMA cohort study, were included. The blood flow signal was detected using SMI and estimated power Doppler (PD) and gray scale (GS) according to JCR atlas. The target joint were ankle, Chopard, Naviculo-cuneiform, Lisfranc, and 2-5MTP. The foot ankle evaluation were performed using SAFE-Q.Results; In 114 patients achieved in DAS28ESR remission, US detected subclinical synovitis was more frequent in midfood and hindfoot than in forefoot. To compare PD-positive (29) with PD-negative (85), there were not statistically difference in age, sex, disease duration, DAS28-ESR, PtVAS, HAQ, and serum reaction, but stage significantly progressed in PD-positive ($P<0.01$). The mean pain score of SAFE-Q were good both groups.Conclusions; In RA patients achieved in clinical remission, US detected subclinical synovitis was more frequent in midfood and hindfoot than in forefoot, in particular, frequent in chopard joint.

W61-4

A power Doppler ultrasonography study of progressive bone destruction in patients with rheumatoid arthritis receiving etanercept

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Conflict of interest: None

[Objectives]We aimed to clarify the usefulness of power Doppler ultrasonography (PDUS) compared to that of clinical assessment methods in patients with RA receiving ETA. [Methods]We included 10 RA patients who received ETA. We semiquantitatively evaluated 22 joints, including right and left proximal interphalangeal, interphalangeal, metacarpophalangeal, and wrist joints on a 4-point scale (0-3) using PDUS, and the sum of scores was defined as PD22 score (score 0, PDUS remission). The effects before and 12 and 24 months after ETA therapy were evaluated using the PD22 score, the Simple Disease Activity Index (SDAI), and TSS of both hands. [Results] SDAI remission at 12 and 24 months were 50% and 50%; and sonographic remission rates were 20% and 40%, respectively. Radiological remission rates (ΔTSS 0) were 80% and 70%, respectively. At 24 months, bone destruction progressed in 1 of 5 (20%) patients with SDAI remission, whereas no patients with sonographic remission had progressive bone destruction. Progressive bone destruction was observed in 2 of 5 patients (40%) with SDAI non-remission and 3 of 6 patients (50%) with sonographic non-remission. [Conclusion]PDUS is a useful measure to determine "pure remission", including radiological remission during treatment.

W61-5

Usefulness of musculoskeletal ultrasonography for prediction of corticosteroid-dependent polymyalgia rheumatica

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Conflict of interest: None

[Object] The aim of this study was to investigate the findings of musculoskeletal ultrasonography (MSK-US) which efficiently predict corticosteroid (CS)-dependent polymyalgia rheumatica (PMR). [Methods] The subjects of this study were 29 PMR patients to whom MSK-US was performed from November 2010 to October 2014. The diagnosis of PMR was made clinically by experienced rheumatologists. We defined CS-dependent PMR as the patients who experienced relapse during tapering CSs to less than 5 mg per day. In shoulder US, long head biceps tenosynovitis and subacromial-subdeltoid bursitis were assessed for gray scale (GS) and power Doppler signal with a semi-quantitative scale from 0 to 3. [Results] The patients with CS-dependent PMR ($n = 13$) had a significantly higher serum LDH and higher GS grade of tenosynovitis, and that of bursitis. Multiple logistic regression analysis identified that total GS score of tenosynovitis and bursitis (odds ratio, 1.96; 95%CI, 1.15-4.30) and LDH (1.04; 1.01-1.09) were associated with CS-dependent PMR. [Conclusions] MSK-US is a useful tool to predict CS-dependent PMR.

W61-6

Diagnostic utility of detecting peripheral enthesitis by ultrasonography in spondyloarthritis

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Conflict of interest: None

Objectives. To evaluate the diagnostic utility of detecting peripheral enthesitis by ultrasonography in patients with spondyloarthritis (SpA). **Methods.** Patients with peripheral symptoms suggestive of SpA (inflammatory back pain, arthritis of lower limbs, tenderness of enthesis and dactylitis) were enrolled. More than ten sites of enthesis were assessed in ultrasonography as well as articular and tendon sheath synovium. Clinical, laboratory (CRP, HLA), radiological (X-ray, MRI) findings and SpA classification criteria (Amor's, ESSG and ASAS) were also evaluated. **Results**. 58 patients were enrolled. A definite diagnosis was retained for 45 patients (24 SpA and 21 non-SpA). 13 patients were still unclassified (SpA suspected) during follow-up more than 6 months. In ultrasonography findings, SpA patients had PD signal of enthesis (92%), osteophyte (67%), calcification (38%), bone erosion (33%), and bursitis (13%). The frequency of enthesis with PD signal was 16%(n=90/554). PD signal of at least one enthesis in ultrasonography was the most useful finding for differentiation of SpA and non-SpA (sensitivity 92%; specificity 71%; accuracy 82%; $p<0.0001$). **Conclusion.** PD signal of enthesis in ultrasonography are useful for the diagnosis of SpA with peripheral symptoms.

W62-1

Implication of ultrasonography for toe joints in rheumatoid arthritis

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Conflict of interest: None

Objective: Toes joints are frequently impaired in rheumatoid arthritis (RA). We studied implication of synovial vascularity (SV) in MTP joints. Methods: 110 patients with RA irrespective of the clinical symptoms were analyzed. SV of MCP, PIP, wrist and MTP joints were measured by quantitative ultrasonography counting vascular pixels in region of interest

and represent as occupancy rate (%). We focused on occurrence of positive SV in each joint and calculated sum of SV of fingers and wrist joint as total vascularity (T-Vs%) which reflected overall disease activity. Results: 74 patients had positive SV (67%). Occurrence rate of positive SV for finger, wrist and toe were 50, 46 and 13% respectively. Patients with positive SV alone in toe were only 2cases. In the MTP, positive SV was detected mostly in 1st MTP and the next was in 5th. Cases with positive SV in 2nd to 5th MTP showed significant higher T-Vs% than positive SV alone in 1st MTP or negative cases. Conclusion: We revealed RA with positive SV alone in MTP joints were minor, most of cases involved abnormality in finger, wrist and toe at the same time. Although ultrasonography for MTP alone might not be useful, ultrasonography combined 2nd to 5th MTP and conventional joints might be useful in assessment of RA.

W62-2

Association of ultrasound-detected monosodium urate crystal deposition with degenerative joint change in the first metatarsophalangeal joints in patients with gout

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Conflict of interest: None

[Object] To determine whether monosodium urate (MSU) crystal deposition detected by ultrasound (US) was associated with degenerative joint change (OA change) in patients with gout. [Methods] US of bilateral first metatarsophalangeal (MTP1) joints was performed in patients with gout who visited our clinic for regular visits. MSU crystal deposition and OA change were assessed retrospectively, and association was analyzed among US findings and clinical backgrounds. [Results] Total of 63 patients (126 MTP1 joints) were evaluated. OA change was found in 74 joints. Among any type of residual MSU crystal deposition, presence of tophi was significantly associated with OA change, especially in patients with average serum urate concentration below 6.0mg/dl for last 5 years and those with treatment duration no longer than 10 years. [Conclusion] Among residual MSU crystal deposition, presence of tophi were associated with OA change.

W62-3

Ultrasonographic assessment of newly developed elderly-onset rheumatoid arthritis: a comparison with younger-onset rheumatoid arthritis

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Conflict of interest: None

Objectives: To clarify specific features in patients with elderly-onset (≧65 years) rheumatoid arthritis (EoRA). **Methods:** We included consecutive patients who were seen to our hospital due to joint pain and later diagnosed with RA. MSUS was performed during initial visit in all patients and the investigation sites included the dominant side of the shoulder, wrist, finger joints and knee. Gray scale (GS) and power doppler (PD) signal were graded using a semi-quantitative scoring methods for each site and the sum of the each score was calculated as total score (t-score) for each joint. We investigated sonographic differences between EoRA and YORA (onset at <65 years) and the correlations between MSUS results and clinical variables were analyzed in EoRA patients. **Results:** EoRA patients (47 patients) had a significantly higher GS t-score than YoRA (34 patients) in the shoulder joint ($P<0.0001$) and knee joint ($P<0.05$) and PD t-score of the shoulder was significantly higher in EoRA ($p<0.0001$). In EORA patients, GS t-score and PD t-score of the shoulder were significantly correlated with HAQ score ($r=0.72$, $p<0.0001$ and $r=0.68$, $p<0.001$, respectively). **Conclusion:** Shoulder joint inflammation was a primary manifestation and contributed to the severity of the functional disability in EoRA.

W62-4

The initial effect of joint injection with hyaluronic acid under the ultrasound guide

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Conflict of interest: None

(Background) Although joint injection of hyaluronic acid have been recognized as a medical practice in Japan, are receiving insurance adaptation is only knee and shoulder. On the other hand, there is also in site of high morbidity and is high relatively arthritis of the hand joints in rheumatoid arthritis, but insurance adaptation is not. (Objective) It was selected to wrist arthritis with ten rheumatoid arthritis patients. (Method) Sodium purified hyaluronic acid under ultrasonic guide is administered intra-particularly. The continued to evaluate of weekly dose 5 times after the 5 weeks. (Result) Immediately after hyaluronic acid injection is all cases PDUS signal is lost. In five weeks to see a decrease in all cases grade even if half of PDUS signal disappeared half, it remained. (Conclusion) Results of hyaluronic acid was injected directly into the synovia to dorsal wrist under ultrasound guidance, after the injection immediately PDUS signal was lost. This we suspect that the pressure of the joint cavity has happened disruption elevated fine blood flow by precise intra-articular injection. Example that was completely disappeared after one month in the weekly administration but was 50% it is believed to have been caused some kind of action to suppress the local inflammation.

W62-5

Active synovitis with intraosseous inflammation progressed to residual synovitis despite achievement of clinical improvement in rheumatoid arthritis

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Conflict of interest: None

Objective: To study pathology of ultrasound detected residual synovitis in rheumatoid arthritis (RA) with clinical improvement state.Methods: Sequential observation for finger joints by ultrasound and MRI were performed. Joints with positive synovial vascularity detected by ultrasound at baseline were judged as active synovitis. Joints with positive synovial vascularity (>semi-quantitative score grade2) at the 24th week were judged as residual synovitis. Joints with bone intraosseous inflammation (bone erosion or edema) at baseline were judged by MRI.Results: 16 of 21 patients who achieved clinical improvement were studied. Totally 320 finger joints were analyzed. 116 joints had active synovitis at baseline and 47 joints had residual synovitis at the 24th week. Active syonovitis with intraosseous inflammation were significantly in accordance with residual synovitis ($P<0.0001$).Conclusion: Active synovitis with intraosseous inflammation tend to progress to residual synovitis. residual synovitis had relation with relapse in RA. Control of residual synovitis may prevent disease relapse.

W62-6

Efficacy of MRI scans of bilateral hands in patients with rheumatoid arthritis ~by MIYAKO study~

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Conflict of interest: Yes

[Objectives] We performed prospective study to evaluate efficacy of abatacept in patients with RA assessed by MRI scans of bilateral hands (MIYAKO study). After that, we evaluate the efficacy of MRI scans of bilateral hands. [Method] MRI of bilateral hands was performed at baseline and after 12 months of intravenous ABT treatment. MRI images were scored according to the RA MRI Scoring System. We performed statistical analysis of a correlation between MRI scores of bilateral hands and SDAI at baseline and after 12 months, and also a correlation between MRI scores of single hand and SDAI. [Results] Synovitis score (SS), and osteitis score (OS) of bilateral hands were correlated with SDAI score at baseline and 12 month (r=0.6-0.50, p=0.007-0.0047). Bone erosion score were not correlated with SDAI score. Also SS and OS of single hand were correlated with SDAI (r=0.32-0.45, p=0.013-0.076), but MRI score of bilateral hands tend to have stronger correlation with SDAI score than that of single hand. [Conclusion] MRI score of bilateral hands showed higher correlations with SDAI. MRI of bilateral hands is efficient at assessment of disease activity in patients with RA.

W63-1

The investigation on the correlation between ulnar deviation of the metacarpophalangeal joint and radial wrist rotation in the patients of rheumatoid arthritis based on the measurement on X-ray images

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Conflict of interest: None

[Object] In this report, we studied the correlation between ulnar deviation (Ud) of the metacarpophalangeal joint and radial wrist rotation (RWR) in the patients of rheumatoid arthritis (RA) using a new radiograph and image measurement methods. [Methods] We examined the radiographs of the 110 hands of the 57patients (female 50, male 7, mean age 61.3 years old) which were taken with dorsal surface down on a cassette to avoid the contact of the fingers with a cassette. We measured Ud of each finger on images. We also measured RWR on images, which was defined as the angle formed by the longitudinal axis of the distal radius and the second metacarpal. We investigated the correlation between the two angles with correlation coefficient and scatter diagram. [Results] Spearman's correlation coefficient (rho) between the mean Ud of index-little finger and RWR were 0.58. Spearman's rho between RWR and Ud of index, middle, ring, and little finger was 0.65, 0.52, 0.59, 0.43, respectively. [Conclusions] We found the correlation between Ud and RWR using new radiographic and measurement method. The correlation in the index finger was especially strong. We validate that RWR was one of the etiologies of Ud in RA, but further study was needed.

W63-2

The validation about the measurement of joint space distance by using super resolution image and curve fitting methods

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Conflict of interest: None

[Objectives] We prepared the phantom model (PM) of joint space that expressed joint space 1mm by using 3D printer and measured it to validate the measurement of joint space distance by using super resolution image and curve fitting methods. We evaluated whether the focus-film distance (FFD) affected the measured value.[Methods] We prepared the super-resolution image of PM with radiographs. We measured the distance of joint space by integration method and normal line method. We measured the distance ten times to adjust the error of measurement. We took radiographs at 90cm, 100cm and 110 cm FFD. [Results] Between integration method and normal line method, the mean of measured value at 90 cm FFD was 0.939, 0.964, respectively. At 100 cm FFD, it was 0.943, 0.969, respectively. At 110 cm FFD, it was 0.943, 0.964, respectively. There were no significant differences with measured value between two methods at each FFD.[Conclusion] The measured value was not affected by a difference of the FFD.We obtained the measured value, 0.937 - 0.970 by two methods, which were equal to 1mm of PM. We validated the measurement accuracy of curve fitting methods.

W63-3

Large joint destruction in patients with rheumatoid arthritis : A prospective study using FDG-PET/CT and ARASHI scoring method

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Conflict of interest: None

Object 18F-fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET/CT) can visualize the disease activity in large joints affected by RA. The aim of this study is to investigate the associations between large joint destruction and FDG-PET/CT findings using a new radiographic evaluation method. *Methods* A total of 260 large joints (shoulder, elbow, hip, knee and ankle) in 26 RA patients (6 males and 20 females; mean age of 66.9 years) were assessed. FDG-PET/CT was performed at 0 and 6 months (M) after the biological therapy. The FDG uptake in large joints was analyzed using the maximum standardized uptake value (SUVmax). Radiographs of the large joints at 0M and after 36M were assessed according to ARASHI method. Statistical analysis was performed to determine the factors concerning joint destruction. *Results* ARASHI status score (score at 0M), SUV at 0M, dSUV (0M - 6M) were significantly higher in the group with high level of ARASHI change score. A logistic regression analysis revealed dSUV was the most associated factor with joint destruction at 36M. *Conclusions* We investigated large joint destruction in RA using FDG-PET/CT and ARASHI scoring method. To decrease SUV value at 6M was important for the prevention of large joint destruction in RA patients.

W63-4

Maximum Intensity Projection like imaging in Ultrasonography

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Conflict of interest: None

Objective: Ultrasonography (US) and MRI are gold standard assessment for rheumatoid arthritis. Contrast-enhanced MRI with maximum intensity projection (MIP) is a convenient tool for detecting synovitis. MRI MIP imaging can depict the distribution of the enhanced tissue, in one image. But it is impossible even to display a particular joint in US. We previously reported the development of the US display data conversion to DICOM data. Using these DICOM data, we developed the MIP like imaging in US. Material and methods: US were performed in 5 healthy volunteer wrists. These US display data were converted to signal data. PD signal was calculated by the dual mode imaging (B mode and PD mode). The timing of the maximum PD signal activity was calculated by the histogram of the PD signals. Selection of the maximum PD signal imaging and image completion was performed. These data were converted to the three dimensional PD signal DICOM data. Finally, these data were converted to the MIP imaging. These conversion was performed by MatLab (MathWorks Inc.) based software. Results: Using conventional US display data, we performed MIP like PD signal imaging, and displayed the whole wrist PD signal imaging.

W63-5

The prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis and psoriatic arthritis

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Conflict of interest: None

[Objective] Traditionally, tender and swollen joint count was relied for the active joint assessment in patients with psoriatic arthritis (PsA). To date, the modern imaging tool such as ultrasound (US) can detect the joint and enthesial inflammation more sensitively than clinical assessment. The aim of this study was to research the prevalence of US arthritis findings in patients with PsA and psoriasis. [Methods] Total thirty-one patients (male 16 and female 15) including 19 patients with PsA and 12 patients with psoriasis were underwent gray-scale (GS) and power Doppler (PD) US of MCP, PIP, DIP and wrist joints in both hands. GS and PD were scored on a 0-3 semiquantitative scale for each joint. [Results] US synovitis was found in 84.2% by GS and 78.9% by PD assessment in 19 patients with PsA. The most common sites for inflammatory synovitis were the wrist. US synovitis was found in 58.3% by GS and 25% by PD assessment in 12 patients with psoriasis, but the most of inflammation was mild (grade 1). [Conclusion] US found that patients with PsA showed a high prevalence of inflammatory synovitis in peripheral joints and subclinical synovitis was also found in patients with psoriasis. US examination is useful to detect the inflammatory condition in patients with PsA and psoriasis.

W63-6

The prevalence of ultrasonographic enthesopathy in patients with psoriasis and psoriatic arthritis

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Conflict of interest: None

[Objective] Traditionally, clinical tender and swollen assessment was relied for the active enthesopathy assessment in patients with psoriatic arthritis (PsA). To date, the modern imaging tool such as ultrasound (US) can detect the joint and enthesial inflammation more sensitively than clinical assessment. The aim of this study was to research the prevalence of US enthesitis findings in patients with PsA and psoriasis. [Methods] Total twenty-eight patients (male 15 and female 13) including 16 patients with PsA and 12 patients with psoriasis were underwent US assessment of lateral epicondyle, triceps enthesis, the proximal and distal patella tendon enthesis, Achilles tendon and fascia plantaris tendon enthesis. [Results] US enthesopathy was found in 62.5%(10 patients) in 16 patients with PsA. The most common sites for inflammatory synovitis were the lateral epicondyle, Achilles tendon, distal and proximal patella tendon enthesis. US enthesopathy was found in 16.7%(2 patients) in 12 patients with psoriasis. [Conclusion] US found that patients with PsA showed a high prevalence of inflammatory enthesopathy and subclinical enthesopathy was also found in some patients with psoriasis. US examination is useful to detect the enthesopathy in patients with PsA and psoriasis.

W64-1

Pretreatment prediction of response to anti-cytokine therapy using serum biomarkers receptors in individual rheumatoid arthritis patient

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Conflict of interest: None

Purpose: It has been noted that each anti-rheumatic therapy delivers a different outcome for individual RA patients and this makes it difficult to prescribe the most efficacious treatment for them. It is critical to identify molecular biomarkers that can predict patient response to anti-TNF-a or anti-IL-6 therapies before patients are treated. Methods: We enrolled 138 RA patients and measured 31 biomarkers in their serum before administering tocilizumab or etanercept for 16 weeks. We selected parameters that correlated with patient's week 16 DAS28-CRP and remission by multiple linear analyses and multiple logistic analyses, repeatedly. Results: Multiple linear regression analysis based on patients' week 16 DAS28 revealed that sgp130, IL-6,IL-8, Eotaxin, IP-10, VEGF, TNFR-I and TNFR-II serum levels before therapy were potential biomarkers to predict biologic naïve patients' week 16 DAS28. Sgp130, IP-10, TNFR-II and IL-6 were predictive of complete remission or non-remission to tocilizumab therapy by multiple logistic analyses. Conclusion: We discovered reliable biomarkers that can predict clinical disease activity and outcome before RA patients undergo anti-IL-6 and anti TNF-a therapy. Personalized therapy will be targeted by measuring biomarkers in pretreatment serum.

W64-2

Consideration of RAID(Rheumatoid Arthritris Impact of Disease) score in the biological use patients in our hospital

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Conflict of interest: None

Objectives:Rheumatoid Arthritris Impact of Disease (RAID) score is an index for overall evaluation of the pathology of rheumatoid arthritis which is included pain due to patient assessment, dysfunction, fatigue, sleep disorders, coping skills, overall physical condition, and composite scores of overall mental state. We examined the validity of the RAID score for patients with rheumatoid arthritis at our institute. Methods:For 271 people who received the administration of biological products in our hospital from December 2012 to November 2015, were analyzed for a total of 2041 times the data. As an indicator of the efficacy, pain joint count, the number of swollen joints, erythrocyte sedimentation rate (ESR), CRP, patient pain VAS (PtVAS), patient grobal VAS (PtGA), were monthly evaluated by physician, HAQ-DI and RAID score as an indicator of QOL we were evaluated for each administration. Result:RAID score showed correlation with almost all the parameters except for CRP, ESR and MMP-3. Especially, RAID score is strongly correlated with patient pain VAS and global VAS. Conclusion:RAID score is simple evaluation,but it can be a effective measure of disease activity. It is storongly co-related with PtVAS and PtGA. This result is same as previous reports in western counrries.

W64-3

Outcome comparison of elderly-onset rheumatoid arthritis (EORA) and younger-onset rheumatoid arthritis (YORA): a retrospective cohort study

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Conflict of interest: None

[Purpose] We examined clinical features of EORA as compared with those of YORA [Methods] Among patients who were diagnosed with RA in our hospital between October 2012 and October 2014, 191 patients treated for more than 1year were analyzed. The 191 patients were divided into two groups, one group comprised 94 patients who were < 65 years old (the YORA group) and the second comprised 97 patients who were ≥ 65 years old (the EORA group). Then we compared the outcome of these two groups. In addition, clinical features of good responders (achievement of low disease activity (LDA)) and those of non-responders (failure of achieving LDA) were also compared among the patients with EORA [Results] No significant differences were observed in the rate of achiev-

ing LDA between the EORA and the YORA groups. In comparison between clinical features of good responders and those of non-responders among patients with EORA, the ratio of patients with negative RF, negative anti-CCP antibody, and early diagnosis of RA (diagnosis within 6months after the development of symptoms) were higher in good responders. [Conclusion] Rate of achieving LDA in the patients of EORA was comparable to that of YORA in this study. RF, anti-CCP antibody, and early diagnosis may be involved in the therapeutic response of EORA.

W64-4

Improving of index of activity speed (Time Up and Go test) by joint surgery in patients with long-standing rheumatoid arthritis: Results from multicenter prospective cohort study for evaluation of joint surgery on physical function

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Conflict of interest: Yes

Objectives: Index of activity speed [Time Up and Go (TUG)] could be very useful to set treatment goal of long-standing RA patients for surgical procedure and rehabilitation. The purpose of this study is to explore relationship between TUG and physical function in RA patients. **Methods:** We collected data at pre- and post-operation (0.5 years, 1 year) on age, sex, disease duration, drug therapies, and disease activity. Functional evaluations (TUG, range of motion in joints, HAQ-DI), and patient subjective evaluations [EQ-5D (QOL) and BDI-II (depression)] were made. **Results:** 347 surgical patients were registered. Mean values for age, and disease duration were 65.2 years, 18 years. TUG was significantly associated with EQ-5D, BDI-II, and high ADL status (total HAQ point <6/60). Cut-off value of TUG for high ADL status was 8.98 seconds (sensitivity 67%, specificity 59%). By total knee and hip arthroplasty, TUG was significantly improved (14.0 s to 11.1 s). To achieve TUG=9 seconds after operation, the cut-off of TUG before operation was 10.3 s (sensitivity 74%, specificity 82%). **Conclusions:** TUG was significantly associated with daily activity and patient-reported outcome. TUG could provide target of surgical procedure and rehabilitation program and index of better timing of joint surgery.

W64-5

Joint index vector-a novel assessment measure for rheumatoid arthritis: A multicenter observational study based on the *NinJa* (National database of rheumatic diseases by IR-Net in JAPAN)

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Conflict of interest: None

Background: Evaluation of involved joints is essential for RA assessment; however, information of joint size and distribution is deleted from composite measures such as DAS28 and SDAI. **Aim:** To examine the features of 3 dimension joint index vector (Vji). **Methods:** Joint index (JI) of upper/large (UL), upper/small (US), lower/large (LL), and lower/small (LS) was calculated as previously decribed[1]. We defined Vji (x, y, z) as $x = JI_{UL} + JI_{US}$, $y = JI_{LL} + JI_{LS}$, and $z = JI_{UL} + JI_{LL} - JI_{US} - JI_{LS}$. **Results:** Scalar of orthographic projection of Vji to the XY plane ($|Vxy| = \sqrt{x2+y2}$) was correlated strongly with SDAI, while it was not correlated with 3-point moving average of mHAQ. On the other hand, z was correlated weakly with 3-point moving average of mHAQ, whereas it was not correlated with SDAI. Multivariate analysis revealed that bigger vector, without steroid treatment, male sex, and short disease duration were the factor of decreasing magnitude of the vector next year. **Conclusion:** Joint index vector, that has information of activity on the XY plane and functional disability on the Z axis, is a novel useful clinical measure for RA. **Reference:** 1. Nishiyama S, et al. Rheumatol Int. 2012:32;2569-71

W64-6

Evaluation of locomotive dysfunction in rheumatoid arthritis patient with GLFS-25 score from NinJa database

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Conflict of interest: None

[Object]To analyze GLFS (Geriatric Locomotive Function Scale)-25 scores in rheumatoid arthritis patients from NinJa database. [Methods] GLFS-25, developed as a screening tool for risk of locomotive syndrome, scores locomtive function from 0 (as best) to 100 (as worst) on the basis of 25 questions. Of 15023 people who are registered in NinJa database in fiscal 2014, 2256 people are possible to calculate GLFS-25 and analyzed. [Results]1823 patients (80.8%) are female and average age is 64.2 years old, mean disease duration 14.3 years, mean DAS28-ESR 3.03, and mean mHAQ 0.42. Mean GLFS-25 score is 22.4 and 926 patients (41.0%) are scored more than 16 as locomotive syndrome grade 2 which requires therapeutic intervention and 403 patients (17.9%) are 7-15 as locomotive syndrome grade 1 which has some kind of locomotive disfunction. Patients with locomotive syndrome grade 2 increase in proportion to age, disease duration, DAS28-ESR and Steinbrocker class and stage. MHAQ and EQ-5D are also correlated with GLFS-25. [Conclusions]Higher and younger morbidity of locomotive syndrome is observed with RA patients than general population. GLFS-25, which has correlation with other QOL scores for RA, is considered as a potentially effective tool for evaluating RA patients.

W65-1

Prognostic factors for abatacept 3-year retention in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To identify prognostic factors for abatacept (ABT) 3-year retention in patients with rheumatoid arthritis (RA). [Methods] 437 RA patients who underwent ABT treatment over 12-weeks at TBCR group were enrolled in this study. Prognostic factors were identified by multivariate analysis using a Cox proportional hazard model. [Results] In univariate analysis, previous biologics medication (Y vs. N), Anti-CCP antibody positivity (Y vs. N), Steinbrocker stage (I/II vs. III/IV), concomitant MTX (Y vs. N), DAS28CRP at 12week were identified as potential prognostic factors. Multivariate analysis revealed that RF positivity (HR: 0.50, 95%CI: 0.27-0.93) and DAS28CRP at 12week (HR: 1.27, 95%CI: 1.05-1.54) were independently identified as prognostic factors. [Conclusions] RF positivity and DAS28CRP at 12week are independent prognostic factors for ABT 3-year retention.

W65-2

Predictors of relapse in patients with rheumatoid arthritis in clinical remission with biological DMARDs

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Conflict of interest: None

[Objective] To identify predictors of relapse in patients with rheumatoid arthritis (RA) in remission with biological DMARDs (bDMARDs). [Methods] A total of 404 patients with RA, who achieved clinical remission (DAS28-CRP<2.6) with the first bDMARD, were included in this study. Relapse was defined as discontinuation of the first bDMARD due to loss of efficacy. [Results] Patients were predominantly female (85%), and had a median age of 57 years, disease duration of 7 years and DAS28-CRP of 2.0. 154 (38%) patients had Steinbrocker stage I or II, 79% received MTX and 50% received glucocorticoids. According to Kaplan-Meier estimates, the cumulative incidence of relapse was 19% at 5 years after achieving remission. Multivariate analysis using the Cox proportional hazards model revealed that Steinbrocker stage (III/IV vs. I/II) (HR: 2.42, 95% CI: 1.04-5.66) and use of glucocorticoids (HR: 4.04, 95% CI: 2.02-8.09) independently predicted relapse. [Conclusions] Steinbrocker stage and use of glucocorticoids at achieving remission are independent predictors of relapse in patients with RA in clinical remission with bDMARDs.

W65-3

The effectiveness and safety of a therapeutic strategy targeting low disease activity (LDA) in elderly rheumatoid arthritis with lung diseases

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Conflict of interest: None

[Objectives] To evaluate the effectiveness of a treatment strategy targeting LDA in patients with elderly RA with lung diseases at baseline and monitor pulmonary complications. [Methods] We conducted a prospective single-center observational study of patients with elderly RA over two years. [Results] Of 190 patients (mean age 74.5 y/o, female 73%,, stageI+II 73%, DAS28 6.2±1.2, HAQ-DI 1.3±0.9), 54 cases with pulmonary comorbidities at baseline were identified, including interstitial pneumonia (IP) 59%, bronchiectasis/chronic bronchitis 37%, and emphysema 26%. They received lower rate of methotrexate (66%vs89%), higher of biologics (59%vs39%) and had more anti-CCP antibody. General linear model analysis showed that pulmonary comorbidities at baseline had no significant influence on the course of the DAS28 and HAQ-DI score. However the patients with lung disease at baseline were less likely to achieve LDA at week 104 (44%vs69%), and had more events of exacerbation of IP (13%vs2.2%) and pulmonary infection (26%vs8.8%) throughout two-year period. [Conclusion] A therapeutic strategy targeting LDA are effective in elderly RA with lung diseases at baseline, however optimal management of IP and pulmonary infections is required in this population.

W65-4

Achieving glucocorticoid free might decrease the risk of the clinical fractures in patients with rheumatoid arthritis - fifth-year results from The TOMORROW study-

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Conflict of interest: None

[Objectives] To reveal the correlation between decreasing dosage of glucocorticoid (GC) and the incidence of clinical fractures in RA (rheumatoid arthritis) patients during five years. [Methods] We investigated the effects of dosing of GC on the incidence of clinical fractures for 5 years in 208 patients with RA (mean age, 58.6 years; mean disease duration, 14.0 years) from a cohort named TOMORROW. [Results] The incidence of clinical fractures in patients with RA was 0.042/person-year. There were 87 patients (41.8%) treated with GC whose incidence rate and number of fractures were significantly higher than those without GC (27.4 vs. 11.9%; p=0.008, 0.063 vs. 0.012 py; p=0.012, respectively). Logistic regression analysis revealed that the use of GC was a significant risk factor for fractures (OR, 2.59; 95%CI, 1.22-5.47, p=0.031). Although the fracture risk did not decrease by reducing GC (OR, 0.61; 95%CI, 0.21-1.78, p=0.362), it was significantly lower if the dose of GC could be reduced to zero (OR, 0.21; 95%CI 0.70-0.65, p=0.006). [Conclusion] If the dose of GC was reduced to free during 5 years, the fracture risk could become lower. In conclusion, after controlling disease activity of RA we should decrease the dose of GC to free.

W65-5

Patient global VAS evaluated before doctors examination in the hospital sometimes differ from de-identified patient global VAS evaluated at home

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Conflict of interest: None

[Objective] To evaluate the reliability of patient global VAS before doctor's examination in hospital [Method] We asked RA patients to answer and mail the EQ5D data set anonymously. EQ5D consist of 5 component questions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and patient assessment global health VAS. EQ5D VAS is de-identified patient global VAS evaluated at home. We compared patient global VAS which is routinely surveyed before doctor examination at hospital with global VAS surveyed anonymously at home. [Result] There were poor correlations between patient global VAS at hospital correlate and de-identified VAS at home (r=0.426). The patient with high patient global VAS at hospital had statistical discrepancy between two VAS. [Conclusion] Patient global VAS is one of the most important evaluation items in RA practice. However, there is sometimes the discrepancy between patient global VAS evaluated before doctors examination in the hospital and de-identified patient global VAS evaluated at home.

W65-6

Predictive factor for forefoot deformity in early rheumatoid arthritis

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Conflict of interest: None

[Objectives]To determine predictive factors of forefoot deformity in early rheumatoid arthritis (RA).[Methods]Twenty-four outpatients with RA were enrolled. The mean age of patients was 57.8 years and the mean disease duration was 11.2 months. The mean DAS28, SDAI and mHAQ was 4.84, 21.9 and 0.29. Eleven patients (46%) were treated with csDMARDs and 8 patients (33%) were treated with glucocorticoids (GCs). Bilateral IP, PIP, MCP, wrist and MTP joints were assessed by semiquantitative assessment (0 - 3) using power Doppler ultrasound (PDUS). The sum score of all joints and MTP joints was used as total PDUS (TPD) and foot PDUS (FPD). Radiographic damages of feet were evaluated by using mTSS (footTSS). Forefoot deformities were evaluated by using hallux valgus, 1st to 2nd metatarsal and 1st to 5th metatarsal angle, and the sum of these angle were used as total deformity score (TDS).[Results] Twenty-one (87.5%) and 18 (75%) patients achieved DAS28 and SDAI remission. At final follow up, TDS was significantly progressed (ΔTDS

9.75), whereas mean ΔfootTSS revealed remodeling. Multiple regression analysis revealed GCs was a risk for forefoot deformity (p=0.01).[Conclusion]GCs use was a predictive factor for forefoot deformity in early RA.

W66-1

Influence of Methotrexate in the predictive biomarker with Tocilizumab effective RA patients

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Conflict of interest: None

The efficacy of biologics is different on individual RA patients, therefore we can never recommend the best biologics for each RA patient. We reported that serum IL-10 and IP-10 level could become predictive makers for the efficacy of TCZ in bio-naïve RA patients. On the other hand, it is known that MTX has an influence on cytokine. Therefore, it is suggested that MTX influence these biomarkers. (Objectives)We investigated the influence of MTX for predictive markers of bio-naïve RA patients. (Method) We classified bio-naïve RA patients in TCZ monotherapy (monotherapy group) and MTX combination therapy (combination group). We measured serum cytokine before TCZ administration using the ELISA in each group, and compared these cytokine between responder and non-responder at 24 weeks. (Result)We enrolled 27 bio-naïve RA patients who measured cytokine before TCZ administration, and classified these patients in monotherapy group (n=12) and combination group. In monotherapy group, serum IL-10 and IP-10 levels were decreased in responder group (P<0.05). There was no significance these biomarkers in combination group. (Conclusion)We suggested that it is necessary to consider the influence of MTX, when we investigated the biomarker to predict the efficacy of TCZ in bio-naïve RA patients.

W66-2

Change in RF Titers Reflects RA Disease Activity and Predicts Therapeutic Response during TNF Inhibitor Therapy

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Conflict of interest: None

[Objectives] To determine whether change of RF levels reflects RA disease activity and predicts therapeutic response. [Methods] Subjects were 61 RA patients who filled ACR RA criteria 1987, were biologics-naïve, were treated with TNF inhibitors, and had moderate to high disease activity and high titer of serum RF (≧100IU/ml). Their medical records were reviewed retrospectively. Serum RF levels were measured every 3 month during TNF inhibitors treatment. When RF levels were changed more than 10%, the change was judged as significant. RA disease activity was measured by DAS28-CRP. [Results] TNF inhibitor reduced RF levels in 90%, decrease of which has tendency to correlate with reduction of disease activity.Change in RF levels at 3Mo failed to predict disease activity at 12Mo.Among patients with RF reduction at 3month, 42.6% of cases showed re-elevation of RF titers and others revealed continuous reduction of the titers.Re-elevation of RF levels during 3-12Mo of TNF inhibitor therapy predict high disease activity at 12Mo in patients who failed to achieve remission or low disease activity. [Conclusion] Change in RF titers predicts therapeutic response of RA; Re-elevation of RF levels in patients who fail to achieve clinical goal predicts poor outcome.

W66-3

Significant radiographic progression as observed in the anti-carbamylated protein antibody (aCaPAb)-positive rheumatoid patients: A study in a group of patients with negative or low-positive ACPA under treatment with biologic DMARDs

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Conflict of interest: None

Background: A newly discovered anti-carbamylated protein antibody (aCaPAb) has been reported to emerge prior to disease-onset, associate with the conversion towards arthralgia, and follow a more severe disease course among the patients negative for ACPA. We here studied aCaPAb in 162 rheumatoid patients who were negative or low titer ACPA2 and under treatment with biological DMARDs. Methods: ACPA2 and aCaPAb were measured by using ELISA in sera of 162 RA patients who were clinically active (fulfilling either DAS28CRP>4.0 or DAS28ESR>4.2 and either CDAI>22 or SDAI>26) and under treatment with biological DMARDs (49 with ETN, 43 with IFX, 36 with TCZ, 13 with ADA, 12 with ABT, 9 with GLM). Results: Among 162 patients with RA, aCaPAb showed no correlation with ACPA2.Radiographic progression of aCaPAb-negative patients was greater as shown by cumulative probability plot and box scatter plots as compared with aCaPAb-positive patients (Mann-Whitney U test P=0.042). However aCarPFCS did not correlate with MMP-3, DAS28CRP or DAS28ESR.

W66-4

Clinical significance of ccfDNA in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Circulating cell-free DNA (ccfDNA) is a biomarker that reflects the medical condition and therapeutic response of solid cancer patients. We report here the relationship between ccfDNA and disease activity in patient with rheumatoid arthritis (RA). Method: The concentration of ccfDNA in joint fluids collected from knee joint of 13 RA patients and 12 patients with osteoarthritis (OA), and those in sera from 30 RA patients and 15 healthy controls, were measured by real-time PCR. ccfDNA in sera was measured for 23 RA patients administrating biological DMARDs, every 4 weeks from baseline to 24 weeks.We also evaluated simplified disease activity index (⊿SDAI) during 24 weeks period. Result: The concentration of ccfDNA in synovial fluids of RA was higher than OA (*P*=0.00011). The concentration of ccfDNA showed no significant difference between RA patients and healthy controls. The concentration of ccfDNA from 11 patients increased from baseline until 12 weeks (Group1), whereas those from 12 patients did not (Group 2). ⊿SDAI was significantly improved in Group1 (*P*=0.021). Conclusion: ccfDNA is considered to circulate in the peripheral blood by the reabsorption of synovial fluid. These results suggest that ccfDNA would be a biomarker to predict the therapeutic response for biological DMARDs.

W66-5

Methotrexate polyglutamates Concentration (MTX-PG) in erythrocytes as predictive factor of treatment response by increased dosage of Methotrexate; post hoc analysis of SAME study

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Conflict of interest: None

[Background and Objective] Recently MTX-PG could be measured and the cohort study concerning about the relationship between MTX-PG and treatment response was published. However, the weekly dosage of MTX in that study was 25mg and these results were not easily translated into our daily practice of RA treatment. Using our previous study, SAME study, we examined the potential ability of MTX-PG as the predictive factor of therapeutic response of MTX in Japan. [Methods] MTX dose was increased in 31 RA patients who had been insufficiently controlled by MTX (8 mg/week). Disease activity and MTX-PGs were monitored at baseline, 4, 8, 12 and 24 weeks. MTX-PGs were also detected by LC-MS/MS. MTX-PG until week 8 as the predictive value of EULAR good response and clinical remission at week 12 and 24 were estimated by using RoC curve analysis. [Result] MTX-PG3 at week 4>7.98 and MTX-PG2 at week 8>29.3 were predictors of EULAR good response at week 12. MTX-PG3 (>23.7) and PG4 (>0) at week 4 might be predictors of EULAR good response at week 24. MTX-PG1 (>28.8), PG2 (>18.6),PG3 (>8.0) and totalPG (>68.8) at week 4 might be predictors of clinical remission. [Conclusion]MTX-PG at week 4 could be predictive factors of clinical response after the increase of MTX dose.

W66-6

Immunophenotypic analysis of peripheral blood and its pathological significance in rheumatoid arthritis

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Conflict of interest: None

Objectives: The pathogenesis of rheumatoid arthritis (RA) consists of immune abnormalities associated with T-B cell interaction and inflammation with active synovitis. We performed immunophenotypic analyses in a correlation with clinical findings and responsiveness to biologic DMARD. **Methods:** The immunophenotyping of PBMC was defined based on comprehensive flow cytometric analysis in 117 RA patients and 26 healthy donors (HD). **Results:** The proportion of effector memory T (Tem) cells and Tfh cells was higher in RA compared with HD. The frequency of Tem cells was correlated with ACPA and that of plasmablasts was correlated with DAS28. The proportion of Tfh positively correlated with that of plasmablasts. Abatacept decreased the proportions of Tfh and Th17 cells. In contrast, TNF inhibitors increased Tem cells mainly Th17 cells. Tocilizumab tended to increase the proportion of Treg cells. **Conclusion:** These results imply that the T-B cell interaction may contribute to disease activity and autoantibody production in RA. In addition, abnormal regulation of lymphocyte differentiation independent on inflammation may underlie in the pathogenesis of RA. The immunophenotypic analysis might be useful in evaluating the pathogenesis and in determining the therapeutic target of each patient.

W67-1

Cytokine profiles in patients with anti-MDA5 antibody-positive dermatomyositis

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Conflict of interest: None

[Objectives]The aim of this study was to clarify clinical importance of the measurement of serum cytokine profiles in patients with anti-MDA5 Ab-positive dermatomyositis (DM). [Methods]We studied 32 patients with DM: 17 were anti-MDA5 Ab-positive and 15 were anti-MDA5 Ab-negative. At each patient's initial visit, serum IFN-α and ferritin were measured by ELISAs, serum mature IL-1βwere measured by immunoblotting using anti-cleaved IL-1β Ab and serum 42 cytokines were measured by multi-suspension cytokine array. The association between cytokine profiles with clinical feature were examined. [Results]Rapidly progressive interstitial lung disease was more complicated in the anti-MDA5 Ab-positive DM patients. Serum levels of 12 cytokines (IFNα, IL-6, IL-1a, IL-1ra, TNF-α, IL-4, IL-9, IL-15, VCAM-1, CCL2, CCL7, CXCL10) and ferritin were significantly higher in the anti-MDA5 Ab-positive DM patients. Serum levels of mature IL-1β were significantly higher in the deceased anti-MDA5 Ab-positive DM patients than the alived anti-MDA5 Ab-positive DM patients. [Conclusions]We observed that the differentiation of cytokine profiles between in the anti-MDA5 Ab-positive and negative DM patients. Mature IL-1β might be related to severity of anti-MDA5 Ab-positive DM.

W67-2

Clinical features and prognostic factor of anti-MDA5(melanoma differentiation-accociated gene 5) antibody-positive patients

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Conflict of interest: None

【Objective】The aim of this study is to investigate the clinical features and prognostic factor of anti-MDA5 antibody-positive patients. 【Methods】We studied 67 patients with DM and PM: 14 were anti-MDA5 Ab-positive and 25 were anti-ARS Ab-positive and 28 were MSA (myositis-specific autoantibody)-negative. Clinical manifestations in the patients with anti-MDA5 antibody were compared with those in the patients with anti-ARS antibody and MSA-negative patients. 【Results】Anti-MDA5 antibodies were detected at a significantly higher frequency in CADM patients than in DM patients. Patients with a positive expression of anti-MDA5 antibodies developed significantly more skin ulcerations than those without anti-MDA5 antibodies. The fatal case was four patients, and all cases were anti-MDA5 antibody positive examples, and an AaDO2 level was significantly higher than survivors, and mediastinal emphysema was found in all fatal cases. 【Conclusion】As for the patients whom a skin ulcer appeared in CADM case, anti-MDA5 antibody is detected in a high rate, we think that it is necessary to examine early multiple drug immunosuppressive therapy.

W67-3

Analysis of prognostic factors of clinically amyopathic dermatomyositis with rapidly-progressive interstitial lung disease at a tertiary medical center

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Conflict of interest: None

[Object] Clinically amyopathic dermatomyositis (CADM) with rapidly progressive interstitial lung disease (RP-ILD) is known to have extremely poor prognosis, mortality rate reaching 60%. There are few long survivors of CADM, and prognostic factors are yet to be clarified. We analyze the long survivors of CADM in our institution and speculate the prognostic factors. [Methods] A total of 11 patients who were diagnosed as anti- MDA-5 antibody-positive CADM with RP-ILD from 2011 to 2014 were analyzed retrospectively. [Results] The median age was 53 (range; 20-71), and the median value of serum albumin at first visit was 3.4 g/dl (range; 1.9-4.0), and that of ferritin was 727 ng/ml (range; 250.9-7440). All patients received immunosuppressive therapy and three died of respiratory failure. Median survival of the three was 120 days. Five patients younger than 50 all survived. Those whose ferritin and albumin levels responded to immunosuppressive therapy have a good prognosis. [Conclusions] Prognostic factors previously reported on dermatomyositis with ILD might not be the case in CADM with RP-ILD. Early responsiveness to immunosupressive therapy and younger patient population might lead to a better outcome. Further accumulation of CADM cases is needed.

W67-4

Mortality risk of anti-CADM-140/MDA5 antibody positive dermatomyositis

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Conflict of interest: None

[Objectives] To elucidate the mortality risk of anti-CADM-140/MDA5 antibody positive dermatomyositis (DM) in our hospital. **[Methods]** Twenty-two patients with anti-CADM-140/MDA5 positive DM were retrospectively evaluated for the mortality risk. Comparisons between responder and non-responder groups were made using chi-square test and student's t-test. **[Results]** Of 22 patients, 14 were alive (responder group) and 8 (non-responder group) were dead. Mean period from hospitalization to death was 48 ±17.9 days. The mortality rate of male was higher compared with that of female (4/5: 80% vs. 4/17: 23.5%, P= 0.02). Non-responder group was significantly more often complicated with pneumomediastinum (P= 0.0008). Mean serum KL-6, SP-D and ferritin levels at first visit were significantly higher in non-responder group compared with those of responder group (P=0.02, P=0.009, P=0.01, respectively). It was remarkable that all patients in non-responder group had high SP-D level whereas only one patient in responder group indicated high SP-D level. **[Conclusions]** These results suggest that complicating pneumomediastinum and serum SP-D level as well as serum KL-6 and ferritin levels were useful factors to predict the mortality risk in anti-CADM-140/MDA5 antibody positive DM.

W67-5

The cause of death in dermatomyositis-related rapidly progressive interstitial lung disease

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Conflict of interest: None

[Purpose] To investigate clinical features and cause of death rapidly progress respiratory failure in dermatomyositis (DM)-related interstitial lung disease (ILD). [Method] We retrospectively investigated 33 patients with idiopathic inflammatory myopathy from April, 2014 to August, 2015. Five out of 33 cases died for respiratory failure.[Results] The average age was 52.6 years. Two cases were DM, and three clinically amyopathic DM. One case did not show an ILD image, and four cases showed NSIP images in chest HRCT at the time of the first examination. The immunosuppressive drugs used before the development of rapid progressive ILD, were steroid pulses in 3 cases, IVCY + CyA in 1, AZP in 1. They showed rapid progressive of ILD with the average period of 40 days from the initial treatment. The immunosuppressive drugs for rapid progressive ILD were steroid palse in all cases, IVCY in 2, IVCY+CyA in 2, TAC in 1. Treatment-related adverse complications included myelosuppression in 2 cases, CMV in 2, aspergillosis in 2. The average period to death was 103.4 days from diagnosis. [Conclusion] Prevention of treatment-related complication is seems most important to improve a prognosis of the DM-related rapid progressive ILD.

W67-6

A case of successfully treated with polymyxin B hemoperfusion (PMX) for rapidly progressive interstitial pneumonia (RPIP) associated with clinically amyopathic dermatomyositis (CADM)

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Conflict of interest: None

Case report: A 55-year-old woman presented with fever and skin rash for the last 2 weeks. She also had progressing dyspnea and visited our hospital. Her physical examination revealed typical cutaneous manifestations (Gottron sign and herliotropic rash). No signs of involvement of muscle were observed. She had anti MDA5 antibody and her serum ferritin were elevated (443/μl). CT scan reveled nonsegmental interstitial shadow mainly distributed in the lower lobes. She was diagnosed as CADM with RPIP and treated high dose corticosteroids and cyclophosphamide, cyclosporine immediately. But her respiratory symptoms or her oxygen demand were not improved. On day 7and 8, she underwent PMX treatment which was carried out at flow rate 80ml/min for 12h. Following PMX treatment, her oxygen demand and CT scans improved remarkably. CADM is occasionally accompanied RPIP that is fatal and resistant to aggressive immunosuppressive therapy. We think that PMX is a potent therapeutic option in combination with the conventional treatment.

W68-1

Clinical characteristics of antisynthetase syndrome patients with hyperferritinaemia

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Conflict of interest: None

[Object] To elucidate the clinical characteristics of antisynthetase syndrome (ASS) patients with hyperferritinaemia. [Methods] The records of ASS patients who had been followed up in our hospital from 1 January, 2009 to 31 July, 2015, were examined. They were divided into two groups; with and without hyperferritinaemia (> 278 or 278 ng/dl), and their clinical characteristics were compared. [Results] Twenty-five patients with ASS were identified, 10 patients with hyperferritinaemia and 15 patients without it. The patients with hyperferritinaemia showed significantly higher frequencies of myositis (10/10 vs 8/15 cases; $p = 0.020$), fever (7/10 vs 4/15 cases; $p = 0.048$), and elevation of CRP (10/10 vs 7/15 cases; $p = 0.007$). Existence of malignancy (6/10 vs 1/15 cases; $p = 0.006$) and positivity of anti-EJ antibody were more frequently detected in hyperferritinaemia group (4/9 vs 0/14 cases; $p = 0.048$). [Conclusions] ASS patients with hyperferritinaemia were associated with myositis, fever, elevation of CRP, and frequent incidence of anti-EJ antibody positivity. Although in generally, the risk of malignancy was not demonstrated in ASS, malignancy could be associated with hyperferritinaemia and anti-EJ antibody.

W68-2

Features of polymyositis and dermatomyositis in patients with anti aminoacyl tRNA synthetase antibodies

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Conflict of interest: None

[Objectives] We investigated features of polymyositis (PM) and dermatomyositis (DM) in patients with anti aminoacyl tRNA synthetase (ARS) antibodies. [Methods] We investigated 50 patients with polymyositis and dermatomyositis, in which from April, 2002 to October, 2015, we treated 104 patients (PM/DM 34/70 respectively) and we detected the results of the anti ARS antibodies. We analyzed features of 13 PM/DM patients with anti ARS antibodies retrospectively. [Results] 9 of DM cases had anti ARS antibodies (9/40, 22.5%), 4 of PM cases had anti ARS antibodies (4/10, 40.0%). In patients with anti ARS antibodies, 12 of cases had interstitial pneumonia (12/13, 92.3%), 3 of cases had cardiac disorders (3/13, 23.0%), and 9 of cases had cancer (9/13, 24.3%). Interstitial pneumonia was commonly in patients with anti ARS antibodies, and 2 cardiac disordes was mainly myocarditis. [Conclusions] It was known that PM/DM patients with anti ARS antibodies had commnly interstitial pneumonia. Recently, it was repoted that patiets with anti ARS antibodies had myocarditis, and the prognosis of that was poor. In patients with unidentified heart failure and myocarditis, it was necessary that we recognized anti ARS antibodies synrdome.

W68-3

Clinical investigation of polymyositis/dermatomyositis associated with interstitial lung disease with anti-ARS antibody.

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Conflict of interest: None

[Objective]The myositis specific antibody (MSA) is significant clinical marker, in particularly associated ILD. We investigated the clinical manifestations with or without anti-ARS Ab in PM/DM patients with ILD. [Methods] Retrospective analysis was performed in 33 PM/DM patients (mean age 58 years-old, observation period 3.8 years) treated from 2013 to 2015. [Results] Positive anti-ARS Ab was detected in 12patients (4 anti-Jo-1, 5 anti-PL-7, 1 anti-PL-12, and 2 anti-EJ antibodies). Negative Anti-ARS Ab was seen in 21 patients (5 anti-MDA5, 3 anti-TIF1γ, 1 anti-MJ, 3 anti-SRP, 2 anti-RNP Ab. PM: DM ratio was not associated with or without anti-ARS Ab. The incidence of complicated ILD was seen more increased 75% in positive ARS than 43% in negative group (P<0.01). No difference of serum KL-6 and ferritin were between them. CNI with adding GC were administered in 7 with positive ARS and in 4 with negative ARS patients. The exacerbation of ILD was occurred in 7 (positive ARS) and 4 cases (negative ARS) and 3 among them were treated by CNI and IVCY. One patient died, but no patient need home oxygen therapy. [Conclusion] Positive ARS patients highly complicated with ILD. Aggressive therapy combined glucocorticoids and calcinurine inhibitor caused the favorable outcome.

W68-4

Anti-SS-A antibody as a risk factor for relapse in patients with polymyositis/dermatomyositis

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Conflict of interest: None

【Objective】To elucidate risk factors for relapse in patients with polymyositis (PM)/dermatomyositis (DM). 【Methods】Fifty patients (21 patients with PM and 29 with DM) who achieved remission at Okayama university hospital in 2004-2014 were included retrospectively. Candidate risk factors, such as patient background, disease-related characteristics, and treatment status, were compared between patients with and without relapse. Relapse was defined as exacerbation of clinical symptoms and/or laboratory data that requiring additional treatments. 【Results】Mean age was 58 years (16 male and 34 female). For mean observation period of 685 days, 21 patients (42%) developed relapse and 5 died. Relapsed patients exhibited muscle weakness less frequently and anti-SS-A antibody (SS-A-ab) positive more frequently (85% vs 100%; p=0.03 and 61% vs 28%, p=0.02, respectively). No significant difference was observed in any other factors. By log-rank test, patients with SS-A-ab exhibited higher relapse rate than those without SS-A-ab (p = 0.0381). After adjusting with age, sex, and lung involvement, SS-A-ab is still an independent risk factor for relapse (odds ratio, 4.92; 95% confidence interval, 1.29-22.0). 【Conclusion】SS-A-ab is a possible risk factor for relapse in patients with PM/DM.

W68-5

A retrospective study: Predictive factors for insufficient improvement of muscle weakness after treatment among patients with polymyositis and dermatomyositis

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Conflict of interest: None

[Object] The aim of this study is to investigate predictive factors for insufficient improvement of muscle weakness among patients with polymyositis and dermatomyositis (PM/DM). **[Methods]** Patients were included in this study when they met all these criteria: 1) fulfilled the Bohan & Peter classification criteria for PM/DM; 2) were administered to our university hospital for the treatment of muscle involvement of PM/DM from 2008 through 2015; 3) excepted for amyopathic DM, overlap syndrome and cancer-associated myositis. The data of clinical findings were retrospectively collected. **[Results]** Ultimately, 45 patients were included in this study (30 and 15 patients were PM and DM, respectively). As a result of multivariate analysis, 65 years old and above (odds ratio [OR] = 16; 95% confidence interval [CI] = 2-342; p <0.01), pre-treatment CK levels above 1900 U/L (OR = 22; 95%CI = 3-526; p <0.005), negativity of anti ARS antibody (OR = 9; 95%CI = 1.3-104; p <0.05) were associated with insufficient improvement of muscle weakness after 6 to 8 weeks from treatment. **[Conclusions]** This study indicated that 65 years old and above, pre-treatment CK levels above 1900 U/L, and negativity of anti ARS antibody were predictive factors for insufficient improvement of muscle weakness in PM/DM.

W68-6

Therapeutic outcome of patients with polymyositis/dermatomyositis

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Conflict of interest: None

[Object] The aim of this study is to clarify the present states of therapeutic outcome and disease activity in patients with polymyositis (PM)/dermatomyositis (DM). **[Methods]** A total of 128 patients with PM/DM were enrolled in this study. We retrospectively compiled the clinical data, which included types of myositis, complication, treatment, survival outcome, and disease activity. **[Results]** The number of DM, clinically amyopathic DM and PM patients was 72, 28, and 28, respectively. The complication of interstitial lung disease (ILD) and malignancy was found in 75 and 18 patients. High-dose of prednisolone (PSL), which the median dose was 50 mg/day, was administered as induction therapy in 119 (93%) patients. Immunosuppressive agents (IS) were also used in 74 (58%) patients. 18 patients died due to progressive ILD or malignancy.

The recurrence was revealed in 50 (39%) patients. Eventually, low-dose of PSL, which median dose was 5 mg/day, was received as maintenance therapy in 72 patients who still visit our hospital. IS was administered in two-thirds of those. High levels of myogenic enzyme or skin rash was rarely found in those patients. **[Conclusions]** Remission is maintained with low-dose PSL or combination with IS in most PM/DM patients without active ILD or malignancy.

W69-1

A new therapeutic approach targeting IL-23 for inflammatory myopathies

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Conflict of interest: None

Objectives A novel therapy for idiopathic inflammatory myopathies (IIM) is expected since some patients are refractory or intolerable to the current treatments. IL-23 plays a key role in some autoimmune diseases through IL-17A induction. The IL-23 blockade is effective and tolerable in psoriasis patients. Although C protein-induced myositis (CIM), an animal model of polymyositis, develops independently of IL-17A, serum concentrations of IL-23 in IIM patients are higher than controls. We hypothesized that IL-23 would be a novel therapeutic target if IL-23 acts on CIM with its bioactivities other than IL-17A induction. In this study, we investigated the role of IL-23 in CIM. ***Methods*** IL-23-null mice were immunized with C protein fragments. Anti-IL-23R antibodies were therapeutically applied to WT mice with CIM. The lymphnode cells from WT mice with CIM were transferred into naïve IL-23-null mice. ***Results*** IL-23-null mice were less susceptible to CIM than WT mice. The anti-IL-23R antibodies therapeutically ameliorated CIM. The severity of the transferred myositis observed in IL-23-null recipients was comparable to that in WT mice. ***Conclusion*** IL-23 has a pathogenic role in CIM independently of IL-17A. IL-23 blockade should be a novel therapy for IIM by attenuating autoreactive T cells.

W69-2

Efficacy and safety of intravenous immunoglobulin therapy in patients with polymyositis and dermatomyositis in a single institute

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Conflict of interest: None

【Objective】To examine the efficacy and safety of intravenous immunoglobulin therapy (IVIG) in patients with polymyositis/dermatomyositis (PM/DM). 【Methods】30 patients with PM/DM fulfilled the criteria of the Ministry of Health and Welfare who were seen at our University between 2011 and 2015 were received IVIG therapy (400 mg/kg for 5 days). We evaluated for the change in clinical symptoms, serum creatine kinase (CK), manual muscle test (MMT) score and activities of daily living (ADL) score. 【Results】Of 30 patients, 25 were DM and 5 were PM. 10 with DM had malignancy. Nine patients had anti-CADM140/MDA5 and other 5 patients had anti-ARS antibody. Mean CK after IVIG treatment decreased compared with that of before treatment (959.9 to 557.9). MMT score after treatment also improved compared with that of before treatment (3.86 to 4.04). 9 of 11 patients (81.8%) improved the symptom of dysphagia and 12 of 25 patients (48%) also improved in skin involvement after IVIG treatment. On the other hand, interstitial change in lung in patients with anti-CADM140/MDA5 antibody did not improve obviously. There was no adverse event except for thrombocytopenia. 【Conclusion】 These results suggest IVIG is effective for muscle and skin manifestations in patients with refractory PM/DM.

W69-3

Analysis of clinical manifestations associated with dose of corticosteroid as maintenance therapy in patients with polymyositis/dermatomyositis

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Conflict of interest: None

[Object] The aim of this study is to clarify clinical manifestations associated with dose of corticosteroid as maintenance therapy in patients with polymyositis (PM)/ dermatomyositis (DM). **[Methods]** A total of 128 patients with PM/DM were enrolled in this study. We retrospectively compiled the clinical data, which included types of myositis, complication, treatment and recurrence. We conducted multivariate analysis using multiple liner regression. **[Results]** Clinical manifestations associated with dose of corticosteroid as maintenance therapy were as follows: disease duration at diagnosis (t value, 2.4, p value 0.016), period from diagnosis to last visit (t value, -2.8, p value 0.019), presence of DM (t value, 2.87, p value 0.005), complication of interstitial lung disease (ILD) (t value, 2.81, p value 0.014), requirement of transfer assistance (t value, 3.12, p value 0.003). On the other hand, complication of malignancy, recurrence and usage of immunosuppressive agents were not significantly associated with corticosteroid dose as maintenance therapy. **[Conclusions]** It is possible to treat with lower dose of corticosteroid as maintenance therapy in PM/DM patients with shorter disease duration, without complication of skin rash or ILD, or without difficulty in transfer at diagnosis.

W69-4

Polymyositis complicated with systemic sclerosis and rheumatoid arthritis successfully treated with Tocilizumab: A case report

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Conflict of interest: None

A 30-year-old woman was diagnosed with systemic sclerosis (SSc) in 1995, and vasodilators had been given for peripheral angiopathy. In November 2014, she had symmetrical joint and muscle pain with CK elevation, and was diagnosed with polymyositis (PM), SSc, rheumatoid arthritis (RA) and Sjogren's syndrome complicated with interstitial pneumonia. Low-dose (8 mg/day) prednisolone (PSL) was started for myositis since the higher risk of renal sclerotic crisis due to high-dose PSL was suggested by the positivity of her anti-RNA polymerase III antibody. But both of PSL and subsequent intravenous cyclophosphamide were ineffective, and high fever was also observed. The following high-dose intravenous immunoglobulin was partially effective to relieve the fever, however, CK remained high. Azathioprine (AZP) was then added, but no obvious response was seen. We decided to administer tocilizumab in May 2015, and AZP was replaced to methotrexate. Finally, muscle symptom gradually improved, and the levels of CK was normalized. Here, we report a case of refractory PM associated with SSc and RA that was successfully treated with tocilizumab without using high-dose PSL. Tocilizumab was suggested to be a promising alternative choice for patients with PM with anti-RNA polymerase III positive SSc.

W69-5

Successful use of rituximab in anti-MDA5 antibody positive dermatomyosis with intractable cutaneous lesions: a case study

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Conflict of interest: None

We experienced a case of anti-MDA5 antibody positive dermatomyositis (DM) with painful rash and cutaneous ulcerations which showed a response to rituximab (RTX). A 52-year-old woman presented with proximal muscle weakness and pain, Gottron's signs, erythema of limbs and dyspnea. Serum creatine kinase and electromyography were normal and muscle biopsy performed and showed only varying degrees of atrophy. The chest high-resolution computed tomography scan revealed bilateral subpleural opacity with ground-glass attenuation. From these findings, she was diagnosed with DM and given intravenous pulse methylprednisolone therapy and intravenous pulses of cyclophosphamide. The muscle pain and interstitial pneumonia had improved after these therapies. However, painful rash did not abate and was marked by the development of ulcerations. She was additionally treated with intravenous immunoglobulin and the tacrolimus, but these had no effect. She was given two dose of rituximab (1g each) and showed remarkable improvement of painful cutaneous lesions. Afterwards, ELISA analysis of the patient's sera revealed anti-MDA5 antibodies. Our case demonstrated that RTX may represent a rescue therapy for patients with anti-MDA5 antibody-associated intractable cutaneous lesions.

W69-6

A case of dermatomyositis with lung cancer that could resume chemotherapy after intravenous immunoglobulin for the relapse of myositis and dysphagia.

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Conflict of interest: None

[Case] A 74-year-old man presented with erythema that developed one month before admission. He had skin rash on his trunk and knuckles, dysphagia, proximal myalgia, and muscle weakness. He was diagnosed as dermatomyositis (DM) from his clinical symptoms and elevated creatine kinase level (9294 mU/ml), and also as lung adenocarcinoma simultaneously. Prednisolone (PSL) (1 mg/kg) was given, followed by rapid improvement of his skin and muscle symptoms and disappearance of dysphagia. The dose of PSL was tapered to 15 mg/day to start chemotherapy. After the start of chemotherapy, febrile neutropenia and pneumonia developed and his skin rash and dysphagia relapsed. Chemotherapy was stopped due to his worsening condition. Because he hoped to restart chemotherapy, intravenous immunoglobulin (IVIG) was added instead of PSL dose-up. After 2 courses of IVIG, he could take oral intake from liquid diets and his symptom improved. High intensity signals of swallowing muscles by MRI disappeared and chemotherapy could resume after 3 courses of IVIG. [Discussion] This is a first case of a patient with DM and cancer treated with IVIG as an alternative therapy of PSL for the relapse of DM. IVIG may be useful to avoid excessive immunosuppressive state by the combination of steroid and chemotherapy.

W70-1

A 3-Year Study of Work Impairment in Patients with Rheumatoid Arthritis Based on the IORRA Cohort

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Conflict of interest: None

[Object] To study how work impairment in RA patients has changed over the past 3 years. [Methods] Patients with RA who participated in both of the IORRA conducted in 2012 and 2015 and those who worked for pay and were under 55 years at baseline were identified. Changes in the absenteeism (AB), presenteeism (PR) and overall work impairment (OWI) scores by the WPAI were evaluated. Patients with work impairment, defined as AB >0% or PR ≥30%, at baseline were classified according to whether or not they still had work impairment at 3 years. [Results] There were 1310 patients in this study. The AB, PR, OWI scores were 1.8%, 16.4% and 17.3%, respectively, at baseline, which remained unchanged at 3 years (2.1%, 16.4% and 17.6%, respectively). At baseline, 206 patients had work impairment, of whom 117 patients (DAS28, 3.1 at baseline [2.8 at 3 years]; J-HAQ, 0.80 [0.75]; %MTX user, 73.5% [76.9%]; %biologics user, 36.8% [38.5%]) continued to have it at 3 years, and 89 patients (DAS28, 3.2 [2.1 at 3 years]; J-HAQ, 0.54 [0.25]; %MTX user, 77.5% [82.0%]; %biologics user, 24.7% [39.3%]) were free from work impairment. [Conclusions] Work impairment has not been improved over the past 3 years; however, as many as 43.2% of patients with work impairment have experienced improved work productivity.

W70-2

Subjective Well-Being of Japanese RA patients who reach the target is higher than Japanese people

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Conflict of interest: None

[Object] To compare the Subjective Well-Being (SWB) of Japanese RA patients and identify the correlation factors [Methods] This study will be done in cooperation with the Cabinet Office Government of Japan Economic and Social Research Institute. This institute had previously conducted the "Well-being studies 2014" surveying the level of happiness of random selected Japanese and consisted of questions involving topics closely associated with well-being such as socioeconomic and health status. The same survey is done for RA patients at Kobe University Hospital and clinical data including disease duration, stage, class, disease activity, HAQ, complications and the therapeutic drug will also be collected at the same time. [Results] We performed multivariate analysis the data on RA patients (n=300) and Japanese people (n=7690). The SWB of RA patient with high disease activity and moderate disease activity is same as Japanese control. However, the SWB of RA patients with remission and low disease activity is higher than Japanese control. [Conclusions] Achieving the target of treatment among RA patients is associated with higher SWB than Japanese control.

W70-3

A Study on Characteristics of Rheumatoid Arthritis Patients Achieving No Depression with 6 Months of Biologic Treatment

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Conflict of interest: None

Objectives To study predictive factors for no depression after using biologics for 6 months. Methods The following 333 RA patient treated with biologic characteristics were investigated: age, gender, disease duration, the type of biologics, steroid and MTX dosage, serum RF, MMP-3, ACPA, TNF-α, and IL-6. SDAI for RA activity, HAQ for ADL, SF-36 for QOL, and HAM-D or SDS for depression were used for evaluation. No depression was defined by HAM-D≦7 or SDS≦39. The subjects were divided into 2 groups according to the presence or absence of depression, retrospectively. We excluded 140 patients and 193 patients were included. Results Compared with a group of RA patients with depression (n=130), without depression (n=63) had younger ($p=0.002$), male ($p=0.046$), lower steroid dosage ($p=0.002$), lower SDAI ($p=0.002$), lower HAQ ($p<0.001$), higher SF-36 ($p<0.05$), lower SDS ($p<0.001$), and lower HAM-D ($p<0.001$) were detected based on univariate analysis. On the other hand, younger age (odd ratio:1.10), males (0.01), lower steroid dosage (0.66), lower RF (0.97), lower HAQ (16.39) and higher SF-36 were detected based on logistic regression analysis. Conclusions It was suggested that RA patients with younger male and higher ADL and QOL at baseline are more likely to achieve no depression with biologic treatment.

W70-4

Assessment of patient satisfaction in patients with rheumatoid arthritis treated with biologic agents

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Conflict of interest: None

[Purpose] To evaluate satisfaction in patients with RA treated with biologics. [Method] Patient satisfaction was assessed utilizing patient satisfactory scores of AIMS-2. Satisfaction was compared before and after 6-months of treatment with biologics. [Results] Patients with RA (n=85) were recruited. 39 patients were treated with tocilizumab, while 46 patients with anti-TNF agents (ADA:16, IFX:17, ETN:13). In both before and after treatment, disease activity such as DAS28-CRP showed no significant difference between 2 groups. All these factors improved after treatment with each biologic. Out of 12 satisfaction scores, all scores except "understanding and support for patients' problems by families or friends", showed significant improvement with treatment by each biologic. Moreover, absence from work, reduction of working time and productivity showed significant improvement after treatment with each biologic. [Conclusion] Patient satisfaction, as well as physical function, pain, mental aspect and work, showed significant improvement by 6-months of treatment with TCZ or anti-TNF agents. However, there was no significant improvement regarding "understanding and support for the problems RA patients have". To solve these problems, health professionals' supports are required.

W70-5

Multicenter study of simultaneous treatment with biologics and intra-articular injection of triamcinolone acetonide in patients with rheumatoid arthritis tolerated with biologics: the efficacy and safety of K-method

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Conflict of interest: None

[Purpose] Efficacy and safety of simultaneous treatment with biologics and intra-articular injection of triamcinolone acetonide in RA for tolerated patients with biologics were analyzed in multicenter biologic cohort (MBC) study.[Methods] 43 patients of RA, 6 male, 37 female, mean age of 63.5 years, mean disease duration of 10.4 years including control group with 19 patients, 3 male, 16 female, mean age of 62.4 years, mean disease duration of 12.0 years, and K-method group with 24 patients, 3 male, 21 female, mean age of 64.5 years, mean disease duration of 9.2 years were compared DAS28 (CRP) at baseline, 4, 8, 12 and 24 weeks. Intra-articular injection of triamcinolone acetonide was performed within 7 days after biologic treatment.[Results] DAS28 (CRP) was 4.68±1.26 in control group and 4.90±1.30 (p=0.51692) at baseline. However DAS28 (CRP) was 3.50±1.29 in control group and 2.53±1.22 (p=0.03548) at 24 weeks. In 28 patients of K-method group, delta DAS28 (CRP) was significantly correlated with the time of injection inversely (p=0.0372, r=-0.396). No adverse events were recognized in this study.[Conclusion] The efficacy and safety were recognized for simultaneous treatment with biologics and intra-articular injection of triamcinolone acetonide in RA by multicenter cohort study.

W70-6

Erosive esophagitis in a patient with rheumatoid arthritis during abatacept treatment

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Conflict of interest: None

A 67-year-old woman admitted to our hospital because of severe stomatitis. She was diagnosed with rheumatoid arthritis in 2007. She was treated with methotrexate, but it was stopped because of stomatitis in 2013. In July 2014, we administered abatacept. One month and half later, she suffered from sore throat and stomatitis, and subsequently she became incapable of eating. She admitted to our hospital. C-reactive protein level elevated to 13mg/dl. Esophagogastroduodenoscopy showed esophagus erosions. We treated with antibiotics and Acyclovir, but she didn't show any improvement. However, she gradually improved without specific therapy in several weeks. Histological examination of the erosion, serological tests such as autoantibodies and anti-herpes virus antibodies, and survey of other organ damage did not show any specific findings for the cause of erosive esophagitis. Then we started tocilizumab therapy for the treatment of rheumatoid arthritis, while she never had pharyngeal erosions and stomatitis. Therefore erosive esophagitis and stomatitis in this patient could be associated with abatacept treatment.

W71-1

The examination of the influence of abatacept therapy for bio-naïve RA patients with MTX inadequate response (MTX-iR) -multi center, prospective clinical study (The examination for time of intervention, Final report) ; Can we select abatacept for RA patients as 1st biologic? - (ORIB study)

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Conflict of interest: None

【Object】We planned ORIB study to find out a treatment strategy of RA. 【Methods】We selected valid 19 subjects compared with duration of start ABA therapy (≤12months;VERA and >12months;other), who were patients enrolled into ORIB study, for analysis of joint destruction. And we examined the influence factors about time to ABA preparation intervention gave for clinical effect. 【Results】We compared with VERA and other. Disease activity» The difference was indicated statistical significant as following items. ·DAS28CRP, SDAI, CDAI and Boolean-based definition at Week 24, 36 and 48 ·DAS28ESR at Week36 In the response, the difference was showed significant on and after week12. Functional assessment by J-HAQ» Every assessment points were no difference, but they showed statistical significant difference about the alternating. Radiographic assessment by mTSS» They signified the difference of Δerosion score statistically. 【Conclusion】 We suggested that ABA therapy from a disease early stage was more effective, and could give the good outcome for RA patient.

W71-2

Examination of the remission and sustained remission rates of abatacept treatment for patients with rheumatoid arthritis with high and moderate disease activity

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Conflict of interest: None

[Objectives and Methods] We investigated the remission and sustained remission rates in 502 rheumatoid arthritis patients enrolled in the Tsurumai Biologics Communication Registry (TBCR) who had started abatacept (ABT) treatment by October 2014. Patients were divided according to disease activity into high (H; n = 274) and moderate (M; n = 139) groups. Remission was defined as the change in DAS28-CRP. Remission and sustained remission rates at week 52 for patients with remission at week 24 based on the baseline DAS28-CRP were compared. [Results] The remission rates at weeks 24 and 52 were 11.4% and 16.9%, respectively, in the H group, and 31.3% and 38.8%, respectively, in the M group. Remission was achieved earlier in the M group. The sustained remission rates at week 52 for patients who showed remission at week 24 were 81.8% in the H group and 72.3% in the M group. [Conclusion] Considering the earlier remission and lower maintenance required for patients in the M group, our results suggest that earlier initiation of ABT treatment when patients show low disease activity may improve remission. Because the remission rates increased from week 24 to 52 in the H group, at least 6 months are required to determine the effect of ABT treatment in this group.

W71-3

The retention rate of abatacept in latter-stage (75 years and above) elderly patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To analyze the retention rate of abatacept in latter-stage elderly patients with rheumatoid arthritis (RA). [Method] Data was collected retrospectively from medical records of RA patients in our center. Abatacept was administered in 58 patients. We divided them into two groups of latter-stage elderly group (over 75 years of age) and the remaining group (under 75 years of age). We analyzed the retention rate of each group by Kaplan-Meier curves and log-rank test. [Results] In the latter-elderly group (29 cases: 81.6 ± 3.3 years), the cumulative retention rates in 12 and 24 months were both 0.558. In the remaining group (29 cases: 63.4 ± 10.7 years), the cumulative retention rates in 12 and 24 months were 0.705 and 0.617 respectively. There was no significant difference in the retention rates in the two groups (log-rank test, p=0.913). The main reasons for discontinuation of abatacept were hospitalization for infection (elderly: 3 cases, remaining: 2 cases) and hospitalization for gastrointestinal symptoms (elderly: 2, remaining: 0). [Conclusion] Our data suggested that abatacept can be used for a long period even for latter-stage elderly RA patients.

W71-4

The usefulness of abatacept switching for rheumatoid arthritis patients who were in remission with biological DMARDs

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Conflict of interest: None

The maintenance of the remission is extremely important by treatment of rheumatoid arthritis (RA), but it is a problem that an infection risk rises to continuously administer an immunosuppressive drug. About the reduction of the infection risk, glucocorticoid, immunosuppressive DMARDs and biological DMARDs (bDMARDs) reduction or cancellation are selected, but RA control does not rarely turn worse. Therefore we consider that whether reduction of infection risk and maintenance remission of RA is possible by changing occupied bDMARD to Abatacept (ABT). The object is 22 RA patients who achieved remission using bDMARD except ABT. 15 cases (C group, two men and 13 women) continued bDMARD and seven cases (S group, two men and 5 women) changed to ABT. The average DAS28-CRP at 0 month is 1.56 and 1.68, average DAS28-CRP at sixth month is 1.79 and 1.85, respectively. For 6 months, infectious disease are not serious and 0.09 person-month in S group and 0.03 person-month in C group. the infection risk was not reduction, but equal. The remission achievement rate was 85.7% in S group, 80.0% in C group, and there was not the significant difference between both groups. It was suggested that the switching to ABT could become one of the option to maintain remission of RA activity.

W71-5

Inhibitory effect of abatacept on small and large joint damage in rheumatoid arthritis patients with or without concomitant methotrexate: a retrospective multicenter analysis of 12 months of abatacept treatment

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Conflict of interest: Yes

Objectives: The purpose of this study was to clarify the inhibitory effect of abatacept on small and large joint damage in RA patients with or without concomitant MTX. *Methods*: We developed FIT-RA registry, and a retrospective multicenter study was conducted using this registry. Patients with RA who underwent abatacept treatment for 52 weeks were analyzed. Radiographs of hand, foot, shoulder, elbow, hip, knee and ankle joints were obtained at baseline and week 52. Joint damage scores were assessed by two independent readers using the modified total Sharp score (mTSS) and the ARASHI change score. *Results*: Radiographic analysis was performed for 43 patients who completed 52-week abatacept treatment. Rates of the structural remission using mTSS was achieved in patients with and without concomitant MTX were 58.3% and 68.4%, respectively. There was no significant difference in achievement of radiographic remission. In shoulder, elbow, hip, knee and ankle joints, there was also no significant difference in achievement of radiographic remission using ARASHI change score between with and without MTX. *Conclusions*: Abatacept showed same inhibitory effect on small and large joint damage with or without concomitant MTX.

W71-6

Effect of tocilizumab treatment on the levels of oxidative stress markers in patients with rheumatoid arthritis: the 52-week analysis

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Conflict of interest: None

< Objective > The prognosis of patients with rheumatoid arthritis (RA) is associated with enhanced risk of atherosclerotic cardiovascular (CV) disease. Oxidative stress is involved in the process of atherosclerosis. In this study we have sought to determine the effect of tocilizumab (TCZ) treatment on the levels of oxidative stress markers in RA patients. < Methods > Levels of 8-OHdG and 8-iso-PGF2a in urine of RA patients treated with TCZ were evaluated by enzyme immunoassay and enzyme-linked immunosorbent assay, respectively, at baseline and 52 weeks. < Results > 32 out of 82 patients with RA (mean age 60.6 years old; mean disease duration 8.7 years; concomitant MTX 56.3%) were studied. The rate of DAS28 (ESR) and CDAI remission at 52 weeks was 79.3% and 33.3%, respectively. In all patients levels of 8-OHdG in urine were decreased (at baseline, 12.4 ng/mg Cr; at 52 weeks, 9.9 ng/mg Cr), while levels of 8-iso-PGF2a in urine were not altered (at baseline, 347pg/mg Cr; at 52 weeks, 380 pg/mg Cr). By subgroup analysis, levels of urinary 8-OHdG were statistically decreased in patients with short disease duration (< 2 years) and low BMI (< 25). < Conclusions > These findings suggest that treatment with TCZ improves the prognosis of patients with RA by lowering the risk of CV events.

W72-1

Effectiveness and treatment persistence of biologics after switching

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Conflict of interest: None

[Objectives]To explore effectiveness and treatment persistence of biologics after switching [Methods]Among patients with secondary failure to biologics switched to other biologics at this institution, we examined effectiveness of tocilizumab (TCZ) (n=61 as second-line and 18 as third-line), abatacept (ABT) (n=26 and 15), golimumab (GLM) (n=16 and 10), certolizumab pegol (CZP) (n=14 and 10), adalimumab (ADA) (n=13 and 4), and etanercept (ETN) (n=9 and 2). Infliximab was used only as first-line. Disease was assessed using DAS28 (ESR) and SDAI. The remission, low disease activity, and treatment persistence rates were compared. [Results] For second-line, the remission and low disease activity rates were highest with TCZ followed by GLM, CPZ, ETN and ABT tied with ADA and the treatment persistence rate highest with TCZ followed by ETN, GLM, ADA and CZP tied with ABT with significant differences between the drugs. For third-line, the remission, low disease activity, and treatment persistence rates were all highest with TCZ followed by CPZ, GLM and ABT with significant differences between the drugs. [Conclusion] Our results may provide a guide for selecting optimal subsequent biologics among various biologics in patients with secondary failure to first-line or later biologics.

W72-2

Switch of bDMARDS in1st Department of physical in Nagasaki University Hospital

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Conflict of interest: None

[Object] a name of 237 patients first given bDMARDS in 418 continuously in our House until December 31, 2014 or newly bDMARDS introduced into by April 30, 2015 from April 1, 2014 using the bDMARDS and changed, a period of service in our course by May 30, 2015. [method] February 4, 2004 to summarize the information of the use situation and the switch of the bDMARDS. I divided a group into 4 group to the change of the introduction drug and examined it. [result] first six, IFX group all cases. for 2 quarters,13 of 29 cases are ETN introduction. 3 sittings are 36 cases; 4 cases are TCZ,16cases are ETN.The 4th 166 cases; 25 are ABT, 37 are TCZ, 1 is tofacitinib, 31cases are ETN, 73 cases are TNF - α group (IFN, adalimumab (ADA), GLM)).2 people continue IFX at the time of the 1st quarter. In 2 quarters 3 example continue IFX, and 5 continue ETN.In three quarters ETN group are 10,TCZ group are 1 and TNF - α group (IFN,ADA)are 5+1 are continued first drug.In four quarters 21 ABT group, 32 TCZ group, 28 ETN group, 48 TNF - α group (IFN, ADA, (GLM), (CZP)) are continued introduction drug. [conclusion]the person who was able to continue it with one drug are amounted to 65%.

W72-3

A review of the picture and feature of biological agents switchers with rheumatoid arthritis in our hospital.

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Conflict of interest: None

[Object] To assesse actual way and the reason for change of biological agents (BIO) on patients with rheumatoid arthritis (RA).[Methods] Three hundreds and thirty six cases were initiated some BIO as a first one.The way of switching BIO (TNF inhibiter[T],non-TNF inhibiter[NT]), their courses and reasons (escape[E], not effective[N], adverse events[AE]), others[O]) were investigated.[Results]Fifty eight switchers were divided into 3 groups as to the count of switching i.e. 47 cases switched one time (group A),8 cases two times (group B), and 3 cases three times (group C).The reason is as follows; group A:T→T:20 (E3,N4,AE7,O6), T→NT;22 (E5,N7,AE8,O2),NT→NT;5 (E0,N2,AE3),groupB:T→T→T;2 (N→N;1O→O;1),T→T→NT;1 (E→AE),T→NT→ T;4 (E→AE;1,AE→AE;1,AE→O;1,O→AE;1),NT→T→T:1 (AE→N),groupC:T→NT→NT→T;1 (O→O→O),T→T→T→NT;1 (AE→N→AE),T→NT→T→T;1 (E→E→E).[Conclusion]These results showed that there is a tendency to choose the same target BIO as previous one for escaped cases, and choose different one for the primary failure.

W72-4

Continuity Analysis on Switching Cases by CISA

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Conflict of interest: None

We analyzed 4,776 cases treated with biological agents in 13 national university hospitals retrospectively by using DRG data. Tocilizmab showed best continuity (median 3.09) in all biological agents, especially in switched cases (median 3.64) while in naïve cases abatacept showed best continuity (median 3.82). In the cases switched to tocilizmab, those from abatacept showed lowest continuity (median 0.92).

W72-5

The best selection of second biologics for patients with rheumatoid arthritis in daily clinical practice

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Conflict of interest: Yes

Objectives: This study aimed to evaluate the effectiveness of biologics as 2nd-line use in RA patients in daily clinical practice. **Methods:** We retrospectively examined 2400 patients who were treated with biologics in our institute. We compared the effectiveness of TNF-inhibitors, TCZ, ABA as 2nd-line use and efficacy of switching from 1st TNFi to 2nd TNFi, TCZ or ABA. Propensity score (PS) were generated using multinomial logistic regression. **Results:** 409 patients were treated with 2nd biologics. Patients with a short disease duration, high titers of ESR, CRP and MMP-3 were treated with TCZ, and ETN was chosen for elderly patients. In terms of switching of biologics, better treatment outcome of ⊿CDAI was observed in order of TCZ (n=107) >2ndTNFi (n=135) >ABT (n=58) but was comparable after the adjustment by PS. Comparison of upper and lower percentile in CDAI at 1 y revealed that higher ESR or MMP-3 predict better outcome in TCZ. **Conclusions:** After adjustment using PS-score, RA patients with prior anti-TNF exposures had similar outcomes if they switched to a new TNFi as compared with initiation of TCZ or ABA. Also our results suggest that higher ESR or MMP-3, suggesting inadequate suppression of IL-6 by first biologics, predict better outcome of TCZ.

W72-6

Clinical features associated with rheumatoid arthritis patients switching of three or more biologic disease- modifying antirheumatic drugs

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Conflict of interest: None

Purpose: The purpose of this analysis is to characterize RA patients switching of three or more bDMARDs in daily clinical practice. Method: Data were collected retrospectively in 27 RA patients. RA patients were divided into 4 cohorts with first switching treatment: those who switched from TNFi to another TNFi (TNFi cycler, n=12), TNF to nTNFi (abatacept, tocilizumab, nTNFi switcher, n=12), nTNFi to TNFi (n=2), and nTNFi to nTNFi (n=1). Differences in baseline characteristics and treatment after switching bDMARDs were analyzed. Results: Baseline of RA patients was as follows: mean age 58.9, female 75%, RF positive 89.3%, ACPA positive 86.4%, concomitant MTX 66.7%, mean SDAI 25.26, mean DAS28 5.25. Rate of continuation at 1 year, DAS28 and SDAI remission in the treatment to TNF cycler by switching to nTNFi (n=11) was 63.6%, 63.6%, and 54.5%. Rate of continuation at 1 year, DAS28 and SDAI remission in the treatment to nTNFi switcher by switching to nTNFi (n=8) was 50%, 25%, and 25%. 75% of treatment to nTNFi switcher by switching to TNFi (n=4) was failed. The correlation with concomitant MTX was less seen above bDMARDs switching treatment. Conclusion: Treatment of switching of three or more bDMARDs to refractory RA was resistance before nTNFi treatment in spite of MTX treatment.

W73-1

Identification of Novel Serum Biomarker for the Salivary Glandular Dysfunction of Primary Sjögren's Syndrome

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Conflict of interest: Yes

«Background» To assess salivary glandular dysfunction of primary Sjögren's syndrome (pSS) patients, stimulated whole salivary flow and the scintigraphy tests have been used. However, these are at a disadvantage in the aspect of versatility or cost-effectiveness. Thus, development of more effective markers is desired in the clinical settings. «Purpose» To identify novel serum biomarker for the salivary glandular dysfunction of pSS «Methods» A total of 1100 serum protein concentration in 30 pSS patients and 30 healthy controls were measured using high-throughput proteomic assay, and differentially expressed proteins (DEPs) in pSS patients were extracted. Next, these were compared with assessments by scintigraphy. «Results» We statistically extracted 57DEPs. Salivary gland functions in 15 pSS patients who underwent scintigraphy were classified into normal or dysfunction groups by time activity curve patterns. We compared the measured values of proteins between two groups and identified 8 proteins such as CXCL13, fractalkine as for parotid glands, and 2 proteins, IL-8 and PD-L2 as for submandibular glands were significantly increased in the dysfunction group. «Conclusion» We identified 10 candidates significantly increased in the pSS patients with salivary dysfunction.

W73-2

Ultrasonagraphic assessment of submandibular glands in early-stage Sjögren's syndrome

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Conflict of interest: None

Objective: The aim of this study was to examine the usefulness of submandibular gland ultrasonography (SGUS) in early-satge Sjögren's syndrome (SS) which was preserved salivary flow. Methods: Thirty-eight anti-SS-A antibodies sero-positive patients were studies. Lip biopsy was performed for the diagnosis of SS. Gum test was performed to examine salivary flow. SGUS findings were evaluated by US staging score and PD grading score. Results: We observed 9 non-SS patients, 13 SS patients with low salivary flow (L/SS) and 16 SS patients with normal salivary flow (N/SS). There were no significant differences among non-SS, N/SS and L/SS in the frequency of antibodies such as RF, FANA and anti-SS-B. However, the size of SG was significantly smaller in L/SS ($216.1\pm59.7mm^2$) than in non-SS ($325.9\pm66.2mm^2$) and N/SS ($311.3\pm98.7\ mm^2$) patients ($p<0.005$). US staging scores and PD grading scores were significantly higher in L/SS (2.85±0.38, 1.62±0.51) than in non-SS (0.89±1.05, 0.33±0.71) and N/SS (1.44±1.15, 0.44±0.51) patients ($p<0.001$, $p<0.001$). Conclusions: SUSG may be a useful tool for the diagnosis of SS which was impaired salivary flow but not for non-SS and early-stage SS which was preserved salivary flow.

W73-3

Utility consideration of salivary gland ultrasonography for Sjogren's syndrome

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Conflict of interest: None

«Object» The revised Japanese Ministry of Health criteria for SS include sialography and scintigraphy. Recent studies have shown that salivary US is also useful. We evaluated whether there is a correlation between finding of parotid US and saliva secretion,ESSDAI,anti SSA,SSB antibody,serum IgG, «Methods» The findings of parotid gland was graded on a scale of 0-4, as Nagasaki classification. «Results» This study subjects were 80patients with SS.The age of the patient was 30~83 years old (mean 56.2±12.8).The saliva secretion in gum test is 0.5-35ml (mean 7.15±7.2). The number of Grade0/1/2/3/4 in parotid US is 7/25/5/16/15 respectively. The average saliva secretion according to US Grade is 12.9/7.4/7.5/3.7/1.7ml and admitted clear negative correlation by

Grade0/1/2/3/4 (r=-0.5453). Positive correlation was also admitted between ESSDAI (r=0.3754) and IgG (r=0.3426) with US Grade. «Conclusions» The findings of parotid US in SS patient is correlated with activity, immune abnormality of SS and saliva secretion. It suggested that a parotid US can be substitution of sialography and sialoscintigraphy.

W73-4

Clinicopathological characteristics of anti-centromere antibody-positive Sjögren's syndrome in the presence or absence of systemic sclerosis

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Conflict of interest: None

Objectives: Few studies have clarified differences in sicca symptoms, ESSDAI score, and organ involvement in anti-centromere antibody (ACA)-positive Sjögren's syndrome (SS) with and without systemic sclerosis (SSc). We compared clinicopathological characteristics between these two groups using our cohort of patients with ACA-positive SS. Methods: We studied 33 patients with ACA+ primary SS and 16 with ACA+ SS with SSc in a retrospective cohort study. All SS patients met Japanese and/or ACR criteria, and those whose results exceeded the focus score by 1 underwent labial salivary gland biopsy. All SSc patients met ACR/EULAR criteria. We analyzed SS and SSc data at diagnosis and organ involvement during follow-up. Results: No significant differences were seen in age, sex, laboratory data, ESSDAI score, organ involvement, and treatment. Focus score was 3.34 ± 2.98 in ACA+ primary SS and 3.57 ± 2.04 in ACA+ SS with SSc (p=0.055). Scores for Saxon's test were 0.59 g vs 0.54 g (p=0.57); Schirmer's test, 6.4 mm vs 5.4 mm (p=0.56); and Raynaud's phenomenon, 21.2% vs 87.5%(p<0.001), respectively. Conclusion: ACA+ SS with and without SSc showed severe sicca symptoms. Focus score was higher in the ACA+ SS group than in the SS+ SSc group.

W73-5

BAFF binding inhibitors which target a BAFF-receptor (BR3) are drug candidates for primary Sjögren's syndrome

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Conflict of interest: None

Background and Purpose: In our previous study, we found that the elevated expression of BR3 on monocytes is involved in overproduction of IgG by B cells in patients with primary Sjögren's syndrome (pSS). In this study, we show our latest data about drug discovery for pSS targeting BR3. Specifically, we extensively investigated the characteristics of BAFF binding inhibitors discovered by our original high throughput screening (HTS) system. Methods: HTS of a chemical library was carried out to search for compounds that block binding of soluble BAFF (sBAFF) to BR3. Peripheral monocytes prepared from pSS patients were cultured in vitro with or without pSS B cells in the presence of sBAFF and BAFF binding inhibitors. IL-6 production by monocytes and IgG production by B cells were measured by ELISA. Results: We discovered two pyrrolopyrimidine derivatives, BIK-12 and BIK-13, which showed substantial inhibition of sBAFF-binding. sBAFF-induced IL-6 production by peripheral monocytes was significantly suppressed by BIK-12 and BIK-13 in a dose dependent manner. Similarly, IgG production by B cells co-cultured with sBAFF-stimulated peripheral monocytes was also significantly suppressed by these compounds. Conclusion: Our findings suggest that these compounds are drug candidates to treat pSS.

W73-6

Analysis of the expresssion and function of toll-like receptor 7-9 in labial salivary glands in patients with Sjogren's syndrome

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Conflict of interest: None

[Objectives]The aim of this study was to clarify the expression and function of toll-like receptor (TLR) 7-9 in Sjogren's syndrome (SS). [Methods]Expression of TLR7-9 and co-expression of TLR7 and cell phenotype were examined by immunofluorescence in labial salivary glands (LSGs) from SS patients and healthy controls. Expression of downstream molecules of TLR7 was examined by Western blot and immunofluorescence in cultured primary salivary gland epithelial cells (SGECs) obtained from SS patients. [Results]TLR7 was found in cell infiltrate and ducts of LSGs from SS patients. TLR9 was found in ducts of LSGs from SS patients. However, it was weakly found in cell infiltrate of LSGs from SS patients. Co-expression of TLR7and CD20 was strongly found, co-expression of TLR7 and dendritic cell marker was also found in cell infiltrate of LSGs from SS patients. In contrast to LSGs, stimulation of SGECs with loxoribine induced the translocation of interferon regulatory factor-7. However, it didn't induced the expression of tumor necrosis factor receptor-associated factor-6. [Conclusions]We observed that expression of TLR7 admitted more predominantly than TLR9 in the cell infiltrate of LSGs from SS patients. However, expression of TLR7 and TLR9 admitted in the ducts of LSGs from SS patients.

W74-1

Clinical analysis of anti-SS-A antibody positive and anti-CCP antibody double positive arthritis patients

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Conflict of interest: None

[Object and Methods] In more than half of primary Sjogren patients (pSS), arthritis is observed during the clinical course. Moreover, anti-CCP antibody (ACPA) had been reported as positive for 18% of pSS. We analyzed the clinical differences between 38 anti-SS-A antibody positive patients (DP group) and 113 negative patients (SP group) in ACPA positive DMARDs naïve arthritis patients. [Results] In an age and the level of ACPA (U/mL), RF (IU/dL), CRP (mg/dL) and MMP-3 (ng/mL), there were no significant difference in DP group and SP group. IgG level (mg/dL) was significantly higher in DP group compared to SP group (1632±433vs1378±296, p<0.0001). DMARDs started patients (Tx+) were significantly lower in DP group (42% vs 69%, p<0.005) compared to SP group. In DP group, ACPA (177±237 vs 526±571, p<0.05), CRP (0.25±0.34 vs 2.00±3.66, p<0.05), MMP-3 (52.9±28.6 vs 164.2±172.9, p<0.005), IgG (1580±545 vs 1798±316, p<0.05) were significantly higher against DMARDs unstarted patients (Tx-). In SP group, RF (79±167 vs 80±94, p<0.05), CRP (0.43±1.07 vs 0.91±1.73, p<0.005) were significantly higher against Tx-. [Conclusion] The administration rate of DMARDs was lower in DP group than in SP group. There were immunoserological differences between the two groups.

W74-2

Assessment of association between inulin clearance and estimated glomerular filtration(eGFR) in patients with rheumatoid arthritis(RA)

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Conflict of interest: None

[Objectives] Recently, eGFR equations based on creatinine (Cr) or cystatin C (CysC) was commonly used for the estimation of renal function. However, we might not make an accurate assessment of the renal function of RA patients. We evaluated the performance of various types of eGFR equations. [Methods] 16 RA patients were enrolled in this study. We measured GFR by inulin clearance, and compared with estimated creatinine-based GFRs (eGFRcreat), and estimated cystatin C-based GFRs (eGFRcys), and heir average values (eGFRave). [Results] mGFR was 75.8±21.9ml/min, eGFRcre was 84.7±34.0ml/min, eGFRcys was 65.4±22.2ml/min, and eGFRave was 75.1±25.6 ml/min. The intraclass correlation coefficients were 0.639, 0.816, and 0.777, respectively (P =0.029, 0.017, <0.001). Althoug the mean differences between Cin and eGFRcys and eGFRave (-10.3±13.4, -0.68±16.2) were significantly lower than difference between Cin and eGFRcreat (9.0±26.1) (p=0.009, 0.009), 20% accuracy of Cin and eGFRcys, eGFRave showed no significantly differences compared with that of Cin and eGFRcreat (p=0.611, 0.197). [Conclusion] In RA patinets, eGFRcys and eGFRave had lower biases than eGFRcreat, but had no differences in accuracy. We must increase enrolled number of cases, and asses the correlation between Cin and eGFRs.

W74-3

The utility of estimated glomerular filtration rate calculated by serum cystatine C in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the accuracy of estimated glomerular filtration rate (eGFR) calculated by serum creatinine (Cr) and cystatin C (cysC) in patients with rheumatoid arthritis (RA). [Methods] Thirty four patients with RA who had been admitted to Niigata University Hospital were included in this study (7 males and 27 females, 3 with rheumatoid vasculitis and 3 with other autoimmune disorders, the mean dosage of daily predonisolone (PSL) was 11.6 mg). Renal inulin clearance (Cin) was measured in each subject, and compared to eGFR using Cr (eGFRcreat) or cysC (eGFRcys), and analyzed by Pearson's correlation coefficient and t-test. [Results] eGFRcreat and eGFRcys were significantly correlated with Cin (r=0.732, p<0.001 vs. r=0.797, p<0.001). The mean eGFRcreat (77.6±26.7 ml/min/1.73m^2) was significantly higher than that of Cin (62.9±23.6 ml/min/1.73m^2), and the mean eGFRcys (54.9±24.1 ml/min/1.73m^2) was significantly lower than Cin. eGFRcys became lower as the daily dosage of PSL increased. Limitted to 28 patients taking PSL less than 30mg, mean eGFRcys was not significantly different to mean Cin. [Conclusion] eGFRcys is useful for estimating kidney function accurately in patients with RA, taking PSL less than 30mg.

W74-4

Variation of serum GP88 reflects the effect of Infliximab treatment?

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Conflict of interest: None

Objective: In this study, we examined the concentration of GP88 on the responder and non-responder in RA patients who were administered infliximab (IFX).**Subjects and Methods:**For Infliximab treated RA patients 50 cases, it was do the judgment of disease activity the measurement of DAS28-ESR before and 14 weeks after administration of IFX. **Results:** The overall GP88 changes in RA patients, prior to administration (Mean ± SE) 63.5 ± 2.5ng / mL, after 14 weeks of responder groups (46 cases) 67.0 ± 2.3ng / mL, non-responder group (4 cases) the 46.1 is a ± 5.8ng / mL, in the non-responder groups had significantly reduced was observed (p <0.01).On the other hand, CRP values (Mean ± SE) after 14 weeks of treatment were 0.86 ± 0.23mg / dL in the responder group, and 2.22 ± 0.34mg / dL in the non-responder group respectively. **Discussion:** In this study, GP88 of investigation was significantly decreased in the non-responder group in the study of 14 weeks of infliximab-treated patients.

W74-5

Correlation between the HLA pattern of patients with , and their clinical character or diagnosis

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Conflict of interest: None

Objective: We clarify the HLA pattern of patients with spondylarthritis in Japan. Method: We enrolled 37 patients who were considered the diagnosis of spondylarthritis at our clinic from November 2011 to November 2015. We analyzed the final diagnosis, HLA-A,B typing, X-ray and MRI image findings (axial change, sacroiliitis and peripheral arthritis), symptoms (such as inflammatory back pain), uveitis, laboratory parameters (RF, ACPA, CRP and ESR), and the treatments (NSAIDs, conventional DMARDs, biological DMARDs and corticosteroid). Result: All the HLA-B27 positive patients were ankylosing spondylitis and were treated with anti TNF inhibitors. Patients with reactive arthritis and inflammatory bowel disease related arthritis had HLA-B51. HLA-B39, 61, 25, 52 were frequent in undifferentiated spondylarthritis. Conclusion: HLA-B27 predict severe ankylosing spondylitis and anti TNF inhibitor use.

W74-6

Risk factors for positive anti-Mycobacterium avium-complex antibody in patients with various rheumatic diseases

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Conflict of interest: None

Measurement system for anti-Mycobacterium avium-complex antibody (anti-MAC antibody) was developed by Kitada, et al. It has been reported that the sensitivity is not so high but the specificity is very high, and that positive antibody suggests tissue invasion of MAC that is enough deep to induce immunological response. We tried to extract risk factors of positive anti-MAC antibody. Subjects were 87 patients (M/F = 9/78) with various rheumatic diseases, with mean age of 69.7 years. All the patients showed chest CT findings that suggest the presence of bronchiolitis or bronchiectasis. Anti-MAC antibody was positive in 11/87 (12.6 %). All the patients with positive antibody were female, and their rheumatic diseases were 5 RA, 6 SjS, and 1 DM, respectively. In 9 patients out of 11, sputum culture for MAC was positive. To extract risk factors for positive antibody, we first performed univariate analysis incorporating factors such as age, gender, BMI, underlying diseases, titers of RF, ACPA and ANA,, usage of bDMARDS, and doses of PSL, MTX, etc.. Using factors with low p values, we performed discriminant analysis, and only 1 significant factor was extracted (low BMI). We conclude that the risk factor for positive anti-MAC antibody was the same as in general population.

W75-1

Postoperative complications in patients with rheumatoid arthritis using a biological agent -A systematic review and meta-analysis-

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Conflict of interest: None

Objectives. To evaluate through a systematic review of the literature the association between the use of biological disease-modifying antirheumatic drugs (bDMARDs) and surgical site infection or wound healing delay after orthopedic surgery in patients with rheumatoid arthritis (RA). *Methods.* A systematic review was performed of articles indexed in the Cochrane Library, PubMed, and Web of Science from 1992 to 2012. The search aimed to identify studies describing SSI or wound healing delay in patients with RA treated with or without bDMARDs. *Results.* We found 75 articles through specific searches of PubMed and Web of Science, and hand searching. After inclusion and exclusion by full-text review, 10 articles were found for SSI, and five articles for delayed wound healing. The use of bDMARDs appeared to increase the rate of SSI slightly, especially in large joint-replacement surgery. Delayed wound healing was not increased by the use of bDMARDs. However, the definitions of SSI and delayed wound healing varied between the reviewed articles. Most of the articles focused on tumor necrosis factor-a inhibitors. *Conclusion.* bDMARDs slightly increase the relative risk of SSI but not that of delayed wound healing after orthopedic surgery and should be used with appropriate caution.

W75-2

Recent five year trends in preoperative disease activity of patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To evaluate the recent trends in preoperative disease activity of rheumatoid arthritis (RA). **Patients and methods:** We investigated 440 cases of RA patients who underwent orthopaedic surgeries from May 2010 to June 2015. The mean age was 61.6 (18-86) years old. Disease duration was 20.3 (0.3-58.1) years. Joint replacement surgeries of large joints (shoulder, elbow, hip, knee) were performed in 134 cases. Background of these patients (age, disease duration, mHAQ, type of surgeries) was compared between remission + low disease activity group (LDA group) and moderate + high disease activity group (HDA group). **Results:** 132 (30%) cases were treated with biologic agents. The mean mHAQ was 0.8 in 2010 and slightly increasing to 1.2 in 2015. But the mean DAS28-CRP and MMP-3 decreased significantly from 3.64 and 189.8 ng/ml to 2.50 and 131.2 ng/ml respectively. Disease duration, mHAQ and number of joint replacement surgeries were significantly smaller in LDA group compared to HDA group. **Conclusion:** The mean preoperative functional score has not improved as a whole group in these five years. But the increasing proportion of orthopaedic surgery under lower disease activity and better physical function was observed.

W75-3

Trends in rheumatoid arthritis-related orthopedic surgery

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Conflict of interest: None

[Object] To investigate trends in rheumatoid arthritis (RA)-related orthopedic surgery. [Methods] The number of operations was determined using a single center orthopedic surgery database from 1980 to 2014. We examined trends in RA-related orthopedic surgeries including prosthetic arthroplasty, arthrodesis, synovectomy and hand/foot surgery. [Results] Total number of RA-related surgery peaked in the 1990s and since have decreased. The number of prosthetic arthroplasty has gradually decreased from the peak level, while that of hand/foot surgery has stabilized from 2005 to 2014. The number of synovectomy, which peaked in the late-1980s, has gradually decreased. [Discussion] The number of RA-related orthopedic surgery peaked in the 1990s and has decreased thereafter, suggesting that early diagnosis and early administration of methotrexate for early RA patients has improved long-term outcomes. The number of hand/foot surgery has stabilized since the late-2000s, suggesting a reflection of RA patients' desire for better function and quality of life.

W75-4

Influences of Total Elbow Arthroplasty in Rheumatoid Arthritis Treated with Biologics on the Disease Activity and Functional Disorders

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Conflict of interest: None

[Objective] In this study, we examined the influences of Total Elbow Arthroplasty (TEA) in RA patients treated with biologics on the post-operational disease activities and functional disorders. [Method] Subjects are 23 joints of biologically treated RA cases during the period of 2006 - 2014 that TEA was done in this hospital. They were ETN14, TCZ4, ADA2, IFX2 and ABT1. Disease activities were evaluated by CDAI, the functional disorders were evaluated by the pre/post-operation HAQ, MEPS and PREE. [Results] Mean age and disease duration was 63.5 years old and 25.8 years.Disease activities after TEA showed significant improvements with CDAI improving from 12.9 to 6.7. PREE score of 73.1 before TEA significantly improved to 16.4. HAQ-DI also showed significant improvement from 2.0 to 0.5. HAQ improved, not only in the upper limb functional items, but also in lower limb function. MEPS also improved significantly from 45.0 to 98.1. [Conclusion] TEA provided the bearing properties and good elbow joint range of motion, and improved the upper limb functions. Also, for RA patients, the elbow joint is load-supporting joint, and TEA was effective to acquire lower limb functions. It was suggested that combined treatment with medical and surgical therapy enabled to acquire better ADL.

W75-5

Effects of biological agent in arthroplasty for Rheumatoid Arthritis

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Conflict of interest: None

【Objectives】We retrospectively compared the complications of using biological (B group) and non-biological (C group) agents in treatment with rheumatoid arthritis after joint replacement surgery.【Methods】Patients who underwent joint replacement surgery at our hospital. Surgery was performed 307 joint. 70 joints treated with biological agent. The mean age of these patients was 58.6 years (B group), 67.5 (N group) and the duration of illness was 12.7 years (B group), 15 years (N group). 【Results】There were no significant differences in infection, delayed wound healing,nor other complications. 【Conclusions】Treatment with biological agents has reported to improve the clinical symptom of RA and delay bone destruction. But Orthopaedic surgery is still needed for some patients with advanced bone destruction. There have been various reports on the influence of biological agents on infection, but no consensus has been reached. The results of our study suggest that biological agents are not risk factors for a significant increase of perioperative adverse events, but an accumulation of cases from many facilities will be necessary to confirm this findings.

W75-6

Clinical results of THA and TKA during the use of biologics in patients with rheumatoid arthritis

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Conflict of interest: None

MATERIALS: We report about the clinical results of TKA and THA during the use of biologics in 7 patients with rheumatoid arthritis. 4 patients were in Stage III, and 3 patients were in Stage IV. Class II patients were 2, III patients were 3, IV patient was 1. The average age was 66.1 years at the time of surgery. METHODS: We researched the following items, 1) administered biologics, 2) washout period, 3) perioperative complications, 4) infection, 5) JOA score. RESULTS: 1)IFX and TCZ were used in 2 cases. ETN, ADA, and GLM were used in 1 case respectively. 2) In the case using IFX, TKA was performed in the middle of the dosing period without washout. In other drug cases patients discontinued the biologics, once before and after surgery. 3) The preoperative CRP was high in one cases of TCZ, so we could not deny infection, and performed 2 - stage surgery (THA). 4) There was no infection during the follow-up observation. 5) In all cases, postoperative JOA score was improved. DISCUSSION: In our cases of THA and TKA using biologics there was no case that led to obvious infection and revision. In some cases the CRP is high in patient that was switched to TCZ from other biologics, it is important that we observe our patients after surgery carefully in RA patients.

W76-1

Treatment for female RA patients in their thirties registered in NinJa 2014

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Conflict of interest: Yes

[Object] To examine the treatment for female RA patients in their thirties. [Methods] We analyzed the data of 12078 female RA patients registered in NinJa 2014. Patients in their thirties (30-39 yrs of age) were divided into 5 groups as follows; A)MTX (+α) user, B)csDMARD-only user, C)Biologics without MTX user, D)steroid-only user, and E)drug-free patients. [Results] The rates of MTX use were 73.9% in 25-29 yrs of age, 49.1% in 30-35 yrs, 63.5% in 35-39 yrs, 73.4% in 40-44 yrs, 75.7 % in 45-49%, and then decreased. Around their thirties, the rates of steroid use, user of csDMARD except MTX, user of steroid only, non-user of DMARD, drug-free patients, user of biologics, and etanercept user were highest in 30-34 yrs of age, respectively, followed by 35-39 yrs. Mean values and rates of moderate/high disease activity in DAS28 and CDAI were highest in 30-34 yrs of age. Among patients in their thirties, mean disease duration was shortest in group B, the rates of Stage 1 was lowest in group C (28.9%), but high in group B (69.8%) and group E (58.8%). Remission rate was lowest in group D. [Conclusions] These data might be important to construct the treatment strategies for female RA patients in their thirties whose treatment was affected by pregnancy, delivery, and lactation.

W76-2

Impact of socioeconomic status on the disease activity and activities of daily living in Japanese patients with rheumatoid arthritis (from ROCKo cohort study)

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Conflict of interest: None

[Objectives] To examine the impact of socioeconomic status (SES) among Japanese patients with rheumatoid arthritis (RA) on disease activity and activities of daily living (ADL) because Japan has the unique national health insurance system. [Methods] A questionnaire survey was conducted among 338 patients with RA in Kobe University Hospital. Clinical characteristics included age, sex, disease duration, Steinbrocker stage and class classification, rheumatoid factor, anti-citrullinated protein antibody, disease activity, Health Assessment Questionnaire (HAQ), use of corticosteroid, methotrexate, and biologics. SES included income, education level and occupation. Univariate and multivariate analyses were conducted to examine the association of SES with disease activity and ADL. [Results] Patients with lower income had significantly higher DAS28-CRP ($P = 0.04$) and HAQ score ($P = 0.001$). Although education level was not associated with DAS28-CRP ($P = 0.31$), patients with lower education level had higher HAQ score and therefore worse ADL ($P = 0.036$). Neither income nor education level was associated with use of biologics. [Conclusions] SES may influence disease activity and ADL among patients with RA in Japan. Effort might be needed to solve equity issue.

W76-3

A cross-sectional study in KURAMA cohort to identify factors associated with medication adherence in patients with rheumatoid arthritis

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Conflict of interest: None

【Purpose】Medication adherence is important to achieve the goal of pharmacotherapy for rheumatoid arthritis (RA). The aim of this study is to identify factors associated with medication adherence in patients with RA.【Methods】A cross-sectional study was conducted in the KURAMA

cohort at Kyoto University Hospital, and a total of 255 patients were analyzed. Medication adherence was assessed with a self-report measure, Morisky Medication Adherence Scale, and classified as “high”, “moderate” and “low”. We examined relationship between the adherence scale and clinical data including age, sex, disease duration, regimen (methotrexate, biologics, steroid), current disease activity (DAS28-ESR), and HAQ score.【Results】Rates of high, moderate and low adherence were 26.7%, 50.6% and 22.7%, respectively. We found that younger patients ($p < 0.05$) and lower score of DAS28-ESR ($p < 0.05$) and use of methotrexate within a year ($p < 0.05$) were associated with lower adherence. Any other factor was not associated with adherence.【Conclusions】These results suggest that age, disease activity and use of methotrexate affect medication adherence in RA patients. Further studies are needed to examine impacts of medication adherence on outcomes of the treatment for RA.

W76-4

Role of anti-CCP Ab (anti-citrullinated antibody, ACPA) in the shift of age at onset of rheumatoid arthritis (RA) toward elderly - Analysis based on NinJa database

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Conflict of interest: None

Purpose: Last year we demonstrated the shift of age at RA onset over the past decade. Elderly-onset RA (EORA) is reportedly associated with lower frequency of ACPA (anti-CCP). Here we aim to characterize ACPA in EORA. Method: We analyzed 4,445 RA patients (pts), whose ACPA were available in NinJa 2014. The cutoff age for EORA and very EORA (VEORA) was 65 and 75, respectively. Results: The percentage of positive ACPA in young-onset RA (YORA) was 78%, which was significantly higher than that in EORA (65%) and VEORA (52%), while the titer of ACPA increased as the age of RA onset (10-year interval) increased. When ACPA was grouped into titer quartile (Q1: 4.5-40, Q2: 40-124, Q3: 124-434, Q4: >434), the proportion of ACPA-negative pts was higher in EORA, while ACPA-positive EORA was associated with higher titer quartile in comparison with YORA. Similar results were obtained with the cutoff set at 99 U/mL. Although the relationship of smoking with ACPA was not clear, there was a tendency of higher proportion of Q4 in pts with history or current smoking. However, since the percentage of smoking decreased after 50’s, extrinsic factors other than smoking could be involved. Conclusion: It is suggested that a different pathogenic factors could contribute to ACPA-positivity in YORA and EORA.

W76-5

Prevalence and factors associated with depression and anxiety in patients with rheumatoid arthritis -Analysis of NinJa 2012-2014 database-

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Conflict of interest: None

Objectives: We aimed to analyze the prevalence and factors associated with depression (Dep) and anxiety (Anx) in RA patients using data from a large Japanese cohort database. **Methods:** We analyzed RA patients (pts) registered in NinJa during the fiscal year of 2012 to 2014 with results from the Hospital Anxiety and Depression Scale (HADS). For Dep, a Dep group (DG) with score ’11 and non-DG with score £10. Differences in clinical data were analyzed between groups. An Anx group (AG) and non-AG were also analyzed. **Results:** We reported the data about the frequency and clinical findings of DG and AG in this annual meeting previously. The number of pts enrolled in this study were increased to 8,905 corresponding to 59% of total RA pts (15,023) registered in NinJa2014. The frequency of DG was 9.4%, which is the same as those in the previous two years but that of AG is going down to 4.8% year by year. Further, work was observed as negative factors for DG and AG ($p<0.001$, OR 0.482,95%CI0.415-0.559 and $p<0.001$, OR 0.467,95%CI0.381-0.574, respectively). Dep or Anx is significantly related not only to physical factors such as physical dysfunction or disease activity but also to social factors. **Conclusion:** This study clarified the prevalence and factors associated with Dep and Anx in Japanese RA pts.

W76-6

Fracture surgeries in rheumatoid arthritis patients: from the “Ninja” registry

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Conflict of interest: None

[Objectives]The aim of this study was to investigate for drug use of rheumatoid arthritis (RA) patients who injured the fracture of limbs requiring surgery using National Database of Rheumatic Diseases by iR-net in Japan (Ninja). [Methods]Presence or absence, injury site, drug use, etc. of fracture surgeries examines in 15023 patients registered in 2014 (12078 females, 2645 males). [Results]There were 72 females patients 6 males patients (Stage I: 8, II: 15, III: 12, IV: 36. Class 1: 6, 2: 31, 3: 29, 4: 6), with a mean age of 71.81years. 5 RA patients were drug free. Of the remaining 73 RA patients, there were 35 (45%) patients treated methotrexate, 26 (33%) patients treated biologic agent (Bio), 6 (8%) patients treated DMARDs. The mean oral steroid dose was 2.3mg/day prednisolone. In the no fracture group, the dose was 1.7mg/day. [Conclusion] There was no significant difference in fracture rate between drugs. Fracture group had oral many steroid than no fracture group.

W77-1

The analysis of CD4+ T cell subsets by the cell surface markers in patients with rheumatoid arthritis

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Conflict of interest: None

[Object] To characterize CD4+T cell subsets by cell surface markers and to analyze their expression of transcription factors in the patients of rheumatoid arthritis (RA). [Methods] We collected peripheral blood mononuclear cells (PBMC) of healthy control (HC) and treatment naïve RA patients. CD4+T cells were isolated from PBMC by magnetic cell sorting and were analyzed by flowcytometry as follows. 1) The rate of Th cell subsets classified from the cell surface makers (CD45RA, CXCR5, CXCR3, CCR6) and their expression of transcription factors (T-bet, GATA3, RORγt) were examined. 2) The rate of Treg cell subsets classified from the cell surface markers (CD25, CD127, CD45RA) and

transcription factor (Foxp3) were examined. [Results] 1) In RA patients, the rate of CXCR5-CD45RA-CXCR3-CCR6-(Th2) cells was higher and of CXCR5-CD45RA-CXCR3-CCR6+(Th17) cells was lower than HC. T-bet expression in the CXCR5-CD45RA-CXCR3+CCR6-(Th1) and GATA3 expression in all Th cell subset were higher than HC. 2) In RA patients, the rate of CD25+CD127low CD45RA-Foxp3low (non) Treg cells was higher than HC. [Conclusions] Our data suggested that the pathogenesis of RA might be related with the disequilibrium of Th cell and Treg cell subsets induced by their expression pattern of transcription factors.

W77-2

Comprehensive analysis of CD4 T cell subsets in rheumatoid arthritis

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Conflict of interest: None

(Objectives) CD4 T cell subset involved in the pathogenesis of rheumatoid arthritis (RA) is still debated. Although Th17 cells were thought as the candidates, IL-17-targeting therapy, which is quite effective in the skin lesion of psoriasis, is not effective in the treatment of arthritis. Besides the plasticity and the overlap, newly identified CD4 T cell subsets were reported. In this study, we aimed to identify CD4 T cell subsets involved in the pathogenesis of RA by comprehensive analysis of CD4 T cells in the peripheral blood and the joints. (Methods) Lymphocytes were obtained from the peripheral blood, synovial fluid, and synovial membrane of RA patients. Following intracellular staining of the cytokines, cells were analyzed by an 8-colour flow cytometer. (Results) IFN-g producing cells were the largest CD4T cell population especially in the joints. An independent T cell population which produced GM-CSF was the next largest CD4 T cell subset, exceeding those producing IL-17 or IL-4, in the peripheral blood. GM-CSF-producing CD4 T cells were also abundant in the joints, but most of them also produced IFN-g. (Conclusion) We found that GM-CSF-producing CD4 T cells are abundant in RA, which might be an important observation as clinical trial targeting GM-CSF are already ongoing in RA.

W77-3

The localization of citrullinated proteins, PAD4 and the deposition of ACPA in RA synovium

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Conflict of interest: None

Objective: To clarify the localization of citrullinated proteins, PAD4 and the deposition sites of ACPA in RA synovium Methods: 1) The expression of citrullinated proteins in RA and OA synovium was identified by immunochemical staining using the AMC antibody. 2) Expressing cells of citrullinated proteins in RA synovium were identified by immunofluorescence multiple staining with CD3, CD20, CD68. 3) The PAD4 expression in RA synovium was identified using an anti-PAD4 antibody. Further, the PAD4 expression cells are examined by immunofluorescence staining. 4) Anti-CCG-2, CCG-7 and CEP-1 antibody were purified from RA serum using the peptide affinity columns. These ACPAs incubated with RA synovium to identify the deposition cells by immunofluorescence staining. Results: 1) Citrullinated proteins were observed in the surface layer of the RA synovium. It was not observed in the OA synovium. 2) Citrullinated proteins in RA synovium were observed strongly in CD68 positive cells. 3) The expression of PAD4 was observed strongly in CD68 positive cells. 4) Anti CCG-2, CCG-7 and CEP-1 antibody were deposited strongly in CD68 positive cells. Conclusion: These findings suggest that PAD4 and citrullinated proteins are expressed in CD68 positive cells of RA synovium, and ACPAs may attach to there.

W77-4

Pathogenic role of midkine in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Midkine (MK) is a heparin-binding growth factor, which induces inflammatory cell migration and inhibition of regulatory T cell expansion. We previously found that serum MK level in rheumatoid arthritis (RA) was significantly increased compared to healthy controls and MK was expressed by RA synovial tissue. In this study, we analyzed correlation of serum MK level with disease activity of RA. MK-stimulated cytokine and chemokine production in rheumatoid synovial fibroblasts (RSFs) was also investigated. [Methods] We measured serum MK level in 146 RA patients by ELISA. MK level was measured before and after treatment with infliximab in 4 RA patients. RSFs were incubated with MK for 48 hours, and concentration of IL-6 and CCL2 in the culture supernatant was determined by ELISA. [Results] Serum MK level was positively correlated with DAS28-ESR ($p<0.05$), Sharp score ($p<0.005$), HAQ ($p<0.05$) and RF ($p<0.00001$). After infliximab therapy, serum MK was significantly decreased (pre: 137.3 +/- 73.2, after: 83.5 +/- 54.0 pg/ml; $p<0.05$). Stimulation with MK enhanced the production of IL-6 and CCL2 by RSFs. [Conclusion] Serum MK level could be a marker of activity in RA and an indicator of a poor prognosis. MK may have a role in the pathogenesis of RA via induction of IL-6 and CCL2.

W77-5

Analysis for the gene expression profiles in rheumatoid synovial fibroblasts regulated by LIGHT

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Conflict of interest: None

[Object]LIGHT is a member of TNF receptor superfamily and expressed on antigen presenting cells through the activation of T cells. LIGHT has the effect of modulating T-cell activation or promoting inflammation through the activation of NFκB by binding to its specific receptor HVEM and LT-βR. In this study, we investigated the genes expression profiles regulated by LIGHT in RA-FLS by comprehensive genetic analysis using microarrays. [Methods]RA-FLS were incubated with 1.0 μg/ml LIGHT for 12 h. Gene expressions were detected by microarray assay, and the relative gene expression profiles in LIGHT-stimulated cells and controls were analyzed. The relative expression levels of mRNA of the top-4 genes upregulated and those downregulated were compared using RealTime-PCR system. [Results]The microarray analysis revealed that 1042 genes were upregulated and 801 genes were downregulated more than twice of controls by the stimulation with LIGHT. The RealTime-PCR analysis confirmed that mRNA expression of the top-4 genes upregulated and those downregulated was actually regulated by LIGHT. [Conclusions]In this study, we first revealed the gene expression profiles in RA-FLS regulated by LIGHT. The involvement of LIGHT-HVEM/DcR3 signaling in the pathogenesis of RA is suggested.

W77-6

Investigating GWAS loci using alternative splicing QTL analysis

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Conflict of interest: None

[Introduction] Although genome-wide association studies (GWAS) have identified many loci for complex diseases, the disease mechanisms are yet to be dissected. Here, by performing alternative splicing QTL analysis, with special focus on variant that changes protein structure, we examined the role of alternative splicing in the GWAS loci [Method] We used the published RNA-seq dataset of 373 lymphoblastoid cell lines in Europeans (Geuvadis Project). We integrated transcripts that have the same ORF sequence in a gene and calculated the expression ratio versus total transcripts. Then, the correlation between this ratio and SNP genotype was tested (trQTL analysis). GWAS SNPs were extracted from the GWAS catalog (EBI). [Result] Of the 4,331 genes examined, 944 genes were identified as trQTL (FDR < 0.05). Among them, *OAS1* gene had the strongest trQTL effect ($P=6.3\times10^{-138}$), and 148 trQTLs had GWAS SNPs in strong linkage disequilibrium ($r^2 < 0.8$). Several splicing variants in *WDFY4* gene, an established risk gene for rheumatoid arthritis and SLE, are also identified as trQTL. [Discussion] Our approach is unique in that we focused on splicing variant that changes the protein structure. Functional analysis of these protein variants would lead to understanding the pathogenesis of diseases.

W78-1

Effect of abatacept on immunological abnormalities of rheumatoid arthritis

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Conflict of interest: None

【Object】The advent of biologics has made a remarkable progress in the treatment of rheumatoid arthritis. Abatacept (ABA), a non-TNF inhibitor biologic, ameliorates synovial inflammation and bone damage, however an effect of ABA on immunological abnormalities remains yet to be elucidated. In this study, we have sought to uncover immunological changes induced by ABA. 【Methods】Twenty-five of bio naive RA patients treated with ABA were subject to the sequential analysis of lymphocyte subsets and the titers of autoantibodies, along with the assessment of clinical activity.【Results】In the treatment of ABA, the proportion of $CD4^+CCR7^+CD45RA^-$ (central memory) T cells including follicular helper T (Tfh) cells and $CD4^+CCR7^-CD45RA^-$ (effetor memory) T cells decreased, whereas that of $CD4^+CCR7^+CD45RA^+$(naive) T cells increased. Overall, T cell activation was remarkably suppressed. Additionally, the proportion of $CD4^+CD25^+CD127^{lo}CCR4^+$ T cells (Treg) decreased. The titers of autoantibodies, such as ACPA and RF, decreased with notable correlation between RF titers and Tfh numbers.【Conclusion】Along with inhibition of disease activity, ABA could correct immunological abnormalities such as the proportion of lymphocyte subsets and the titers of autoantibodies in patients with RA.

W78-2

The Metabolism of Hyaluronic acid in the Patients with Rheumatoid Arthritis

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Conflict of interest: None

Purpose: Hyaluronic acid synthase (HAS)-1 and -2 synthesize high molecular weight (MW) HA, while HAS-3 synthesizes low MW one. We studied the relationship between Hyaluronidase (Hyal) and HASs in the patients with rheumatoid arthritis (RA). **Methods**: We studied Hyals and HASs expression by *in situ* hybridization and immunohistochemistry in articular tissue. In addition, we investigated Hyal activity and protein expression in synovial fluid (SF) by HA substrate gel zymography and western blotting. Then we examined HA MW in SF by HPLC. **Results**: The number of positive cells of Hyals was higher in RA than in non-inflamed control. The activity of Hyal in SF was higher in the active stage of RA. There was negative correlation between Hyal activity and MW of HA in SF. The activity of Hyal was positively correlated with the number of positive cells of Hyals in synovial tissues. The number of positive cells of HAS-1 and HAS-2 was lower although that of HAS-3 reached maximum level in the active RA. The number of HAS-3 positive cells was negatively correlated with the HA MW in SF and positively correlated with histological score of inflammation. Hyal-1 protein was also detected in SF. **Conclusions**: The results suggest that HA may become to smaller size in inflammatory stage of RA.

W78-3

Activation status of circulating platelets is associated with disease activity of rheumatoid arthritis (RA)

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Conflict of interest: None

[Purpose] To elucidate the association between activation status of platelets and pathogenesis and disease activity of rheumatoid arthritis (RA). [Methods] Fifty-seven patients with RA, 7 with Sjogren's syndrome, 4 with systemic lupus erythematosus, and 16 healthy controls were involved. Activation status of platelets was examined by expression of CD62P or production of microparticles (MPs) using flow cytometry. Correlation between activation status of platelets and clinical characteristics of RA patients was also examined. [Results] Proportion of activated platelets and that of MPs were higher in patients with RA compared with healthy controls ($P < 0.001$, $P < 0.00001$, respectively). Also, proportion of activated platelets and that of MPs were correlated each other. Furthermore these proportion were positively correlated with serum CRP levels, erythrocyte sedimentation rate, and CDAI. Serial analysis of the 6 patients who were treated with MTX or biologics revealed that these proportions were decreased along with improvement of the disease ($P < 0.05$). [Conclusions] Proportion of activated platelets and MPs can be used as biomarkers for RA. These results suggest that activation of platelets might play a significant role in the pathogenesis of RA.

W78-4

Roles of evaluating morning stiffness in rheumatoid arthritis

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Conflict of interest: None

Objectives: We re-evaluated the roles of measuring morning stiffness (MS) in the management of rheumatoid arthritis (RA). Methods: We enrolled 76 RA patients who underwent ultrasonography. We collected detailed information on MS in the dominant hand and performed ultrasound assessment for synovitis and tenosynovitis. Results: Mean age was 58.4 years and 60 patients were women. In the dominant hand, swollen joint count and tender joint count were significantly correlated with synovial power Doppler (PD) score (rho=0.561, 0.379, respectively) but only weakly with tenosynovial PD score (rho=0.388, 0.276, respectively). The correlation of MS with synovial PD score was weak. On the other hand, the intensity and the improvement of MS were significantly correlated with tenosynovial PD score (rho=0.503, 0.561, respectively), whereas the correlation between the duration of MS and tenosynovial PD score was much weaker (rho=0.280). In multivariate linear regression models, the intensity and the improvement of MS were the only independent factors that were significantly correlated with tenosynovial PD score. Conclusions: These data suggest that MS in RA reflects tenosynovitis rather than synovitis and that the intensity and improvement are more important than the duration when MS is evaluated.

W78-5

A risk factor for fracture in patients with rheumatoid arthritis is not the disease per se but the use of glucocorticoid and low BMD-the 5th year results of the TOMORROW study-

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Conflict of interest: None

Background: Rheumatoid arthritis (RA) per se is thought to be one of the risk factors for osteoporotic fracture. In the present study, we conducted TOMORROW study which prospectively determines risk factors for fracture in RA patients. Methods: 208 RA patients and 205 age- and gender-matched healthy volunteers (84% female, average age 58 yo, average disease duration 14 years) were enrolled in this study. Measurements included history taking on falls and fractures, prescription history in every year, blood test and whole body DEXA at baseline and at year 5. Results: There was no significant difference in fracture incidence rate between RA (0.038 person-year) and Vo (0.028py) during 5 years (p=0.23). Multiple regression analysis revealed that low bone mass of the thoracic spine (<0.7g/cm2) (RR=4.94 p<0.001) and glucocorticoid (GC) use at baseline (RR=2.59 p=0.031) were the risk factors for fracture in RA patients. In the patients with RA taking GC more than 2mg/day, the fracture risk get worse (RR=4.05 p=0.001). Conclusion: The fracture incidence rate did not significantly differ between RA and Vo., although GC use and low bone mass was evident in RA patients. Therefore, high risk group for fracture were supposed to exist in RA patients.

W78-6

Accelerometry based gait analysis in patients with rheumatoid arthritis

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Conflict of interest: Yes

Object; Gait disturbance is an important factor to influence QOL in rheumatoid arthritis (RA). The purpose of this study is to clarify factors related with gait disturbance using accelerometry based gait analysis in RA observational cohort.Methods; 379 patients (319 women, mean age 61.9ys, mean disease duration 12.8ys) who were registered in KURAMA cohort, were included in this study. Gait parameters (step cadence, step length, walking speed, and acceleration) using portable gait rhythmogram, skeletal muscle mass index (SMI) using BIA, and isometric knee extension muscle strength were measured. Factors influenced gait disturbance were searched.Results; Mean step cadence was 111.3steps/m, mean step length was 53.5cm, mean walking speed was 60.2m/mim, mean SMI was 5.95kg/m2, mean knee extension muscle strength was 191.7N, and rate of sarcopenia was 35.6%. The factors influenced gait elements (step cadence, step length, walking speed) were older age, higher disease activity, consumption of PSL, higher HAQ, and muscle weakness in multivariate analysis.Conclusions; Our study suggest that functional disability related with arthritis and joint destruction, inflammatory cytokine, protein catabolism with steroid usage, and muscle weakness may induce gait disturbance in RA.

W79-1

Clinical features and fetal outcomes of pregnancy in mothers with connective tissue diseases

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Conflict of interest: None

<Objectives> To clarify clinical features and fetal outcomes of pregnancy in mothers with connective tissue diseases (CTDs). <Methods> We identified 79 pregnancies (59 mothers) accompanied with CTDs at our hospital from Jan 2006 to Oct 2015. We examined 1) patients' background, 2) profile of auto-antibodies (Ab), 3) exacerbation of CTDs during pregnancies, 4) treatment, and 5) fetal outcomes, retrospectively. <Results> 1) Mean age of mothers was 31.7±5.2 years old. Underlying CTDs were SLE (N=34), RA (N=13), Sjögren's syndrome (N=10), MCTD (N=8), Behçet's disease (N=5), Takayasu's aortitis (N=3), PM/DM (N=2), ANCA associated vasculitis (N=2), and others (N=2). 2) Anti SS-A Ab was detected in 41 cases (60.3%), and anti phospholipid Ab was in 8 cases (12.9%). 3) Exacerbation of CTDs occurred in 20 cases (25.3%). Flares of SLE were most frequent (N=7). 4) During pregnancy, corticosteroid was administered in 64 patients, biologics in 1 patient, immunosuppressant in 4 patients.5) Preterm delivery or abortion occurred in 29 pregnancies (36.7%). Preterm delivery or abortion significantly correlated with exacerbation of CTDs and steroid use (p<0.05). <Conclusion> Exacerbation of CTDs and steroid use might relate to an increased risk of perinatal complications in mothers with CTDs.

W79-2

Clinical feature of 118 pregnancies complicated with connective tissue disease in our institution

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Conflict of interest: None

【Objective】We examine the issue of pregnancy and delivery complicated with connective tissue diseases (CTD) by the analysis of the cases in our institution.【Method】We investigated 118 cases retrospectively; ex-

acerbation of underlying disease, anti SS-A antibody (also examined anti-52KDa and 60KDa antibody), antiphospholipid antibody, preterm birth, neonatal birth weight, perinatal complication and dose of corticosteroid. 【Result】In 17 cases among all cases underlying diseases were exacerbated, and they needed to increase dose of corticosteroid. 7 needed corticosteroid pulse therapies. In SLE (17.9%) and MCTD (22.2%) disease activities were more exacerbated. Positive SS-A antibody was found in 48.3% of all cases, and there was no complication related with its antibody. The most cases with high titer of SS-A antibodies, whose cases were also higher in anti-52KDa and 60KDa antibody, had corticosteroid therapies. There was a relationship between dose of corticosteroid and birth weight, delivery week, and they were also related with the exacerbation of underlying disease. Preterm birth, light for date and perinatal complication tended to arise in SLE, APS and MCTD.【Conclusion】In pregnancy complicated with CTD, we need to control the disease activity strictly on each disease.

W79-3

Clinical feature of cases of pregnancy and desiring to bear children complicated with rheumatoid arthritis in our institution

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Conflict of interest: None

【Objective】We examine the issue of pregnancy and delivery complicated with rheumatoid arthritis (RA) by the analysis of the cases in our institution.【Method】We investigated 6 pregnancy cases and 4 cases desiring to bear children which had administered biologics retrospectively; treatment from onset of RA to pregnancy (including immunosuppressant and biologics), exacerbation of disease during pregnancy, treatment on postpartum.【Result】In 6 cases among all cases immunosuppressant were administered from onset of RA, and discontinued after achieving remission and planing for pregnancy. Infliximab (3cases), golimumab (1case) and tocilizumab (1case) were also discontinued on planing for pregnancy, and changed into coriticosteroid or other biologics. Certolizumab pegol and Etanercept were discontinued on getting pregnant. We maintained pregnancy by corticosteroid only or no drug in all cases. In 2 cases RA disesase activities got worse, but in other cases those were stable during pregnancy. In the cases which exacerbated on postpartum, lactations were discontinued and MTX or biologics were resumed.【Conclusion】In pregnancy complicated with RA, we treat for remission by immunosuppressant and biologics, and we might maintain pregnancy stably.

W79-4

Treatment of infected total knee arthroplasty using antibiotic-impregnated hydroxyapatite

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Conflict of interest: None

[Object] We evaluated the results of 2-stage revision using antibiotic-impregnated hydroxyapatite for the treatment of infected total knee arthroplasty.[Methods] Seven patients consisting of 4 men and 3 women with an average age of 73 years were followed up for an average of 39 months. The initial diagnoses were rheumatoid arthritis in 2 and osteoarthritis in 5 patients. All patients received resection arthroplasty and thorough debridement, followed by implantation of antibiotic-impregnated hydroxyapatite. Two-stage revision was performed in all patients. We reviewed range of motion and clinical score according to Knee society. Radiographic implant loosening as well as recurrent infection were evaluated.[Results] The mean flexion angles were 84° preoperatively and 107° at the last follow up. Knee score improved significantly from 36 to 92 points (p=0.02). Function score improved significantly from 25 to 74 points (p=0.04). There was no evidence of implant loosening nor recurrent infection. [Conclusions] Antibiotic-impregnated hydroxyapatite is an excellent drug delivery system, and is considered to be the useful method for the infected total knee arthroplasty.

W79-5

The actual situation of Calcium Pyrophosphate deposition (CPPD).

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Conflict of interest: None

[Objectives]EULAR has recommended that disease traditionally called “Pseudogout” to be categorized into 4 phenotypes, and is equal to Acute CPP crystal arthritis in the narrow sense. We report the prognosis of CPPD patients who came to our hospital from Jan. 2011 to Oct. 2015. [Methods]We have studied 26 patients diagnosed with EULAR recommendation for CPPD. [Results]26 patients had 9 males and 17 females, the median age of diagnosis was 83.5 year-old (69-102 year-old). High fever in 17 cases, the average CRP level was 14.6±7.2 mg/dl (23 cases). Affected joints included knee, wrist, ankle, cubitus, shoulder, cervical, figer (18, 6, 6, 3, 2, 2, 2 cases each), multiple in 10, simple in 16. Joint aspiration in 15 cases (existence of CPP crystal in 12 cases), X-ray exam in 24 cases (calcification confirmed in 18 cases). Treatment included removal of crystal (5 cases), NSAIDs (16 cases), intraarticular injection of steroid (3 cases), oral steroid (2 cases, 30mg/day), and colchicine (3 cases). 5 cases were observed during infection, cerebral infarction. [Conclusions]The results indicate that CPPD are observed in elderly people, and sometimes require steroid/colchicine. It demands caution for some patients develop CPPD during admission for other disease such as cerebral infaction.

W79-6

Treatment of septic knee arthritis by intermittent intra-articular distension-irrigation and injection of antibiotics

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Conflict of interest: None

Purpose: The purpose of this study was to examine the effectiveness of intermittent intra-articular distension irrigation and injection of antibiotics (DIA) for the treatment of septic knee arthritis and infection after total knee arthroplasty. **Methods:** 20 cases of septic knee arthritis including 8 of periprosthetic knee infection were enrolled in this study. In the operating room, infected knees were treated by irrigation with drainage tubes or debridement. Postoperatively, DIA was maintained for 14 days. Under sterile conditions, intermittent intra-articular distension irrigation was performed using 1000 ml saline followed by an injection of antibiotics dissolved in saline into the knee joint through the drainage tubes, which were clamped for 3 h after the injection. Results: In 19 cases, infection was eradicated in one procedure. Infection recurrence was observed in one case of a prosthetic knee with subcutaneous infection. After a second debridement followed by both intra-articular and subcutaneous DIA for 14 days, the infection was eradicated. At final follow-up, infection was controlled in all cases. No complications occurred during the surgery and postoperative period. **Discussion:** The DIA method was effective for treating knee joint infections.

W80-1

Nested Case-Control Study to Explore the Prognostic Factors of Connective Tissue Disease Associated Pulmonary Arterial Hypertension

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Conflict of interest: None

[Object] To explore the prognostic factors of connective tissue disease associated pulmonary arterial hypertension (CTD-PAH). [Methods] The cohort includes 34 patients with CTD-PAH admitted at our rheumatology department from 1995 to 2015. Patients who died within 5 years from the admission were selected as poor prognostic group (cases), and patients who survived over the same period of time were considered as good prognostic group (controls). Study parameters assessed on admission and 3 months after the initiation of vasodilator treatment include: age, sex, underlying disease, presence of interstitial lung disease (ILD), WHO functional class, 6 minute walk distance, %DLCO, BNP, echocardiography, cardiac MRI, and right heart catheterization findings. [Results] Six patients were included in the cases and 22 in the controls. Presence of ILD (100% vs 23%, p=0.0012), decreased %DLCO after 3 month-treatment (median 19.5 vs 47.5, p=0.0012) and increased BNP after 3 month-treatment (median 843.5 vs 26, p=0.0013) were identified as prognostic factors. There was a significant correlation between presence of ILD and decreased %DLCO (r=-0.6797, p<0.0001). [Conclusions] In patients with CTD-PAH, the presence of ILD and increased BNP after 3 month-treatment lead to a poor prognosis.

W80-2

Retrospective Analysis of Clinical Efficacy of Intermittent Intravenous Cyclophosphamide (IVCY) in the Patients with Systemic Sclerosis-Related Interstitial Lung Disease (SSc-ILD) Using Chest CT Imaging

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Conflict of interest: None

[Objective] The aim of this study was to evaluate the efficacy of IVCY therapy on our patients with SSc-ILD. **[Methods]** Selected in this study were progressive ILD patients who received IVCY after 2009 in our Department among SSc patients who were diagnosed based on the 2003 criteria by the Japanese Ministry of Health, Labor and Welfare. The treatment effects were evaluated by a radiologist and a rheumatologist comparing the chest CT images taken before IVCY, immediately after IVCY, and during a period of half to 1 year after IVCY. **[Results]** Fourteen SSc-ILD cases (9 showed fNSIP pattern and 5 showed UIP + fNSIP pattern) were classified as "improved", "unchanged", and "advanced" based on the chest CT images. Immediately after IVCY, there were 8 "improved", 3 "unchanged", and 3 "advanced" cases. Seven of 8 "improved"(4 fNSIP and 3 UIP + fNSIP) moved to "unchanged" during a period of half to 1 year after IVCY, but the other (fNSIP) was more improved. One of 3 "unchanged"(fNSIP + UIP) was still unchanged, but the others (2 fNSIP + UIP) were advanced. Two of 3 "advanced"(2 fNSIP) were changed to "unchanged", but the other (fNSIP + UIP) worsened. **[Conclusion]** We concluded IVCY was tended to be effective for SSc-ILD patients.

W80-3

A Long Term Prognostic Prediction Factor in the Collagen Tissue Disease Related Pulmonary Arterial Hypertension (CTD - PAH) — The effect of intensive immunosuppressive therapy—

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Conflict of interest: None

[Purpose] The prognosis of CTD-PAH is improved by the intensive immunosuppressive therapy including IVCY, except for SSc. However, it is not known in details. We investigated the long term effect of IVCY and prognostic prediction factors. [Methods] We obtained the patients (SLE15, pSS5, MCTD7, SSc16) between 2000□2015. A right heart cauterization was carried, measuring mPAP, PVR, CO. The mPAP change (Δ NO-mPAP) is gauged by NO reaction test. Δ final of mPAP was calculated as a difference of baseline and latest mPAP. Most of SLE, pSS, and MCTD cases were treated with IVCY except 3 cases. Disease activity was evaluated by SLEDAI, ESSDAI. Data was analyzed by Spearman test. [Result] A decline of Δ NO-mPAP was correlated with Δ final-mPAP significantly in SSc (R2=0.75, P<0.05). Although 10 SLE and 2 pSS cases had low disease activity, they developed PAH. Δ final-mPAP (mean±SD) were SLE-14±9, pSS-15±2.5,MCTD-8±1, IVCY untreated+5±7, and SSc-3±11mmHg. The mortality was SLE 87, pSS 100, MCTD71, and SSc75%. [Discussion] NO reaction test predicts the vascular reversibility, and might be useful as a prognostic factor of SSc-PAH. SLE and pSS would develop PAH regardless disease activity. [Conclusion] IVCY would be useful to improve the mortality of SLE, pSS-PAH.

W80-4

Evaluations of exertion dyspnea in patients with collagen disease by CPX(cardiopulmonary exercise testing)

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Conflict of interest: None

Background: Patients with collagen disease often complain of exertion dyspnea, due to various reasons, interstitial pneumonia (IP), pulmonary arterial hypertension (PAH), and so on. Early diagnosis of PAH is important because recently many choices of treatment are available. Cardiac ultrasonography or right heart catheterization at rest is not always useful to diagnose early PAH. We tried to detect it by CPX. Methods: From June 13th to November 11th in 2015, We performed CPX and evaluate their clinical state in 5patients, 27-51 years 5females, 2mixed connective tissue disease (MCTD), 1systemic sclerosis (SSc), 1systemic lupus erythematosus (SLE), 1Sjögren syndrome. Results: 4 of 5 cases presented decreased peak oxygen consumption (peak VO2), and 3cases presented decreased anaerobic threshold (AT). Elevated VE (minute ventilation)/ VCO2 (carbon dioxide production) ratio and slope, which represent increased ventilation-perfusion mismatch, increased in a case with MCTD and a case with SSc. We did not detect PAH at rest in these two. We started to treat the MCTD case with PDE5 inhibitor at the thought of early PAH. Conclusions: We performed CPX in every patient safely. Although more research is required, CPX may provide valuable information notably in detection of early PAH.

W80-5

Treatment selection of chronic interstitial pneumonia(CIP) patients associated with connective tissue disease(CTD) of our institute

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Conflict of interest: Yes

Background: There are no established tratements of CTD-CIP. We aim to know treatment selections of patients CTD-CIP of our institute. Methods: We reviewed clinical data concerning treatment and HRCT imaging of CTD-CIP patients in October 2015. Results: Total CTD-CIP pa-

tients were 387 (107M). Among them, RA-CIP patients are 102 (49M), SSc-CIP patients are 119 (16M), DM/PM-CIP patients are 97 (22M), Angiitis-CIP patients are 36 (14M). The majority of Angiitis-CIP patients have UIP pattern on HRCT imaging. But the majority of other CTD-CIP patients have NSIP pattern on HRCT imaging.310 patients of CTD-CIP are treated with immunosuppressive therapy. Corticosteroid, tacrolimus, cyclosporin, and azathiopurine are prescribed for 68%, 36%, 12%, 21% of CTD-CIP patients. Conclusions: Concerning about HRCT imaging, NSIP pattern is predominant in CTD-CIP patients other than angiitis.In the treatment of CTD-CIP patients, we preferred corticosteroid, tacrolimus, cyclosporin, and azathiopurine.

W80-6

Rheumatoid Arthritis Patient revealed large vessel vasculitis restricted to lower limb arteries and multiple bursitis on ^{18}F-FDG PET-CT scan, and developed venous thromboembolism

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Conflict of interest: None

Rheumatoid Arthritis (RA) is a common disorder, however, its clinical feature is extremely variable, largely dependent on its complications and associated conditions. Here we report a 74-year-old female patient with RA complicated with large vessel vasculitis (LVV) and multiple bursitis. She was diagnosed as RA 21 years ago, controlled with PSL 5 mg per day and MTX 6 mg per week. Two months before admission, she developed a low-grade fever and pain of PIP joints of left hand. On admission, however, she revealed high-grade fever and polyarthralgia with high RA disease activity. We, then, performed PET-CT scan and diagnosed LVV and multiple bursitis in Lower Extremities (LEs), and high dose glucocorticoid (GC) treatment was initiated. Although the patient' conditions were rapidly improved, thrombocytopenia and elevation of D-dimer occurred in the course of tapering GC and deep vein thrombosis and pulmonary embolism were diagnosed. The patient was immediately treated with anticoagulants and rescued. In summary, PET-CT might be considered in patients with RA when LVV and/or multiple bursitis were suspected. Moreover, these diseases, when occurred in the LEs, might prophylactically be treated with various antithrombotic modalities to prevent venous thromboembolic complications.

W81-1

Analysis of autoantibody profile and its significance on clinical features in patients with ANCA associated vasculitis

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Conflict of interest: None

[Backgrounds] Autoantibodies other than ANCA are often detected in ANCA associated vasculitis (AAV). [Objects] To examine autoantibody profile and its significance in AAV. [Methods] We retrospectively collected the data of autoantibodies in MPO-ANCA positive AAV (MPO-AAV) (n = 85) and PR3-ANCA positive AAV (PR3-AAV) (n = 17) in our division from 2005 to 2014. [Results] In MPO-AAV and PR3-AAV, RF was positive in 42/61 (68.9%) and 5/11 (45.5%), LAC 15/22 (68.2%) and 4/10 (40.0%), anti-CL-IgM 3/18 (16.7%) and 3/10 (30.0%), and anti-CCP antibody 5/46 (10.9%) and 1/7 (14.3%), respectively. In only MPO-AAV, ANA (22/77, 28.6%), anti-SS-A antibody (10/44, 22.7%), anti-SS-B antibody (3/32, 9.4%), and anti-dsDNA antibody (4/40, 10.0%) were positive. In MPO-AAV, there was no difference in two years-relapse free rates between anti-phospholipid antibody (aPL)-positive (66.7%) and aPL-negative patients (56.3%) (log-rank, p = 0.237). In PR3-AAV, relapse free rate tended to be lower in aPL-positive patients than in aPL-negative patients (0.0% vs. 71.4%, log-rank, p = 0.086). [Conclusions] Various autoantibodies were detected in AAV. There was a tendency toward lower relapse free rate in aPL-positive patients with PR3-AAV. Autoantibody other than ANCA may have an impact on clinical features of AAV.

W81-2

Activated partial thromboplastin time reflects the disease activity in patients with ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] To investigate the relationship between hypercoagulability and the disease activity in patients with ANCA-associated vasculitis (AAV). [Methods] Fifty-five patients who had been referred to Niigata University Hospital and diagnosed as AAV between 2009 and 2015, were recruited. Plasma fibrin degradation products (FDP), D-dimer, and activated thromboplastin time (APTT) were measured, and APTT ratio was calculated using the data from control plasma. Other laboratory data and BVAS were also examined, and analyzed using Spearman's rank correlation coefficient and stepwise multiple regression analysis to determine the relationship with these coagulation tests. [Results] In Spearman's rank correlation coefficient analysis, FDP and D-dimer was positively associated with CRP, daily urinary protein excretion, and BVAS, and negatively correlated with eGFR, whereas APTT ratio was positively associated with BVAS. Although there was no factor significantly affected FDP or D-dimer in stepwise multiple regression analysis, BVAS was selected as a positive independent variable for APTT ratio (rho=0.3401, p=0.01186). [Conclusion] Prolongation of APTT reflected the disease activity and is considered as one of possible biomarkers in patients with AAV.

W81-3

Anti-lactoferrin antibodies enhance neutrophil extracellular trap formation and are associated with disease activity in eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

Background: Lactoferrin (Lf) is one of the antigens of ANCA and is shown to suppress neutrophil extracellular trap (NET) formation. On the other hand, excessive NET formation is involved in the pathogenesis of ANCA-associated vasculitis (AAV). **Objective**: To determine the positive rate and pathogenicity of anti-Lf antibodies (aLf) in AAV. **Methods**: 65 sera from AAV (MPA: 41, GPA: 5, EGPA: 19) were subjected for aLf detection. Clinical characteristics were compared between aLf (+) and aLf (-) patients. Neutrophils from healthy donors were exposed to suboptimal dose of PMA with aLf followed by evaluation of NET formation. **Results**: 4 out of 65 AAV sera (6.2%) were aLf (+). All of them were EGPA sera (4/19, 21.1%). In EGPA, the frequency of renal involvement, serum CRP levels, and BVAS in the aLf (+) patients were significantly higher than those in the aLf (-) patients, and the aLf titer was correlated positively with the serum CRP level and BVAS. The NET formation was particularly enhanced by combined stimulation of 10 nM PMA and aLf. IgG eluted from sera of the aLf (+) EGPA patients enhanced NET formation, and the effect was cancelled completely by absorption of the aLf. **Conclusion**: aLf enhance NET formation and are associated with disease activity of EGPA.

W81-4

Peptigylarginine deiminase 4 inhibitor suppresses MPO-ANCA production through inhibition of neutrophil extracellular trap formation

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Conflict of interest: None

Objectives: MPO-ANCA is a pathogenic autoantibody in MPO-ANCA-associated vasculitis. It has been shown that excessive neutrophil extracellular trap (NET) formation is implicated in the MPO-ANCA production. The aim of this study is to determine that inhibition of peptigylarginine deiminase 4 (PAD4), which plays a pivotal role in NET formation, can suppress MPO-ANCA production. **Methods:** NETs were induced in neutrophils derived from healthy donors by stimulation with phorbol myristate acetate (PMA) or PMA plus anti-thyroid drug, propylthiouracil (PTU). The effect of PAD4 inhibitor, Cl-amidine, on NET formation was determined. Next, we established mouse models with MPO-ANCA production. BALB/c mice given oral administration of PTU and intraperitoneal (i.p.) injection of PMA produced MPO-ANCA. These mice were divided into two groups, namely Group 1 with i.p. injection of Cl-amidine and Group 2 with i.p. injection of PBS. Two weeks later, mice were killed to examine NET formation in the peritoneal cavity and MPO-ANCA production. **Results:** NET formation was inhibited significantly by Cl-amidine both *in vitro* and *in vivo*. Serum MPO-ANCA levels of Group 1 mice were significantly lower than Group 2. **Conclusion:** PAD4 inhibitor suppresses MPO-ANCA production through inhibition of NET formation.

W81-5

Presence of anti-moesin antibodies in cutaneous arteritis patients with severe manifestations indicating progression to systemic polyarteritis nodosa

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Conflict of interest: None

Background Cutaneous arteritis (CA) is a new classification under single-organ vasculitis. Some reports have suggested involvement of serum anti-moesin antibodies in the exacerbation of systemic vasculitis. We investigated serum anti-moesin antibody levels in CA patients who presented with several severe symptoms indicating progression to PAN prior to and after treatment with IVCY or steroid pulse therapy. Methods All 14 patients were treated at an early stage with IVCY or steroid pulse therapy to prevent progression to PAN. We examined clinical BVAS and Vasculitis Damage Index prior to and after treatment with IVCY or steroid pulse therapy. Results We found a significantly positive correlation between serum anti-moesin antibodies and BVAS in the 28 samples obtained from the 14 patients, pre-treatment (n=14) and post-treatment (n=14). We similarly found a significantly positive correlation between serum anti-moesin antibodies and VDI in the 28 samples. Serum anti-moesin antibody levels were significantly higher in patients following IVCY or steroid pulse therapy compared to pre-treatment levels. Discussion We believe that measuring serum anti-moesin antibodies levels could be a useful tool for determining the severity of damage caused by CA and the effects of treatment.

W81-6

Identification of novel biomarkers of ANCA-associated vasculitis by large-scale quantitative analysis of the serum proteome using the mass spectrometry

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Conflict of interest: None

[Objectives] We screened biomarkers of activity, severity and organ damage of AAV by quantitative proteome analysis using the mass spectrometry (MS). [Methods] Serum samples of 202 AAV patients who were registered with New RemIT-JAV-RPGN or admitted to our hospital were examined. Serum proteins were identified by MSMS. The serum proteins before and after treatment were compared by the quantitative selected reaction monitoring (SRM) method. Moreover, we performed the SRM analysis about 109 proteins related to vascular endothelium and NETs. [Results] Approximately 400 proteins were identified with MSMS analysis of 7 patients. Of these, 37 marker candidates were screened with SRM method of 42 patients. The SRM method (47 patients) about the 109 proteins related to endothelium and NETs was able to quantify 46 proteins. We identified four markers of disease activity (TIMP1, TNC, S100A8 etc) and five markers related to BVAS (MMP9, TKT, FGA etc). Quantitative analyses of those using ELISA are now in progress in the samples of AAV, RA and SLE. [Conclusion] We identified the novel biomarkers of AAV from the variability analysis (ng/mL) of serum protein.

W82-1

A case of systemic lupus erythematosus with mononeuritis multiplex and myeloperoxidase-anti-neutrophil cytoplasmic antibody-positive

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Conflict of interest: None

A 63-year old woman developed pain and numbness in the bilateral feet and right hand. A neurological examination revealed mononeuritis multiplex. Then, she was referred to our hospital. She had photosensitivity and livedo reticularis in the bilateral feet. A blood test revealed that the levels of CRP, IgG, the leukocyte, and lymphocyte counts were 0.47 mg/dl, 4179 mg/dl, 3,300/μl, and 800/μl, respectively; and ANA, anti-cardiolipin antibody IgG isotype, and myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) were positive. On examination of the skin biopsy sample, immunofluorescence staining-negative medium vessel vasculitis was found. She satisfied 4 of the 11 SLE classification criteria (ACR 1997). Therefore, we diagnosed her with SLE involving peripheral nerves due to vasculitis. We started a combination therapy of high-dose glucocorticoid and intravenous cyclophosphamide. Consequently, she improved. We report this rare case of SLE with mononeuritis multiplex and myeloperoxidase-anti-neutrophil cytoplasmic antibody-positive.

W82-2

A retrospective study of peripheral neuropathy in 12 patients newly diagnosed with Eosinophilic Granulomatosis with polyangiitis (Churg-Strauss)

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Conflict of interest: None

All of the patients with EGPA, who have visited the Dept. of Rheumatology, Hiroshima University Hospital between Jul. 2009 and Mar. 2012, or Hiroshima City Hospital between Apr. 2012 and Aug. 2015, were included. Clinical findings, obtained through retrospective chart review, were analyzed. Five men and seven women were included. The average age was 53 years. All of them had peripheral neuropathy (at the initial visit in 11). All of them had abnormal sensation or pain; 7 had a history of falls or weakness. Of the 10 evaluable cases, the initial sensory disturbance was considered as involvement of the branches of the common peroneal nerve, the branches of the tibial nerve and the sural nerve in 7, 2 and 2, respectively. Of the 7 evaluable, the initial symptom was sensory disturbance or rash in 5 and 3, respectively. Of the 11 patients,

abnormal neurological findings were found in the superficial peroneal, the deep peroneal, the tibial, the sural, the lateral cutaneous nerve of calf, the median, and the saphenous nerve in 10, 9, 8, 7, 6, 2, and 1, respectively. In patients with EGPA abnormal sensation or pain tended to occur firstly, which might be synchronized with the skn lesion. The initial symptom tended to be due to involvement of the branches of the common peroneal nerve.

W82-3

Three cases of resistant vasculitic neuropathy improved by intravenous immunoglobulin

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Conflict of interest: None

[Case 1] A 74-year-old woman was admitted to our department because of mononeuritis multiplex, alveolar hemorrhage and cutaneous vasculitis, and she was diagnosed as microscopic polyangiitis. Remission was achieved with high-dose steroid and intravenous cyclophosphamide therapy (IVCY), however neurological symptoms remained. Two courses of intravenous immunoglobulin (IVIg) partially improved the persistent neuropathy. [Case 2] A 59-year-old woman with bronchial asthma was admitted to our department because of mononeuritis multiplex and positive PR3-ANCA. She was diagnosed as eosinophilic granulomatosis with polyangitiis. She was treated with high-dose steroid and IVCY, and IVIg was started one month later. Her neurological symptoms gradually improved after two courses of IVIg. [Case 3] A 47-year-old woman was admitted to our department because of mononeuritis multiplex due to Sjogren syndrome. High-dose steroid and IVCY failed to improve her neurological symptoms, and IVIg was administered. The persistent neuropathy partially improved shortly after IVIg was started, and the symptoms did not deteriorate after two more courses of IVIg. [Discussion] Repeated courses of IVIg can be effective in the treatment of vasculitic neuropathy resistant to high-dose steroid and IVCY.

W82-4

Clinical feature of ANCA-associated vasculitis (MPA, GPA) with renal involvement

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Conflict of interest: None

【Objectives】 To reveal clinical feature of MPA and GPA with renal involvement. 【Methods】 From January, 2000 to August, 2015, 129 patient of MPA and 41 of GPA patients who visited to our hospital were enrolled and analyzed the clinical data retrospectively from medical records. 【Result】 Renal involvement was found 79 (61.2%) in MPA and 18 (43.9%) in GPA. Renal involvement was revealed significantly higher in positive MPO or PR3 ANCA. Seventeen cases were needed dialysis at the diagnosis, however, 2 cases were leave dialysis, one of them was undergo maintenance dialysis after 4 months. 7 cases were newly undergo dialysis after diagnosis. Renal involvement were trend to high mortality (14.4% vs 5.5%), renal dysfunction (Cr≧1.7mg/dl) was significantly associated with high rate of dialysis (33% vs 0%) and death (19.7% vs 3.2%) after 1 year of diagnosis. Renal biopsy was administered 43 cases and classificated as Sclerotic 6, Focal 13, Crescentic 2, Mixed 22. After 1 year treatment, the rate of ESRD were as follows, Sclerotic 100%, Focal 0%, Crescentric 0%, and Mixed 13.6%. Non responder for combination therapy of glucocorticoids with CYC had many chronic lesion. Renal biopsy may be useful for estimate renal prognosis, because chronic lesion were may be associated to poor renal outcome.

W82-5

Clinical characteristics of four cases of microscopic polyangiitis (MPA)with tubulointerstitial nephritis (TIN) without glomerular lesions

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Conflict of interest: None

Background: Although MPA usually cause crescentic glomerulonephritis, cases with TIN without glomerular lesions (GL) have been reported. According to lesions of vasculitis, TIN is mainly classified into 3 types;(1)capillary of glomerulus, (2) peritubular capillary, and (3)small-sized artery. The clinical outcomes of such cases have not been elucidated. Methods: Out of 23 cases with MPA who underwent renal biopsy between Nov. 2011 and Nov. 2015, we found 4 cases presenting TIN without GL. We evaluated clinical characteristics of these patients. Results: A)78 F. Cr 1.96 mg/dl, CRP 24.9 mg/dl, MPO-ANCA 70 IU. Pathology;(2), (3). B)73 M. Cr 0.61 mg/dl, CRP 6.39 mg/dl, MPO-ANCA 2340 IU. Pathology;(2), (3). C)79M. Cr 1.96 mg/dl, CRP 2.29 mg/dl, MPO-ANCA 246 IU. Pathology;(3). D)69M. Cr 5.99 mg/dl, CRP 6.29 mg/dl, MPO-ANCA 229 IU. Pathology;(3). Pt. A was treated with PSL and CPA, while Pt. B and D were successfully treated with 1mg/kg of PSL only. Pt. C was initially treated by10mg of PSL, resulting relapse 7 months later. Conclusion: MPA with TIN without GL accounted for 17%(4/23).Two of them could be treated without immunosupprressants, suggesting the possibility that MPA with TIN without GL can be treated with steroid only.

W82-6

Long-term prognosis and renal survival in patients with ANCA associated vasculitis

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Conflict of interest: None

[Purpose] To investigate long-term outcome and associated factors in patients with ANCA associated vasculitis (AAV). [Methods] Patients who had been diagnosed as AAV in Niigata university hospital between 1989 and 2014 (n=131) were recruited. Overall and renal survival was calculated by the Kaplan-Meier method. Prognostic factors for overall or renal survival were analyzed by Spearman's rank correlation coefficient and multivariate Cox proportional hazard models.[Results] One-year survival rate was 81.4%, 2-year 74.6%, and 5-year 64.9%, respectively. Age, serum Cr, eGFR, microscopic polyangitis, and initiation of dialysis were significantly associated with higher mortality by Spearman's test, and age and initiation of dialysis were identified as independent poor prognostic factors for overall survival in Cox regression analysis. Renal survival was 95.7% at 1 year, 94.4% at 2 years, and 92.4% at 5 years. Age, serum Cr, eGFR were significantly correlated with renal survival by Spearman's test, and eGFR was identified as an independent poor prognostic factors for renal survival in Cox regression analysis. [Conclusion] Kidney dysfunction at the time of diagnosis and induction of dialysis are factors associated with poor prognosis in patients with AAV.

W83-1

Survey of the development of lymphoproliferative disorders in patients with rheumatoid arthritis

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Conflict of interest: None

Objectives: To investigate the occurrence of lymphoproliferative disorders (LPDs) in patients with rheumatoid arthritis (RA) seen at our hospital. *Methods:* RA patients who had been treated at our hospital between October 2007 and September 2015 were enrolled. The patients' data were obtained retrospectively from their medical records. Data indicated are median values. *Results:* We analysed the data for 19 RA patients with LPDs. The median patient ageat the time of LPD diagnosis was 71 years, and the duration of RA was 15.5 years. Sixteen patients were treated with methotrexate (MTX), and 7 with biologics. Eight patients were diagnosed as having DLBCL, and 4 as having HL. By September 2015, 8 patients had died, and the median survival period was 31 months. Although the CRP level rose from 0.2 mg/dL at 6 months before LPD diagnosis to 3.2 mg/dL ($p<0.001$, Wilcoxon signed-rank test) after LPD diagnosis, neither the number of tender and swollen joints nor the MMP-3 level showed any significant change (0.0 vs 0.5, $p=0.343$, 0.0 vs 0.0, $p=0.595$, and 90.8 to 96.3 ng/mL, $p=0.35$, respectively). *Conclusion:* Sixteen out of 19 patients who developed LPDs were receiving MTX. CRP elevation that is disproportionate to RA activity might be one of the signs of underlying LPDs.

W83-2

Analysis of methotrexate-related lymphoproliferative diseases (MTX-LPDs) in rheumatoid arthritis

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Conflict of interest: Yes

[Objective]Methotrexate (MTX) is the first choice drug for RA and is referred to as an "anchor drug". However, MTX-related lymphoproliferative diseases (LPDs) have emerged as important complications in the patients with RA, its pathogenesis has not been remained unclear. The aim of this study was to evaluate the clinical feature of MTX-LPDs in RA. [Methods] 41 patients developed LPDs in our cohort (about 6000 patients). We compared the clinical feature between patients with LPDs and 123 patients who do not develop LPDs despite of taking MTX. [Results] At the manifestation of LPDs, The average age was 70.6 and duration of RA was 154 months. The dose and duration of intake of MTX were 8.4mg/week and 68.5 months respectively. Concomitant use of steroids was 1.2mg and average DAS28 ESR was high as 4.42. 27 patients were treated with biologics. Two of third of pathology of lymphnode showed diffuse large cell B cell lymphoma. Age, disease duration of RA, stage, disease activity and dose of steroids but not dose of MTX were higher compared with those in patients without LPDs. [Conclusion] MTX-LPDs were observed the patients with higher disease activities and inadequate response to treatments. It seems only 9 patients recovered LPDs after discontinuation of MTX might be MTX induced.

W83-3

Characterization of methotrexate (MTX)-induced pneumonia which we experienced over the past 5 years

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Conflict of interest: None

[Objective] To describe the clinical feature and outcome of MTX-induced pneumonia (IP). [Method] Clinical data of 9 patients with MTX-IP were analyzed retrospectively, regarding the period from MTX start to IP onset, clinical and laboratory findings. [Results] In 4 patients, MTX-IP developed within 3 months after starting treatment. MTX-IP initially presented as fever, followed by the development of respiratory failure after 5 days. Their condition promptly improved in response to high-dose steroids. All 4 patients with MTX-IP had elevated β-D-glucan levels. Trimethoprim/ sulfamethoxazole (TMP-SMX) was administered concurrently, but allergy to TMP-SMX occurred. By contrast, in 5 patients, MTX-IP developed more than 1 year after starting treatment. MTX-IP progressed slowly in all but 1 patient. Two patients had high β-D-glucan levels. [Conclusion] MTX-IP responds well to steroids and has a good prognosis. MTX-IP that develops within 3 months after starting treatment tends to progress rapidly, while MTX-IP seen after more than 12 months was less severe. In patients with severe disease, the β-D-glucan level is high, and differential diagnosis from pneumocystis pneumonia is necessary

W83-4

Management of liver impairment and gastrointestinal symptoms in patients on MTX treatment ~Usefulness of daily administration of Foliamin 1mg/day~

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Conflict of interest: None

Background From February 2012, use of MTX up to 16 mg/week became possible. However, dose-dependent adverse events such as liver impairment and gastric disorders posed challenges. Interventions such as increased foliamin dose were routinely applied. ***Objective*** Clinical efficacy of changing foliamin dose from 5 mg/week to 1 mg daily for liver impairment and gastric disorders in MTX-treated patients was investigated at the author's institution. ***Methods*** RA out-patients on MTX, 86 with liver impairment and 28 with gastric disorders were studied. Mean age was 57.1 years, mean MTX dose 11.3 mg/week, mean AST (GOT) at the change was 54, and mean ALT (GPT) 83. Changes in symptoms were assessed up to 3 months. ***Results*** 1) Liver impairment symptoms improved significantly at 1 month, and continued uneventfully up to 3 months. MTX dose decrease was needed for 1 patient while an increase was possible for 6. 2) Gastric symptoms disappeared in 25 patients after 1 month, in 6 after 2 months, 1 after 3 months, and 2 after 4 months with no decrease in MTX dose, the remaining 2 patient applied self control but the symptom persisted. ***Conclusion*** Changing the foliamin dose to 1 mg daily was shown to be an effective intervention option for such gastric and liver adverse reactions of MTX.

W83-5

The analysis of risk factor and its management for transient transaminase elevations found in rheumatoid arthritis medical treatment

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Conflict of interest: None

We defined rheumatoid arthritis patients as "liver damage group", in whom transient transaminase elevations were detected between November 1 2013 and October 30 2014. Age, gender, the use of disease-modifying antirheumatic drugs (DMARDs) and HBV infection were considered to be the risk factors of live damage. In the control group 421 cases and liver damage group 56 examples, there was a significant difference using a univariate analysis in the presence or absence of MTX. In using logistic regression analysis, furthermore, the presence of MTX affected significantly the transient transaminase elevations.We separated RA patients whose transaminase newly elevated in the same period into "improvement", "delay", "intervention", "observation" group in regard to the course and management. Though the titer of elevated transaminase was significantly higher in the intervention group 14 cases than in the observation group 74 cases, the number of improvement group was significantly higher in the intervention group than in the observation group. In this study, we suggested that transaminase tended to deteriorate in using MTX, the titer reduced easily by intervention, and the use of DMARDs other than MTX and HBV infection were not the risk factor of transaminase elevation.

W83-6

A case of rheumatoid arthritis (RA) complicated with severe liver dysfunction and pure red cell aplasia by Bucillamine(BUC)

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Conflict of interest: None

[Case] 73 year old female. The patient continued to treat with oral prednisolone and tacrolimus for RA onset in 2012, complicated with expulmonary tuberculosis and interstitial pneumonia. For poorly-controlled RA, she began to treat with BUC in July 2014. She presented our hospital because of jaundice. In laboratory finding, severe liver dysfunction appeared and we diagnosed drug-induced liver dysfunction by BUC. It prolonged after cessation of the drug, in addition anemia by pure red cell aplasia developed. We began to high-dose glucocorticoid, but with compromised condition caused by prolonged liver dysfunction and immunosuppression, she suffered sepsis and pulmonary aspergillosis and died in November 2014. [Discussion] In this case, severe liver dysfunction and pure red cell anemia caused us hardship. We consider this case presentation to important side effects of BUC.

W84-1

Retention rate of golimumab treatment for rheumatoid arthritis is independent of concomitant methotrexate or prednisolone: results from the multicenter biologic registry

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Conflict of interest: None

Objective: The objective of this report was to clarify the factors affecting the retention rate of golimumab (GLM) used as a treatment for rheumatoid arthritis (RA). **Methods:** A prospective analysis was performed on 152 RA patients treated with GLM in our multicenter registry. We assessed the age, body weight, disease duration, disease activity, numbers of biologic agents before GLM, methotrexate (MTX) use and dosage, and prednisolone (PSL) use and dosage as baseline characteristics. **Results:** In the 152 patients observed, the total retention rate over 52 weeks was 71.6%. The group consisting of individuals weighing <50 kg showed better retention rates than the group with those weighing ’50 kg (P = 0.040). However, no other factors resulted in any statistical differences between the subjects. No differences were observed with respect to concomitant MTX or the dosage (P = 0.829 and 0.259, respectively), nor concomitant PSL (P = 0.523). **Conclusion:** In our registry of RA patients treated with GLM, a lower body weight was associated with better retention rate, and they did not show differences with concomitant MTX or PSL. These results may indicate that RA patients treated with GLM in combination with MTX can reduce or stop taking MTX.

W84-2

The rates of combined treatment of methotrexate (MTX) and non-anti-TNF agents for rheumatoid arthritis (RA)

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Conflict of interest: Yes

[Object] Although biologic agents are well established as part of MTX combination regimens in patients with RA, biologic monotherapy is common in clinical practice. We investigated rates of combined treatment of MTX and biologics, focusing especially on non-anti-TNF agents, in our clinic. [Methods] We analyzed medical records of 529 RA patients who have received treatments with abatacept (ABT), tocilizumab (TCZ) or etenercept (ETN) from 2010 to 2015. The rates of combined treatment of MTX and biologics were examined by fixed point observations in December of each year. We further evaluated one-year treatment persistence rates for each biologic. [Results] In 2015, rates of combined treatment of MTX and ABT, TCZ or ETN were 69.6%/38.8%/72.2%, respectively. The trend in the low rate of combined treatment of MTX and TCZ was stronger in elderly patients. One-year treatment persistence rates for each biologic (MTX combination/biologic monotherapy) were ABT 79.2%/67.7%, TCZ 79.3%/76.9% and ETN 81.8%/38.6%. [Conclusion] The rate of combined treatment of MTX and TCZ was low at 40% as against that of MTX and ABT at 70%. One-year treatment persistence with TCZ monotherapy was the same as that in combination with MTX, indicating low dependence of TCZ on MTX in real-world clinical practice.

W84-3

Study on the necessity of metothorexate(MTX) in tocilizumab(TCZ) therapy in rheumatoid arthritis(RA)---Cohort study carried by Michinoku Tocilizumab Study Group(MTGS)

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Conflict of interest: None

(Object)The necessity of MTX in TCZ therapy in RA is controversial. The object of this study is to clarify the necessity of MTX in the patients who achieved remission. (Methods)Thirty six months observational study on the clinical effectiveness of TCZ in RA was carried out in 311 patients by MTGS. The selection of the use and dose of MTX as well as other DMARDs depended on decision of attending doctors. The numbers of patients discontinued taking MTX, decreased the dose of MTX, continued the dose of MTX and increased the dose of MTX were 56, 12, 59 and 13, respectively. The group discontinued taking MTX (discontinue group=33) after achieving remission was compared with the group maintained the same dose of MTX (maintain group=37). (Results)The discontinue group was older than the maintain group. The discontinue group was suffering from RA significantly longer and bone destruction was significantly advanced. Adverse event as infection was more in the discontinue group, whereas unusual laboratory data were seen more in the maintain group. The values of DAS28ESR in the discontinue group always kept remission in the observation period. (Conclusion)Once the patients treated by TCZ with MTX achieve remission, cessation of MTX administration did not change the clinical course.

W84-4

Prospective study on the possibility of MTX cessation in RA patients who have remained remission with combination of MTX plus tocilizumab

Akiko Shibata, Ryota Sakai, Jun Kikuchi, Kentaro Chino, Tsuneo Kondo, Ayumi Okuyama, Hirofumi Takei, Koichi Amano
Saitama Medical Center, Saitama, Japan

Conflict of interest: None

[Object]To evaluate the possibility of MTX cessation in RA patients remained in remission with combination of MTX plus tocilizumab (TCZ). [Method]RA patients who have been in remission with combination of MTX plus TCZ for more than 6 months were randomly assigned to the MTX cessation group and MTX continuation group.We compared the efficacy and safety of these 2 treatment groups. [Results]Ten were assigned to the cessation group,and 12 cases were to the continuation group.At week 48,DAS28-ESR and CDAI were 2.109 and 49.6 in the cessation group,and 1.590 and 20.6 in the continuation group respectively.Six of 10 patients in the cessation group and 8 of 12 cases in the continuation group were remained in remission.Average HAQ-DI scores were 1.07 and 0.74,and the change of van der Heijde modified Sharp score during 48 weeks were 1.625 and 2.111 respectively.These were not significant between the 2 groups.As for the adverse events were seen in 8 patients in

the continuation group and only one patient in the cessation group. [Conclusions]As a whole DAS28-ESR and CDAI scores and remission rate were maintained in the cessastion group,although some patients relapsed.Cessastion of MTX may be possible in patients with sustained remission with TCZ plus MTX and may be safer than MTX continuation.

W84-5

Abatacept therapy combined with tacrolimus shows superior efficacy than without tacrolimus

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Conflict of interest: None

[Objective] The effectiveness of abatacept (ABT) and tacrolimus (TAC) for the treatment of rheumatoid arthritis (RA) is apparent, however the efficacy and safety at concomitant use of ABT and TAC was not unclear. The aim of this study is comparison between ABT therapy for RA patients with and without TAC. [Methods] Forty eight RA patients were included in this study who were undertaken intravenous ABT therapy at Osaka Rosai Hospital after February 2011 and observed over 52 weeks. Patient background, efficacy, and safety were examined. [Results] Patient background between ABT + TAC group (n=15) vs ABT group (n=33) were not significantly different. DAS of ABT + TAC group decreased significantly greater than ABT group at 16 weeks, maintained until 52 weeks. Adverse event between ABT + TAC and ABT group was not different. Factor that achieve the low disease activity at 52weeks were Steinbrocker class1/2, concomitant use of TAC and DAS<3.3 at 12 weeks by logistic regression analysis. [Conclusion] ABT therapy concomitant with TAC has the possibility to show higher effectiveness for RA patients than without TAC.

W84-6

Taking low-dose prednisolone may influence serum MMP-3 as an indicator of disease activity in rheumatoid arthritis treated with abatacept

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Conflict of interest: Yes

MMP-3 has been used as a biomarker for assessing disease activity in RA patients. But MMP-3 is reported to be higher in patients treated with glucocorticoids. Our study aimed to investigate whether low-dose prednisolone (PSL) influence MMP-3 in RA patients treated with abatacept (ABA). Patient characteristics are collected at Tsurumai Biologics Communication Registry (TBCR) institutes. A total of 124 RA patients who we matched based on the propensity score were analyzed. Both patients taking ABA with and without concomitant PSL showed significant improvement in disease activity at 4, 12, and 24 weeks. In comparison between groups, almost parameters did not significantly differ at each time point. Only as for MMP-3, patients with concomitant PSL had significantly higher at 4, 12, and 24weeks. ROC curves for DAS28-CRP (DAS) and MMP-3 for achievement of remission of DAS at 24 weeks are constructed. In patients with concomitant PSL, DAS had significantly better AUC at 4,12weeks than MMP-3 for predicting remission. In conclusion, low-dose PSL may make MMP-3 higher in RA patients with low disease activity but not with high disease activity. And in patient with concomitant low-dose PSL, MMP-3 is not useful biomarker for clinical remission achievement.

W85-1

Does the upper extremity surgery for the patients with rheumatoid arthritis improve QOL and depressive condition?

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Conflict of interest: None

(Objectives) A prospective cohort study was performed to know whether upper extremity surgery for the patients with rheumatoid arthritis (RA) improves QOL and depressive condition. (Patients and methods)A primary upper extremity surgery was scheduled in 157 patients (male:22, female:135) with RA. The average age were 63 yrs. old and the mean duration of the disease was 16 yrs. Steinbrocker stageIII and classII were most frequent. The surgical site was shoulder:7,elbow:27,wrist:77,finger:47 (hands). The procedure was synovectomy:27,arthroplasty:39,arthrodesis:32,joint replacement:59. EQ-5D (health related QOL) and BDI-II(depression, mental) were investigated before surgery, 6 mos. and one yr. after surgery. (Results) As a whole, EQ-5D and BDI-IIimproved significantly at 6 mos. and one yr. after surgery. EQ-5D did not change in shoulder and finger surgeries, however it improved significantly in elbow and wrist surgeries. EQ-5D improved significantly in arthroplasty, arthrodesis and joint replacement. There was not a remarkable change in BDI-II in shoulder and finger surgeries. BDI-II decreased significantly in elbow and wrist surgeries. (Conclusions) Elbow and wrist surgeries, arthroplasty, arthrodesis and joint replacement improved patient's QOL and depressive condition.

W85-2

Patient-reported outcome of upper extremity surgery for rheumatoid arthritis

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Conflict of interest: None

[Object] To investigate the patient-reported outcome of upper extremity surgery for rheumatoid arthritis (RA). [Methods] Between 2011 and 2014, 158 RA patients underwent the surgical treatment of upper extremities. The clinical outcome of the surgery was assessed by HAQ, DASH, Hand20, BDI-II. The patients were divided by surgical site into 3 groups (elbow, wrist and finger groups) and by the use of bDMARDs into 2 groups (bDMARDs and non-bDMARDs groups) to compare and evaluate the outcome. [Results] All outcomes significantly improved after the surgery. All outcomes except for HAQ improved significantly in the elbow group, but BDI-II did not reach significant improvement in wrist/finger groups and the bDMARDs group. We further examined the postoperative change in each query of DASH and Hand20, and found the characteristic improvements in queries for weakness in elbow group, for pain in wrist group and for cosmetic factor in finger group. [Conclusion] There were surgical site-specific pattern and the influence by the use of bDMARDs in the patient-reported outcome, which would be useful information for better decision making of surgical indication and more accurate prediction of surgical outcome.

W85-3

The utility of Self-Administered Foot Evaluation Questionnaire (SAFE-Q) in evaluation of foot disability in patients with rheumatoid arthritis

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Nakahara[1], Takahiro Machida[1], Masahiro Horita[1], Ayumu Takeshita[1], Masahito Watanabe[1], Toshifumi Ozaki[1]
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Conflict of interest: None

[Objectives] The aim of this study is to examine the utility of Self-Administered Foot Evaluation Questionnaire (SAFE-Q) in evaluation of foot disability in patients with rheumatoid arthritis (RA). [Methods] Preoperative SAFE-Q, JSSF, HAQ-DI, patient pain VAS, patients' global assessment, Dr. VAS, MMP-3, ESR, CRP, DAS28-CRP, SDAI, CDAI and radiographic evaluations such as HVA, M1M2A, M1M5A, CPA, sesamoid deviation were determined in 29 patients with RA who underwent the foot surgery. The patients were one male and 28 female, and the average age and disease duration was 63.0 years old, and 24.4 years, respectively. [Results] Items of SAFE-Q other than "Shoe-Related" was significantly correlated with JSSF. SAFE-Q, but not JSSF, significantly correlated with disease activities such as DAS28-CRP, SDAI, CDAI, and HAQ-DI. JSSF, but not SAFE-Q, significantly correlated with radiographic evaluations. [Conclusion] SAFE-Q is self-administered utility score. The current study suggested that disease activity might influence the value of SAFE-Q. The fact that structural evaluation showed close relationship with JSSF, but not with SAFE-Q, suggests both evaluation system should be used in combination for the assessment of rheumatoid foot.

W85-4

Long-term surgical results of arthroplasty for rheumatoid elbow

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Department of Bone and Joint Surgery, Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives]we reviewed our surgical results of arthroplasty for rheumatoid elbow. [Methods]A retrospective review of arthroplasty for rheumatoid elbows (radial head resection + synovectomy) performed between 1993 and 2005 was undertaken. There were 28 cases with 29 elbows. All cases could be available for follow-up over 10 years or more. Their average age was 53.4 (21-72)y and the average follow-up term was 13y 4m (10y - 21y9m). The items evaluated were arc of motion of the elbow, pain at the last examination, radiographic change of carrying angle and existence of surgical revision. [Results] The average arc of motion was 86 (45-130) degrees before surgery or 84 (30-120) degrees at the last exam. 9 patients had elbow pain at the last. The average value change of carrying angle was 4.18 (-8 -13) degrees, however there were only 4 elbows which had 10 or more degrees change. There were no patients who underwent second surgery. [Conclusions] Arthroplasty has been considered as palliative surgery to fill up time to total elbow arthroplasty. However, there were no patients had necessity of surgical revision in this study. Therefore, good long-term result might be expected with only arthroplasty, in combination with tight control of RA activity with agents.

W85-5

An original idea of total wrist arthrodesis for the rheumatoid wrist -Wrist Fusion Rod (WFR®)-

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Conflict of interest: None

[Objectives] For the severely deteriorated rheumatoid wrist in Larsen grade IV or V with subluxation, total wrist arthrodesis was indicated. To clarify the feature of wrist arthrodesis utilizing Wrist Fusion Rod (WFR®), a retrospective study was performed. [Patients and methods] Between January 2007 and June 2015, total wrist arthrodesis utilizing WFR was performed on 40 wrists in 34 patients (male:7, female:27) with rheumatoid arthritis. The mean age was 67 years old, the mean disease duration was 18 years and the mean follow-up period was 4 (1~9) years. Twelve wrists were in Larsen grade IV and 28 were in V, and 19 were with finger extensor tendon rupture. [Results] A stable and painless wrist was provided by a WFR and grip power increased in most of the patients. Delayed wound healing was noted in 6 wrists, breakage of the rod was in one, and no infection was noted. Bone union occurred at the radiocarpal joint in all. The patient's satisfaction level was high. [Discussion] It was easy to get the wrist in a neutral position or in a slight extension with rotational stability. Additional fixation was needed in the wrist with some mobility at the 3rd CM joint. [Conclusion] A WFR® matched well to the fragile bone and a steady fixation could be obtained without high technical demands.

W85-6

Natural history of deformity in the rheumatoid hand; a 10 year time course study

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Conflict of interest: None

【Introduction & Objective】 Rheumatoid hand deformities, such as Swan-neck and Boutonnière deformity progress and impair hand function despite advancement in drug therapy. But its natural course of progression is still unknown. We assessed these deformities over 10 years. 【Method】 We registered 69 patients 138 hands and started a 10 year time course study in 2004. and evaluated finger deformity and disease activity. Fifty-two patients 100 hands were available in 2009, and finally 37 patients 63 hands in 2015 were available for evaluation. Deformities were evaluated by using the Nalebuff classification in 2004, 2009 and 2015. Disease activity were measured by using disease DAS28 at these end points. 【Results】 The number of remission cases had increased. For Nalebuff classification, both Swan-neck deformity and Boutonnière deformity progressed and increased. Swan-neck deformity was frequent in the radial side of the hand. Boutonniere deformity was evenly present in all finger. 【Conclusion】 In this study, finger deformities increased and progressed over time. Even in the case of remission had improved, deformity progression might be unavoidable in patients with rheumatoid arthritis. This suggests that early surgical interventions are still important.

Poster Session

P1-001

Comparison of gene expression profiles between synovial mast cells from patients withrheumatoid arthritis and osteoarthritis

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Conflict of interest: None

Comparison of synovial mast cells (MCs) from patients with rheumatoid arthritis (RA) and osteoarthritis (OA)

Background: We have previously reported that the synovial MCs from patients with RA and OA expressed similar expression levels of Fc receptors, and IgE- or IgG-dependent stimulation induced similar amounts of TNF-α from both MCs. The aim of this study was to compare the synovial MCs from RA and OA patients. Methods: Synovial tissues were obtained from patients with RA or OA undergoing joint replacement surgery, and synovial MCs were enzymatically dispersed. Synovium-derived cultured MCs were generated by culturing synovial cells with stem cell factor. GeneChip® analysis was used to compare the gene expression profiles of MCs from patients with RA and OA. The results were confirmed by quantitative RT-PCR. MC mediators were measured using EIA. Results: The expression levels of COX_1 and COX_2 in synovial MCs from patients with RA were significantly higher than in those from patients with OA. The synovial MCs from RA patients produced significantly higher amounts of prostaglandin D_2 (PGD_2) following aggregation of FcεRI or FcγRI, compared with the MCs from OA patients. The amounts of PGD_2 levels in synovial fluids from RA patients were significantly higher than those from OA patients. Conclusions: The synovial MCs might regulate inflammation in RA through the hyperproduction of PGD_2.

P1-002

Expression of IL- 17A in synovial mast cells from patients with rheumatoid arthritis and osteoarthritis

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Conflict of interest: None

Background: The synovial mast cells (MCs) in rheumatoid arthritis (RA) and osteoarthritis (OA) reportedly expressed IL-17A, but the frequencies of IL-17A expression in synovial MCs have varied. The aims of this study were to investigate the frequencies of IL-17A expression in synovial MCs in RA and to elucidate the mechanism of IL-17A expression in synovial MCs. *Methods:* Synovial tissues were obtained from patients with RA or OA undergoing joint replacement surgery, and synovial MCs were enzymatically dispersed. Synovium-derived cultured MCs were generated by culturing synovial cells with stem cell factor. IL-17A expression was investigated using immunofluorescence in synovial tissues. IL-17A mRNA expression and its production from MCs were examined using RT-PCR and ELISA, respectively. *Results:* The number of IL-17A+ MCs and the percentage of IL-17A+ MCs in all the IL-17A+ cells in synovium from patients with RA were not significantly higher than in those from patients with OA. The synovial MCs spontaneously released small amounts of IL-17A. IgE- and IgG-dependent stimulation, IL-33, tumor necrosis factor-α, C5a, lipopolysaccharide or IL-23 plus IL-1β did not affect IL-17A production in MCs. *Conclusions:* The synovial MCs might not be a main source of IL-17A in RA.

P1-003

Enhancement of Mitochondrial Biogenesis Inhibits Joint Destruction in Collagen-Induced Arthritis (CIA) Mice

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Conflict of interest: None

[Objectives] Joint destruction of rheumatoid arthritis (RA) proceeds by hyper proliferation of synovium, and secretion of MMP3 and RANKL-activated osteoclast from fibroblast-like synoviocytes (FLS). We have reported that the expressions of mitochondria-related genes in RA-FLS were decreased and enhancement of mitochondrial biogenesis inhibits cell proliferation and MMP3/RANKL on inflammation in RA-FLS. Therefore, we investigated the effect of mitochondrial activation in CIA mice on joint destruction and swelling using AICAR (mitochondria-activation drug). [Methods] CIA mice and normal mice (DBA/1JJmsSlc) was used. For evaluating the effect of AICAR (500 mg/kg, every day for 3 weeks), we assessed the joint destruction in CIA mice by CT and histopathological analysis, the swelling by measurement of hand and foot thickness and arthritis score, and the side-effect by body weight loss and pulmonary inflammation of histopathological were used. [Results] AICAR reduced the hand and foot thickness, arthritis score and joint destruction in CIA mice. Moreover, AICAR inhibited body weight loss and histopathological pulmonary inflammation. [Conclusion] Enhancement of mitochondrial biogenesis may suppress of disease activities and joint destruction of RA without side-effect.

P1-004

Upregulated MicroRNA-155 Expression in Fibroblast-Like Synoviocytes(MH7A) in Rheumatoid Arthritis

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Conflict of interest: None

Objective. This study was to investigate miRNA expression profiling stimulated with EP4 agonist and to evaluate the function of miR-155 in RA-FLS. *Methods*. Agilent miRNA Array systems.was used to screen for differentially expressed miRNAs in RA-FLS. Enforced over expression of miR-155 were used to investigate the function of miR-155 in RA-FLS (MH7A). Expression of Twist1, POSTN and MMP1 which were previously identified as the actual target of activity of RA-FLS were examined by Western blot and real-time PCR in MH7A. *Results*. miR-155 levels were increased in FLS of RA and could be induced by IL1β. Upregulation of miR-155 decreased Twist1, POSTN, and MMP-1 levels. The expression of miR-155-5p was decreased in EP4 agonist treated MH7A. *Conclusion*. miR-155 is upregulated in RA-FLS, and it may be a protective factor against the inflammatory effect.

P1-005

Evaluation of the synovitis in murine arthritis models using tenascin-C

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Conflict of interest: None

[Objectives]We have demonstrated that tenascin-C (TNC) could contribute to accelerate chondrocyte proliferation and prevent cartilage degeneration in osteoarthritis model. On the other hand, Midwood et al showed that TNC could promote joint inflammation (Nat Med 2009). In this study, we examined the effect of TNC for synovium and cartilage with murine models for rheumatoid arthritis (RA).[Methods]Eight-week-old male BALB/c mice were used. 15μg/ml of zymosan to both knee

joints. After injecting zymosan, subsequently mice were injected TNC 0.1μg (GroupI)or PBS for control (GroupII). Mice were sacrificed at 4days, 2weeks, 4weeks postoperatively. Synovitis and cartilage were evaluated using Synovitis score, and Mankin score.[Results]Average synovitis scores were better in GroupIthan in GroupII at 4days (GroupI;1.6,GroupII;3.6 ($p<0.05$)). At 2weeks and 4weeks, there were no significant differences in average scores between two groups. At 4days, 2weeks, 4weeks, average Mankin scores showed no significant differences.[Conclusion]This study demonstrated TNC could suppress the synovitis in murine RA models only at an early period.

P1-006

A novel method for detection and identification of proteins released from the cell surface by shedding

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Conflict of interest: None

【Objective】Cell surface proteins, digested at an extracellular domain and released from cell surface (shedding), are known to be associated with rheumatoid arthritis. However, when and which proteins are digested and released by shedding have not been elucidated because there has been no effective and comprehensive method to analyze the proteins. The aims of this study were to establish a novel method to analyze proteins released by shedding.【Materials and Methods】Human synovial sarcoma cell line of SW 982 was used. The cell surface proteins of living cells were biotinylated and then the cells were cultured. Biotinylated proteins released from the cell surface into media were captured using streptavidin beads.【Results】Proteins captured by streptavidin beads were able to be detected as bands by western blot analysis with HRP-conjugated streptavidin. Among them, intensity of multiple bands was decreased by treatment with a sheddase inhibitor. Intensity of some bands was increased by treatment with TNF-α.【Conclusion】These results suggest that our method is an effective and comprehensive method to analyze proteins released by shedding. Identification of the proteins affected by TNF-α would help understanding of the association of shedding with rheumatoid arthritis.

P1-007

Proteomic analysis of exosomes derived from serum of rheumatoid arthritis patients

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Conflict of interest: None

[**Objectives**] To elucidate features of protein profile of serum-derived exosomes in rheumatoid arthritis.[**Methods**] Serums were obtained from 43 participants (12 with high activity RA (A-RA), 11 with remission RA (R-RA), 10 with OA (OA), and 10 healthy controls (HC)). Exosomes were isolated from the serums using Exoquick®. Then, exosomal proteins were comprehensively analyzed by 2-dimensional differential image gel electrophoresis (2D-DIGE). Protein spots intensity of which was significantly altered between above groups were identified by mass spectrometric (MS) analysis.[**Results**] 204 protein spots were detected in the exosome preparations. Among them, 24, 5, 7 spots showed more than ±1.3-fold expression with statistical significance in A-RA, R-RA, and OA groups respectively, as compared with HC. As one example of the identified protein, TLR-3 was identified from the spot which showed more than 4-fold expression in A-RA, as compared with other groups. [**Conclusion**] Exosomes derived from serum of high activity RA patients contain much TLR-3 than other groups.

P1-008

A 3' Untranslated Region Reporter System to Screening for Factors that Regulate Rheumatoid Arthritis-Related Transcripts

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Conflict of interest: None

[Object] The changes in the expression of genes are closely related to disease-associated events such as inflammation, aberrant immunity, and joint destruction in RA. In this study, we attempted to identified stimuli that regulate metabolism of RA-related mRNAs. [Methods] We generated duel luciferase reporter plasmids to study the influence of cytokines on transcript stability and activity via the 3' untranslated region (3'UTR) of genes associated with RA. The 3'-UTR sequences of these RA-related genes were inserted into the 3'-UTR of the firefly luciferase gene in the pmirGLO Dual-Luciferase miRNA Target Expression Vector. U2OS cell was transfected with these reported plasmids 2 hours before cytokine treatment. The transfected cells were stimulated with cytokines for 12 hours and were lysed for luciferase activity analyses. [Results] Cytokine treatment affected the luciferase activities of the reporters. In particular, IL-1β treatment increased the luciferase activities of the reporters harboring the 3'-UTR of *CXCL2* mRNA. IFNα and IFNγ increased those of the reporters harboring the 3'-UTR of IFNα. These results will be presented as a heat map style. [Conclusions] Our data suggest that cytokines regulate the stability or translation of mRNA of RA-related genes.

P1-009

Expression of connexin 43 in synovial tissue of patients with rheumatoid arthritis

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Conflict of interest: None

[Object] The aim of this study is to examine the expression level of Cx43 gene in synovial tissue in patients with rheumatoid RA compared with osteoarthritis. [Methods] The expression of Cx43 in synovial tissue from eight patients with RA, five patients with osteoarthritis was analyzed by real time RT-PCR and immunohistochemistry of tissue sections. Induction of Cx43 following stimulation of human RA synovial fibroblasts with tumor necrosis factor-alpha (TNF-a) cultures was examined by real time RT-PCR. The effect of small interfering ribonucleic acid targeting Cx43 (siCx43) on the expression of TNF-a and interleukin-6 was examined using real time RT-PCR and ELISA. [Results] Cx43 was highly expressed in RA synovial tissue, which also expressed TNF-a. Expression of Cx43 was markedly up-regulated in RA synovial fibroblasts after stimulation with TNF-a. The over-expression of pro- inflammatory cytokines was suppressed by transfection of siCx43. [Conclusion] This study shows that Cx43 is expressed in RA synovial tissue and that its expression is induced by stimulation with TNF-a. The expression of the pro-inflammatory cytokines was inhibited by transfection of siCx43. Cx43 may be a novel marker of inflammation in RA synovial tissue.

P1-010

Effect of omega-3 lipid mediator on inflammatory in human Rheumatoid synovial fibroblasts

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease as the proliferative synovitis and bone destruction. The production of specialized pro-resolving mediators as resolvin E1

(RvE1) and protectin D1 (PD1) were derived from the omega-3 polyunsaturated fatty acids (ω-3 PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). We investigated the effects of these lipid mediators on synovial inflammation in RA synovial fibroblasts (RASF).[Methods] Human primary RASF were obtained at the time of joint replacement surgery. RASF were treated with pro-resolving mediators such as RvE1 or PD1, followed by interleukin (IL) -1βstimulation. Cyclooxygenase (COX) 2 and prostaglandin (PG) E2, IL-6, and matrix metalloproteinase (MMP) -3 mRNA and protein expression were analyzed by real-time PCR and Western blotting.[Results] The expression of COX2, PGE2, IL-6, and MMP-3 were reduced by pro-resolving mediators compared to vehicle control. [Conclusion] The pro-resolving mediators such as resolvin E1 (RvE1) and protectin D1 (PD1) derived from ω-3 PUFAs inhibits inflammatory cytokine.

P1-011

The profiling analysis and identification of arthritis inhibitory lipid mediators in adjuvant induced arthritis mice

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Conflict of interest: None

Purpose: Recently, some reports have shown that several lipid mediators (LM) contribute to the disease progression and recover in RA. These facts suggest that metabolized LM were involved in inflammatory regulations, however, it is unclear whether what kind of LM related in local environment of RA joints. The purpose of this study is to determine these LM profiles in inflammatory joints, and identify LM that contributes to inflammatory regulations. **Method:** We used CIA mice model. Mice were bred by a long chain ω-3 fatty acid rich diet (ω3D) and then induced CIA. We analyzed LM in joints and plasma by LC-MS. **Result:** We determined methods for measured LM in foot joints, and created LM profiles. LM in foot joints and plasma obtained from ω3D treated mice were measured, and diet derived LM metabolites were markedly increased in these samples. **Conclusion:** Analysis of LM in arthritis joints could be understood the precise state of inflammatory environment in joints. Indeed, it was suggested that the inhibition of CIA arthritis under the treatment of ω3D was caused by the increase of diet-derived anti-inflammatory LM in joints. Additionally LM are common among species. We concluded that the identification of anti-inflammatory LM, could contribute to the control of arthritis in RA.

P1-012

Effect of Omega-3 Lipid Mediators on Modulation of Osteoclast Formation and Bone Resorption

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Conflict of interest: None

The endogeneous pro-resolving lipid mediators, which are resolvin, protectin and maresin, derived from the long chain omega-3 polyunsaturated fatty acids display beneficial effects in human diseases. But the mechanism for the inhibiton of bone destruction in rheumatoid arthritis is not well understood. The aim of our study is to investigate the inhibitory effect of the ω-3 pro-resolving lipid mediators for the osteoclast formation. RAW264.7 cells, which are from a macrophage cell line, are cultured with sRANKL (100ng/ml) with or without ω-3 pro-resolving lipid mediators. After 6days, the osteoclastogenesis and differentiation were analyzed using TRAP staining and the bone resorption assay kit. And the gene expression of NFATc1 and c-fos were analyzed by real-time PCR. The number of TRAP positive cells and the osteoclast resorption activity were significantly suppressed pretreatment with ω-3 pro-resolving lipid mediators compared to vehicle control. And also, the NFATc1 and c-fos gene expression are significantly inhibited by ω-3 pro-resolving lipid mediators pretreatment compared to vehicle control. These result indicated that ω-3 pro-resolving lipid mediators might inhibit the bone destruction via the modulation of the osteoclast formation and bone resorption.

P1-013

Non-synonymous single nucleotide polymorphisms of Hypoxia-inducible factor-3A gene in the patient with connective tissue diseases associate with pathogenesis of pulmonary arterial hypertension

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Conflict of interest: None

Pulmonary arterial hypertension (PAH) is a life-threatening complication in the patients with connective tissue diseases (CTDs). Increased endothelin-1 (ET-1) is a hallmark of PAH, and contributes to its pathogenesis. Mechanism for ET-1 induction in PAH, however, is still unclear. Numerous cellular responses to hypoxia are mediated by Hypoxia-inducible factors (HIFs) composed of HIF-α and HIF-β subunits. We once detected high frequency non-synonymous single nucleotide polymorphisms (SNPs) of HIF-3A gene in the patients with systemic sclerosis (SSc) complicated with PAH. In HeLa stable cell lines overexpressed HIF-3A gene carrying those SNPs (SNP HIF-3α), SNP HIF-3αshowed a strong promoter activity in human ET-1 promoter region. We overexpressed SNP HIF-3αin Human pulmonary artery endothelial cells (HPAEC) and cultured Human pulmonary artery smooth muscle cells (PASMC) in conditioned media from HPAEC overexpressed SNP HIF-3α in this time. Therefore, ET-1 mRNA expression and ET-1 induction were increased in HPAEC and conditioned media from HPAEC overexpressed SNP HIF-3α enhanced cell proliferation and migration in PASMC. Our findings suggested that SNP HIF-3αmight cause pulmonary arterial remodeling and contribute to pathogenesis of PAH.

P1-014

Analysis of the mechanism of activated T-cell induced endothelin production from monocytes : the similarity between human and mice system

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Conflict of interest: None

Objective: Endothelin (ET) is a vasocontricting factor derived from vascular endothelial cells and could play a pivotal role in the pathogenesis of pulmonary hypertension. We have already reported elsewhere that activated T-cells induced the production of ET from monocytes in human *in vitro*. In this study, we examined whether such phenomenon could be confirmed *in vitro* when using murine immune cells prior to clarifying the significance *in vivo*. Methods: First, murine spleen cells were cultured with immobilized anti-CD3 Ab. After 24h, ET in the supernatant was measured with ET ELISA kit. Second, a double chamber assay for ET production was carried out by putting activated antigen-specific CTL in the lower chamber and bone marrow-derived monocytes in the upper chamber with/without anti-TNF-α or IFN-γ neutralizing Ab. Results: ET production from murine spleen cells with immobilized anti-CD3 Ab was increased in cell count-dependent manner. Antigen-specific CTL activation induced ET production from bone marrow-derived monocytes separated with a porous membrane. Furthermore, it was diminished by anti-TNF-α and IFN-γ Ab. Conclusion: Activated T-cells induce ET

production from monocytes through IFN-γ and TNF-α also in mice *in vitro*. *In vivo* experiments are now under investigation.

P1-015

Studies on the contribution of endoplasmic reticulum stress to antigen cross-presentation and the induction of lupus tissue injury

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Conflict of interest: None

Objective: Our 'self-organized criticality theory' explains that SLE is induced after repeated immunization with antigen in mice normally not prone to SLE, where cytotoxic T lymphocyte generated *via* antigen cross-presentation induces lupus tissue injury. Here we examine the contribution of endoplasmic reticulum (ER) stress to antigen cross-presentation and the induction of lupus nephritis. **Methods:** Mice were repeatedly immunized with ovalbumin (OVA), and unfolded protein response (UPR)-related molecule Bip in splenic DC (spDC) was detected. Bone marrow-derived DC (BMDC) was cultured with OVA and/or an inducer of ER stress tunicamycin, in which EEA1, Sec61 or OVA was immunoprecipitated and detected. **Results:** Expression of UPR-related protein Bip was increased in the spDC of the mice which developed glomerular injury. In BMDC, co-culture with tunicamycin increased both the amounts of Sec61 co-precipitated with EEA1 and OVA in the cytoplasm, suggesting that ER stress increased endosomal Sec61. **Conclusion:** ER stress increased not only endosomal Sec61 but also the export of antigen from endosome to cytoplasm, suggesting that antigen cross-presentation can be increased in proportion to the amount of antigen accumulated in the cytoplasm of DC, thereby leading to lupus glomerular injury.

P1-016

Role of the intracellular [Ca^{2+}] in circadian rhythm of rheumatoid synovial cells

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Conflict of interest: None

Objective: Expression of the clock gene *Bmal1* is regulated by the transcriptional activator *Rorα* and the repressor *Reverbα*. We previously showed that TNFα modulates the clock gene expression via calcium signaling in rheumatoid synovial cells. In this study, we further investigated the role of intracellular [Ca^{2+}] in circadian rhythm of the cells. Methods: After incubation with an intracellular [Ca^{2+}] chelator BAPTA-AM (0.25 to 25μg/mL) or a calcineurin inhibitor FK506 (25 μg/mL) for 1h, synovial cells were cultured every 8h for 32h. *Bmal1*, *Rorα* and *Reverbα* mRNA expression and cell viability were analyzed by qPCR and Cell Counting Kit-8. Results: Circadian oscillation of *Bmal1* gene expression was lost, and *Rorα* and *Reverbα* were upregulated by treatment with BAPTA-AM, but not FK506. In addition, TNFα-induced cell proliferation as well as *Bmal1* overexpression, was inhibited by BAPTA-AM. Conclusions: Calcium signaling affects cell proliferation of rheumatoid synovial cell via clock gene, and a novel therapeutic target of RA was indicated.

P1-017

Effects of Methotrexate on circadian clock genes of RA-FLS

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Conflict of interest: None

OBJECTIVE: Effects of MTX on the growth potential of RA-FLS are still unclear. We have been reported that the proliferation of RA-FLS is increased by reduction of the clock gene Per2 expression. In the present study, the effect of MTX on clock genes was examined. METHODS: RA-FLS was cultured with MTX (1/10/100nM,1mM) for 24/48/32h to examine cell viabilities using Cell CountingKit-8. Further, we measured the expression level of the clock genes and its related factors, Tbp / Per2 / Clock / Bmal1 / Dbp mRNA, by quantitative PCR under the stimulation of MTX (10nM) for 24/48/32h, respectively. RESULTS: The cell viability was significantly reduced by MTX (1 and10nM). By the stimulation of 10nM MTX, expression levels of Per2 / Dbp were significantly increased, and that of Bmal1 was significantly reduced. CONCLUSION: Dbp expression level is increased by MTX, results in increased amount of Per2 expression, presumably due to accelerate the binding of Dbp to D-box on Per2 translation area. A novel mechanism of MTX to reduce the RA-FLS viability is suggested through clock gene, Dbp and Per2.

P1-018

Comparison between Human Synovial Fibroblasts and Mouse Osteoblasts in the Capacity to Differentiate Mouse Osteoclasts

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Conflict of interest: None

Aim:Osteoclasts can be differentiated *in vitro* when mouse osteoclast precursor cells and osteoblasts are co-cultured with, for example, VD3 and PGE2 (co-culture system). Synovial fibroblasts are believed to play a similar role in rheumatoid arthritis (RA). The aim of this study was to establish a chimeric co-culture system utilizing mouse macrophage -lineage cells and human synovial fibroblasts. Methods:Synovial fibroblasts from RA patients were cultured with osteoclast precursors from mouse bone marrow in the presence of VD3/PGE2 for 7 days. $TRAP^+$ multinuclear (>5 nuclei) cells were judged as osteoclasts. Results:Mouse cells gradually decreased in number and only synovial cells remained 7 days later. When M-CSF was exogenously added, mouse cells survived but $TRAP^+$ multinuclear cells were still not observed unless RANKL was also added. Expectedly, M-CSF was not detected in the culture supernatant of synoviocytes even in the presence of VD3/PGE2 and OPG, natural inhibitor of RANKL, was detected at concentrations higher than mouse OPG produced from osteoblasts. Conclusion:Human synovial fibroblasts are unable to replace mouse osteoblasts, probably because (1) they do not produce enough of survival factor (s) for osteoclasts, and (2) production of OPG was too high compared to RANKL.

P1-019

The functional difference among NFATc1 isoforms during osteoclastogenesis

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Conflict of interest: None

[Objectives] Nfatc1 is the essential transcriptional factor for osteoclast differentiation. Serfling *et al*. reported that the short isoform, NFATc1/A, which is highly induced in activated T cells, was unable to promote apoptosis, which stands in contrast to other, longer isoforms, NFATc1/B and C. The aim of this study was to investigate the functional difference of the Nfatc1 isoforms in osteoclastogenesis. **[Methods]** First,

we isolated the isoforms that were expressed during osteoclastogenesis in vitro. Next, we quantified the expression at the mRNA and protein levels using qRT-PCR and Western blot analysis, respectively. Finally, we examined the effect of the forced expression of each Nfatc1 isoform in BMMs (bone marrow monocyte/macrophage precursor cells) using a retroviral vector. [Results] Three *Nfatc1* isoforms were detected. The short isoform, NFATc1/A, was highly induced by RANKL. The other two isoforms were barely induced by RANKL. Interestingly, the forced expression of each Nfatc1 isoform in BMMs in the absence of RANKL did not induce the differentiation of osteoclasts. [Conclusion] This result indicates that there are other factors or signals required for osteoclastogenesis in cooperation with Nfatc1. Further analysis should reveal the roles of each Nfatc1 isoform.

P1-020

Expression of the c-*fos*-enhanced green fluorescent protein fusion gene in the spinal cord and the hypothalamus in transgenic rats after inflammatory pain

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Conflict of interest: None

[Object] We have generated c-*fos*-enhanced green fluorescent protein (eGFP) transgenic rats. In this study, we examined eGFP expression in the spinal cord and the hypothalamus after inflammatory pain in the rats. [Methods] We counted eGFP fluorescence cells in lamina I and II of the L5 spinal cord, the supraoptic nucleus (SON) and the paraventricular nucleus (PVN) of the hypothalamus after subcutaneous (s.c.) injections of capsaicin and formalin in both rat hind paws. Non-trearted, saline and ethanol s.c. injected rats were used as control groups. [Results] In the capsaicin and formalin groups, the number of eGFP fluorescence cells in lamina I at 1.5 h, in lamina I, the SON and the PVN at 3 h after s.c. injections were significantly increased. The number of the cells in lamina II at 6 h after s.c. injection of capsaicin, in lamina I and II and the PVN at 6 h after s.c. injection of formalin were also significantly increased. [Conclusions] We were able to readily visualize and quantitatively evaluate neuronal activations after inflammatory pain, using the transgenic rats. In addition, we visually identified that the neurons in lamina II may contribute to pain modulation. c-*fos*-eGFP transgenic rats are useful to visualize neuronal activations after inflammatory pain.

P1-021

Monomeric CRP binds to integrins and mediates pro-inflammatory action

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Conflict of interest: None

Introduction: The acute phase reactant C-reactive protein (CRP) is not only a marker but also a potential contributor to inflammatory diseases. CRP exists as the circulating native, pentameric CRP (pCRP) and the monomeric isoform (mCRP), formed as a result of a dissociation process of pCRP. mCRP is highly pro-inflammatory, but pCRP is not. The mechanism of pro-inflammatory action of mCRP is unclear. **Methods and Results:** We studied the role of integrins in pro-inflammatory action of mCRP. We found that mCRP bound to integrins αvβ3 and α4β1. We studied the role of integrins in CRP signaling in monocytic U937 cells. mCRP induced AKT phosphorylation in U937 cells. Notably, mCRP induced robust chemotaxis in U937 cells, and antagonists to integrins αvβ3 and α4β1 and an inhibitor to phosphatidylinositide 3-kinase effectively suppressed mCRP-induced chemotaxis in U937 cells. These results suggest that the integrin and AKT/phosphatidylinositide 3-kinase pathways play a role in pro-inflammatory action of mCRP in U937 cells. **Conclusion:** We propose that integrins act as receptors of mCRP and mediate pro-inflammatory actions of mCRP.

P1-022

Mechanism of the effect for combination therapy with methotrexate and tacrolimus in rheumatoid arthritis

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Conflict of interest: None

【Objective】The combination therapy with methotrexate (MTX) and tacrolimus is effective in rheumatoid arthritis (RA). That mechanism is associated with solute carrier family 19A1 (SLC19A1),which import to the cell, and multidrug resitsance-associated protein 2 (MRP2),which export from the cell. We investigated the production of SLC19A1 and MRP, and the change of inflammatory cytokines in the combination of MTX and tacrolimus. 【Method】We exmined the expression of SLC19A1 and MRP2 using synovial cells line of RA and osteoarthritis (OA), and its influence of combination of MTX and tacrolimus. We also investigated the cytokines (TNF-α, IL-6 and IL-1β) inside and outside of the cell in the combination of MTX and tacrollimus on synovial cells.【Result】The expressions of SLC19A1and MRP2 were inhibited by combination of MTX and tacrolimus on RA synovial cell line, but they were not inhibited on OA synovial cell line. In addition, the production of TNF-α, IL-6 and IL-1βwere also reduced by combination of MTX and tacrolimus on RA synovial cell line.【Conclusion】We suggest that the expression of SLC19A1 and MRP2 and the change of inflammatory cytokines were associated with the mechanism of efficacy by combination therapy.

P1-023

Effects of interleukin-2/anti-interleukin-2 monoclonal antibody immune complex on collagen-induced arthritis

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Conflict of interest: None

Objectives: To clarify complex regulatory network of IL-2 and cellular interactions involved in autoimmune arthritis, we examined the effects of IL-2IC administration during the course of collagen-induces arthritis (CIA) model. Methods: CIA model was performed with the compound in DBA/1 mice. IL-2ICs were prepared by mixing anti-IL-2 antibody with mouse IL-2 for 15 minutes. The mice were injected with either PBS as a control or IL-2IC intraperitoneally for 3 days. Mouse paws were scored for arthritis using a macroscopic scoring system. IL-1β, IL-6 and TNF-α in arthritis were examined by immunohistochemistry. Tregs were analyzed by flow cytometry in peripheral blood cells. Results: To define the effect of IL-2IC of disease induction, we administered IL-2IC from day 0 and from day 21 after first immunization and observed a decrease in both the incidence and severity of arthritis. The expression of IL-1β, IL-6 and TNF-α in arthritis was reduced by IL-2IC. Injection of IL-2IC effectively elicited expansion of Tregs in peripheral blood cells. Conclusions: These observations indicate that IL-2IC might decrease in both the incidence and severity of autoimmune arthritis.

P1-024

Mice deficient in *SPACIA1/SAAL1* ameliorates the progression of collagen-induced arthritis

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Conflict of interest: None

【**Object**】A key characteristic of rheumatoid arthritis (RA) is the proliferative synovitis. *SPACIA1/SAAL1* is a gene associated with the aberrant proliferation of RA synovial fibroblasts. We previously reported that collagen-induced arthritis (CIA) in *SPACIA1/SAAL1* transgenic mice progressed more rapidly and were more severe compared with the WT mice; however, the rheumatoid pathophysiologic role of endogenous *SPACIA1/SAAL1* has not been fully elucidated. In this study, we evaluated the effects of *SPACIA1/SAAL1* deficiency on CIA development. 【**Methods**】We generated *SPACIA1/SAAL1*-deficient (KO) C57BL/6 mice. Mice were obtained by backcrossing them with DBA/1J mice for 8 generations. Susceptibility to CIA was compared between these mice and wild-type (WT) littermates. 【**Results**】*SPACIA1/SAAL1* KO mice were fertile and had no visible anomalies. The incidence and severity of CIA were significantly decreased in the KO mice compared with the WT mice. However, all the KO mice had developed CIA. Attenuation of the disease was slightly, although not significantly, associated with milder bone destruction and decreased production of anti-CII Abs in sera from the KO mice. 【**Conclusion**】Our results indicate that SPACIA1/SAAL1 expression may be involved in the progression of CIA.

P1-025

The analysis of clinical factors of Rheumatoid Arthritis in SKG mice with *Porphyromonas gingivalis* oral administration

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Conflict of interest: None

[Object] Periodontitis is a chronic inflammatory disease caused by infection of the periodontopathogenic bacteria. Recently, it is reported rheumatoid arthritis (RA) patients shows high periodontitis morbidity. We previously reported that *Porphyromonas gingivalis*(Pg) infection showed the association with RA. In this study, clinical parameters impact on the RA with Pg infection were analyzed by patient serum and RA model mice.[Methods] The serum was collected from the patients of Hiroshima University Hospital. Patients were classified by anti-Pg IgG titers, and were evaluated the RA-associated marker. RA was induced by intraperitoneal (i.p.) injection of laminarin (LA) into SKG mice. Pg W83 (10^8 CFU/mouse) was suspended into PBS containing 2% CMC and administrated every 3 days for 6 weeks until analyzation. Pg infection was confirmed by anti-Pg IgG. RA was assessed by Arthritis score (AS), serum levels of MMP-3, ACPA, LRG1.[Result] The patients'serum of elevated anti-Pg IgG showed the increase of ACPA, VAS, and LRG1. The increase of AS and bone resorption of ankle joint were observed in Pg/LA group. The levels of MMP-3, ACPA, and LRG1 were also significantly elevated in Pg/LA group. [Conclusion] These results suggests that Pg infection is involved in the progression of RA.

P1-026

Neutrophils play a critical role in the arthritis of a knock-in mouse gp130F759 facilitated by the systemic infection with *Mycoplasma fermentans*

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Conflict of interest: None

[Objectives] Microorganisms have been suggested to involve in the development and pathophysiology of autoimmune diseases. Previously, we reported that development of arthritis in a knock-in mouse gp130F759 having the gp130Y759F mutant was accelerated by systemic infection with *Mycoplasma fermentans*(Mf) at 3 M.O., much earlier than spontaneous arthritis. We analyzed the kinetics of the synovial cell populations at the preclinical phase of Mf-induced arthritis. Furthermore, we examined the effects of neutrophil-depletion on the arthritis. [Methods] The scores for arthritis of gp130F759 based on the restriction of joint flexibility were determined from day 3 to 28 after intravenous infection with Mf. The cellular populations and numbers in the synovium were analyzed with flowcytometer. 0.25 mg of anti-Gr-1 antibody (Ab) was injected intraperitonealy 10 days after infection. [Results] Kinetics study revealed that the numbers of the synovial cells predominated by neutrophils increased at day 10. At 1 month after infection, no mice in the group treated with anti-Gr-1 Ab showed development of arthritis and increase of the synovial cells. [Conclusion] Neutrophils increased in the synovium after systemic infection of Mf play a pivotal role in the development of arthritis in gp130F759.

P1-027

Exploration of the mechanisms of production with citrullinated proteins and its autoantibodies in autoimmune arthritis

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Conflict of interest: None

[Objectives] To explore the pathogenic relevance of citrullinated proteins (Cit-P) and its autoantibodies participate in peptide GPI-induced arthritis (pGIA). [Methods] 1) The titers of anti-pGPI antibodies and ACPA in sera were analysed by ELISA. 2) Cit-P expression in joints and skins were examined by immunohistochemistry. 3) C1-amidine (PAD inhibitor) were injected intraperitoneally to pGIA, and clinical score, the titer of ACPA and Cit-P expression were assessed. [Results] 1) The titers of anti-pGPI antibodies and ACPA in sera from pGIA were elevated after day14, and were significantly higher than those from CFA immunized (control) mice. 2) In immunohistochemistry, Cit-P was detected in joints on day14 and in skins on day7 with pGIA, whereas not detected with control mice. 3) C1-amidine treatment significantly decreased clinical score. But the titer of ACPA from C1-amidine treatment mice was not reduced significantly against those from control mice. Cit-P expression in joints and skins from treatment mice were clearly reduced. [Conclusions] Cit-P expression and the titer of ACPA were increased in pGIA, and the inhibition of PAD suppressed arthritis and Cit-P expression. These results suggest that PAD activity is involved with the pathogenesis and maintenance of autoimmune arthritis.

P1-028

Functional analysis of TIARP in osteoclast differentiation

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Conflict of interest: None

[Background]TIARP is a protein induced by TNF-α and IL-6.Its deficient mice known to develop spontaneously polyarthritis. However the role of TIARP in osteoclast (OC) differentiation is mostly unknown. [Objective]To elucidate the role of TIARP in OC differentiation. [Methods]1) Femur from $TIARP^{-/-}$ and WT mice were analyzed by micro CT.2) Bone marrow cells from WT mice were induced to OC. TIARP mRNA was assessed by RT-PCR.3) Bone marrow cells from $TIARP^{-/-}$ and WT mice were induced to OC and CTSK mRNA was assessed by RT-PCT.4) Bone marrow cells from $TIARP^{-/-}$ and WT mice were induced to OC. OC and its bone resorption capacity were examined by TRAP staining and fluorescent intensity. [Results]1)$TIARP^{-/-}$ mice showed less bone mineral density than WT mice. 2)TIARP mRNA expression was increased after RANKL stimulation. 3)CTSK mRNA expression was higher in $TIARP^{-/-}$ mice than WT. 4)The number of OC was significantly higher from

TIARP$^{-/-}$ mice than from WT mice. [Conclusions]These findings suggest that TIARP suppress bone erosion by inhibiting osteoclastgenesis.

P1-029

Suppressive ability of altered peptide ligand transgenic rice against glucose-6-phosphate isomerase peptide induced arthritis

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Conflict of interest: None

Objective: To reveal the suppressive effect of altered peptide ligand (APL) transgenic rice against glucose-6-phosphate isomerase peptide (pGPI) induced arthritis model mouse. Methods: We designed APL construct containing T cell epitopes (AA325-339) of GPI peptide, in which one amino acid was substituted, with conserved anchor motif for binding to MHC class II molecules, and then generated APL transgenic rice. Before immunization with pGPI, APL transgenic rice (APL-TG) or non-transgenic rice (Non-TG) was orally administered to pGPI-induced arthritis (pGIA) for 7 days. 1) Severity of arthritis, 2) histopathological analysis of ankle joints (day14), 3) cytokines (day14, 28) and 4) titers of serum anti-pGPI IgG antibody (day 28) were compared. Results: 1) Severity of arthritis was significantly suppressed in mice treated with APL-TG at day10, 14 and 16 (p<0.05). 2) Synovitis in ankle joints at day14 was significantly suppressed in those with APL-TG (p<0.05). 3) IL-17 production from draining LN cells after stimulation with pGPI was significantly suppressed in those with APL-TG (p<0.05). 4) Titers of anti-pGPI IgG antibody at day28 was significantly lower in those with APL-TG (p<0.05). Conclusion: Oral prophylactic treatment with APL of pGPI transgenic rice suppressed severity of pGIA.

P1-030

Deficient leptin signaling ameliorates sialoadenitis in MRL/lpr mice

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Conflict of interest: None

[Object]Leptin is secreted by adipocytes, the placenta, and the stomach. It not only controls appetite through leptin receptors in the hypothalamus, but also regulates immunity. In the present study, we investigate the potential role of leptin in sialoadenitis of MRL/lpr mice.[Methods] We produced leptin-deficient MRL/lpr mice. The effects of leptin deficiency on sialoadenitis were investigated in MRL/lpr mice. [Results]Submandibular sialoadenitis was suppressed in leptin-deficient MRL/lpr mice compared with leptin-intact MRL/lpr mice.[Conclusions] Leptin may promote the sialoadenitis in Sjogren's synderome. Blockade of leptin signaling may be of therapeutic benefit in Sjogren's syndrome.

P1-031

Experimental induction of SLE in the interferon alpha transgenic mice of varied genetic background

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Conflict of interest: None

Objective: We have successfully established an IFNα transgenic mice (IFNα Tg) that induces anti-dsDNA autoantibody and glomerular diseases akin to human SLE. In these mice, activated effector T cells were predominant, and $CD3^+CD4^-CD8^-$ double negative T (DNT) cells, considered responsible for glomerular injury, were expanded in the spleen. In the present study, we examined whether genetic background other than IFNα contributes significantly to the disease. **Methods:** Autoantibody and proteinuria were examined in IFNα Tg mice of C57BL6/FVB or C57BL/6 background. $CD3^+CD4^-CD8^-$ DNT cells in spleen and the expression of CD4, CD8, CD44 and CD25 in thymocytes were studied by using flow cytometry. **Results:** Anti-ds DNA antibody and proteinuria were induced under not only C57BL6/FVB but also C57BL/6 backgrounds. In either mice, $CD3^+CD4^-CD8^-$ DNT cells in the spleen and $CD4^-CD8^-$ DN in the thymus were expanded. It was noted that most of DN thymocytes remained at $CD44^+CD25^-$ DN1 stage. **Conclusion:** Regardless of genetic backgrounds, IFNα seems able to induce SLE.

P1-032

Role of allograft inflammatory factor-1 in bleomycin-induced lung fibrosis

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Conflict of interest: None

Allograft inflammatory factor-1 (AIF-1) is a protein expressed by macrophages infiltrating the area around the coronary arteries in a rat ectopic cardiac allograft model. We previously reported that AIF-1 is associated with the pathogenesis of rheumatoid arthritis and skin fibrosis in sclerodermatous graft-versus-host disease mice. Here, we used an animal model of bleomycin-induced lung fibrosis to analyze the expression of AIF-1 and examine its function in lung fibrosis. The results showed that AIF-1 was expressed on lung tissues, specifically fibroblasts, from mice with bleomycin-induced lung fibrosis, and that recombinant AIF-1 increased both the migration and proliferation of lung fibroblasts in vitro. Recombinant AIF-1 also increased the production of IL-6 and TNFα by lung fibroblasts. These results suggest that AIF-1 plays an important role in the mechanism underlying lung fibrosis, and may provide an attractive new therapeutic target.

P1-033

miRNA Expression Profiles in Plasma Samples from Rheumatoid Arthritis Patients with Interstitial Lung Disease

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Conflict of interest: None

Background: Interstitial lung disease (ILD) is frequently associated with rheumatoid arthritis (RA) and influences the prognosis of the disease. Micro RNAs (miRNAs) are small noncoding RNAs with approximate 22 nucleotide length and miRNAs in the circulation could be potential biomarkers for various diseases. In this study, the plasma micro RNA profiles were investigated to explore markers for ILD in RA. *Methods:* ILD was diagnosed from computed tomography findings. Real-time RT-PCR analysis was performed to evaluate 752 miRNA expression profiles in plasma pools from RA patients with or without ILD. Nineteen selected miRNA levels were analyzed in individual plasma samples from 64 RA patients with or without ILD. *Results:* Expression levels of hsa-miR-214-5p (P= 0.0156) and hsa-miR-7-5p (P= 0.0362) were higher in plasma samples from RA patients with ILD than in those without. *Conclusion:* This is the first report of plasma miRNA profiles of ILD in RA. These data suggest that hsa-miR-214-5p and hsa-miR-7-5p in plasmacould be potential biomarkers for ILD in RA.

P1-034

Clinical features in combined pulmonary fibrosis and emphysema (CPFE) with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] We evaluated the clinical features in CPFE with RA. [Methods] The patients who had interstitial pneumonia (IP) by chest HRCT with RA were enrolled in this study. The patients were divided into 2 groups: CPFE with RA-IP (RA-CPFE) and RA-IP alone (RA-IP). We assessed clinical features at the initial visit. [Results] 65 patients diagnosed with RA-CPFE, and 92 diagnosed with RA-IP. In RA-CPFE, mean age was 70.1±8.7 years old (49 male, 16 female), 57 patients had a smoking history. In respiratory function test, %VC was 93.1±21.6%, %FVC was 88.7±17.4%, FEV1.0% was 76.3±10.6%, and %DLco/VA was 53.6±19.1%, and 10 patients diagnosed with lung cancer. On the other hand, in RA-IP, 68.5±8.7 was years old (29 male, 63 female), 29 patients had a smoking history. %VC was 91.3±17.3%, %FVC was 91.3±21.0%, FEV1.0% was 79.6±9.3, and %DLco/VA was 71.4±16.3%, and 2 patients diagnosed with lung cancer. [Conclusion] Patients with RA-CPFE were seen significantly more prevalently in male patients, smokers, showed a reduction in diffusion in respiratory function tests, and diagnosed with lung cancer.

P1-035

Evaluation of 11 RA patients with MTX-LPD

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Conflict of interest: None

MTX associated lymphoproliferative disease occasionally develops in RA patients treated with MTX. Methods: We retrospectively analyzed 11 cases of MTX-LPD and collected clinical information from medical records. Results: We experienced 11cases of MTX-LPD at Omaezaki Municipal Hospital. Mean age was 68.7±5.23 (range62-77),male-to-female ratio was 2:9, RA disease duration was 8.3±12.3 years. Steinbrocker's stage was I:1, II:3, IV:7 and class was I:1, II:4, III:6, respectively. EULAR response by DAS28-ESR at MTX-LPD onset was remission: 5, LDA: 2, MDA: 3, respectively. An administration of MTX /week was 10.0±4.1mg (range 6-16), total MTX dose was 1980.9±2542.9mg (range192-9000), duration of MTX administration was 4.06±4.45 years (range 1-9) Pathological findings were obtained in 11cases of 4 diffuse large B cell lymphoma, 2 peripheral T cell lymphoma, 1 Hodgikin's lymphoma, 1 Maltoma and 3 MTX-LPD. EB virus related protein LMP-1 or RNA (EBER) expression was found in 7 of 8 patients. Chemotherapy was begun in 7 of 11 patients and the remaining 4 patients showed spontaneous regression from MTX withdrawal. All patients achieved complete remission. Conclusions: MTX withdrawal and follow up in RA patients should be considered for MTX-LPD management.

P1-036

A case of rheumatoid arthritis diagnosed from pleural effusion

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Conflict of interest: None

A 46-year-old Japanese man suffered arthralgia of wrist and small joints of both hands. He suffered cough at the same time and had right pleural effusion on chest radiography. Anti CCP antibody and RF were highly positive in blood test, but he did not have obvious synovitis in physical examination. We suspected paraneoplastic syndrome or arthritis induced by infection, but malignant tumor was denied and a wide spectrum antibiotic medication was not effective. As MRI of hand showed active synovitis, rheumatoid arthritis (RA) and tuberculous pleurisy and related arthritis were suspected. In order to obtain a definitive diagnosis, we performed medical thoracoscopy. Small granular parietal pleural surface was found, and pleural biopsy showed lack of a normal mesothelial cell covering and necrotic tissue with palisading histiocytes. Tuberculosis was denied from tissue culture and Ziehl-Neelsen stain. We diagnosed him as RA and rheumatoid pleurisy, and started treatment with prednisolone 30 mg/day. He achieved remission and pleural effusion disappeared. Pleural effusion usually occurs during the course of a previously diagnosed RA and is rarely seen at the same time or before the onset of arthritis. We encountered a rare case of a rheumatoid pleural effusion without obvious synovitis.

P1-037

Vasculitis and MTX-LPD complicated with RA

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Conflict of interest: None

A 65-year-old female was diagnosed as seronegative RA and treated with NSAIDs. Fifteen months before admission, she complained of pain in shoulders and knees, and ACPA became positive. She was diagnosed as RA and initially treated with MTX (6 mg/week) and PSL (5 mg/day), but did not respond to these medications despite the loading MTX to 12mg/week. Nine months before admission, she was treated with IFX, but showed no response. Three months later, the IFX was replaced with ABT, but the patient still had no response. A week before admission, arthralgia increased after hard housework, and she was admitted to our hospital with systemic lymphadenopathy and elevated CRP and RF. After admission, palpable purpura appeared in her legs, and cutaneous vasculitis was found by biopsy. In Right inguinal lymph node biopsy, expanded paracortical area, increased T cells and plasma cells, and EBER positive cells were found. We diagnosed vasculitis and LPD complicated with RA, and replaced MTX and ABT with TCZ and PSL (0.5 mg/kg/day). This treatment induced RA remission, and lymphadenopathy was disappeared. This case was a rare case of RA complicated with vasculitis and LPD. It has been reported that bDMARDs and high disease activity are associated with complication of vasculitis and LPD.

P1-038

A case of rheumatoid arthritis (RA) complicated with FGF23-related hypophosphatemic osteomalacia

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Conflict of interest: None

A 77-yr-old female diagnosed with compression fractures from osteoporosis 2 weeks ago, was referred to our hospital due to intractable flank and low back pain. RA had been treated with PSL and TAC. Laboratory data was as follows: Cre 0.64mg/dl, Ca 8.4mg/dl, P 0.6mg/dl, iPTH 31pg/ml, 1,25 (OH)2D 9.6pg/ml, bone density was 0.180g/cm^2 and MRI revealed compression fractures (Th 6-8). Dipotassium phosphate and alfacalcidol were administered to correct the hypophosphatemia. According to the calculated FEP (46%) and TmP/GFR (0.35mg/dl), hyperphosphaturia was suspected as the cause of hypophosphatemia. On the tenth hospital day, FGF23 (170pg/ml (≧30)) revealed elevated, thus confirming the diagnosis of FGF23-related hypophosphatemic osteomalacia. Tumor-induced osteomalacia was suspected, and PET-CT was performed but tumor was not found. As serum phosphorus levels increased, the generalized pain gradually disappeared. We report a rare case of RA complicated with FGF23-related hypophosphatemic osteomalacia. Atypical generalized pain and hyperphosphaturic hypophosphatemia provided the clues to differentiate it from osteoporosis.

P1-039

A case of rheumatoid arthritis associated with pulmonary infarction by protein C deficiency

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Conflict of interest: None

A 49-year-old woman presented to our hospital with 1-month history of acute onset pain of bilateral knees, hips and side chest. She was hospitalized in community hospital to investigate the cause of the pain and di-

agnosed with rheumatoid arthritis (RA) due to strongly positive anti-CCP antibody and findings of MRI. She was transferred to our hospital to receive treatment of RA. On admission, she presented arthritis of the bilateral wrist, elbow and shoulder joints. She also had pain of the knees and side chest without arthritis. Laboratory examination revealed high level of D-dimer so we suspected of deep vein thrombosis and pulmonary infarction, which were confirmed by ultrasound sonography and chest CT. After edoxaban 30mg was started, the pain of the knee and side chest was immediately improved and emboli didn't recurred. Laboratory examination revealed that enzyme activity and antigen level of protein C (PC) was reduced and deficiency of PC gene was confirmed by PCR afterward. Arthritis was gradually improved by methotrexate and low dose predonisolone. It is little reported that development of RA provoked thrombosis by PC deficiency, although both diseases are not so rare. We report this case with literature review.

P1-040

The evaluation of rheumatoid arthritis were performed from onset to 5 years by Power Doppler sonography

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Conflict of interest: None

Case: Dec 2011, she was 40yrs old female and suffered pain and swelling in right wrists. Mar 2011, she consulted our clinic. Clinical findings: both wrists and fingers and toes were swollen. CRP 1.0mg/dl, RF 195IU/ml, anti CCP antibody 89, MMP-3 80.4ng/ml, radiological findings of both hands and foots were Larsen 1. MTX was prescribed. Feb, 2012, DAS 28 ESR 2.0, CRP 0.1mg/dl, PDS (Power Doppler score) 1+ of R wrist. Infliximab 200mg was added on MTX 8mg week. Sep, 2014, joints space narrowing of right wrist was found but DAS and PDS showed remission and Infliximab therapy was stopped. Feb 2015, DAS showed 4.38 and PDS showed positive in left wrist left MP and right PIP joints. Infliximab BS 200mg was started DAS became remission promptly. Discussion: RA activity was remission under early biologics treatment but first involved right wrist was suffered with joint cartilage damage. Recurrent arthritis occurred at other new joints. CRP became negative under early MTX therapy. Recurrent arthritis showed little CRP change. PDS monitored RA therapy have the possibility of changing arthritis impairments to better one.

P1-041

A case of meningitis with rheumatoid arthritis

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Conflict of interest: None

A case is 72-year-old male. At 70-year-old, rheumatoid arthritis and interstitial pneumonia were diagnosed and had received oral medical treatment of prednisolone (PSL). Consciousness was impaired on admission. Disorientation and high order brain dysfunction was in the course of acute few days. Active synovitis was also observed in examination. In magnetic resonance imaging, non-uniform, bilateral dural and leptomeningeal lesion showed high signal range in diffusion-weighted image and FLAIR image. Cerebrospinal fluid examination showed a rise of cell count. He was diagnosed with rheumatoid meningitis and treated with PSL 50mg/day. Consciousness was improved rapidly. Possibility of hypertrophic pachymeningitis by ANCA-associated vasculitis should be considered since PR3-ANCA was positive. We report a case of rheumatoid meningitis.

P1-042

A case of rheumatouid arthritis developed myocardial infarction with clean coronaries

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Conflict of interest: None

73 years-old female patients with rheumatoid arthritis (RA) were transferred and hospitalized to our hospital with a suspicious of septic arthritis. She was diagnosed as RA in 1970. Despite of the treatment with several conventional synthetic DMARDs, RA was uncontrollable for a long period. Moreover, there was a contraindication to biological DMRADs because of the iteration of infectious episodes. After the hospitalization, antibiotics were administrated immediately. On day 4, she complicated nausea, dyspnea and showed low blood pressure. She was diagnosed as acute myocardial infarction because of elevated Creatininekinase with elevated ST in ECG. Although she was treated with vasopressors and oxygen immediately, she passed away after three hours while preparing for coronary angiography (CAG). An autopsy revealed the myocardial infarction, however, the coronary artery showed no stenosis and thrombosis. However, it revealed AA amyloid depositions in intramyocardial arteriole, micro muscular type artery. Thus, she was diagnosed as "Myocardial infarction with clean coronaries" due to amyloidosis. It is known AA amyloidosis subsequent to RA is resistant to treatments. Actually, this case was considered to be unrescuable even by CAG.

P1-043

Sagital Alignment of the Whole Spine in Patients with Rheumatoid Arthritis

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Conflict of interest: None

【Purpose】 So far,little has been reported on the characteristics of standing posture and its significance in patients with Rheumatoid Arthritis (RA) compared with joints and cervical spine involvement. The aim of the present study is to clarify features of the sagittal alignment of the whole spine in RA patients and its relation with QOL and medication. 【Methods】 Consecutive some 310 RA patients from April to December 2012 were evaluated with a lateral radiograph of the whole spine in standing position, 190 of whom completed ODI questionnaire as well. Pelvic Incidence (PI), Lumbar Lordosis (LL), Pelvic Tilt (PT), Sagittal Vertical Axis (SVA),Thoracic Kyphosis (TK) were measured and the correlation among these parameters, ODI, age, disease duration,DAS-28ESR,the sorts of medication were statistically analyzed. 【Results】 ODI correlated with PI-LL ($p=0.016$), PT ($p=0.0017$), SVA ($p=0.0003$),age ($p<0.001$), disease duration ($p=0.0067$),DAS-28ESR ($p<0.001$).PI-LL was related to PT linearly while alignment parameters did not correlate with the sorts of medication. 【Discussion】 The present study indicates that the sagittal spinal alignment is important in patients with RA in terms of QOL and that the compensatory mechanism of maintaining posture in RA patients is like that in healthy people.

P1-044

A case of rheumatoid arthritis with rheumatoid vasculitis after discontinuance of MTX in MTX-LPD

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Conflict of interest: None

A 49 year-old women with rheumatoid arthritis (RA) had received MTX for 4years. She had fever and dull feeling in the throat. Right tonsillar ulcer was found and MTX-LPD was suspected by an otolaryngologist after tonsillar ulcer biopsy, she was consulted to our department. We instruct discountinuance of MTX (12mg/wk). After two weeks, she had high fever, skin rash and rheumatoid nodules. She was diagnosed as rheumatoid vasculitis (RV).High dose PSL therapy was intiated after skin biopsy. After good response to the treatment, PSL was gradually tapered. The pathological diagnosis of the tonsillar specimen was diffuse large B-cell lymphoma (DLBCL). Positive EBV DNA was found in blood. The DLBCL lesion was diminished by MTX discontinuance and high dose PSL therapy. RV typically occurs in RA patients with longstanding and high disease activity. As MTX-LPD was usually accompanied by immu-

nosuppressive state, it is very interesting that the patient had high RF and high disease activity. [Conclusion] When immunosuppression related LPD was suspected, the drug must be discontinued. In that case, close monitoring should be done, if the patient has high RF and high disease activity.

P1-045

Active Rheumatoid Arthritis Accelerates Progression of Atherosclerosis Purpose

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Conflict of interest: None

To determine whether elevations of brachial-ankle pulse wave velocity (baPWV) levels, which is one of brief examination to assess atherosclerosis are accelerated in patients with rheumatoid arthritis. Patients and Method We measured elevation of baPWV levels for 2 years of 101 RA patients and compared with those of 134 local residents visited for health examinations as non-RA controls. In patients with RA, we investigated correlations between elevation of baPWV levels for 2 years and several disease activity indexes of RA. Results The elevation of baPWV level for 2 years was higher in RA patients compared with controls (3.27±15.91 % vs. -4.90±9.16 %, P=0.000). After adjustment of age, sex, and other risk factors of atherosclerosis, RA contributed the elevation of baPWV (P=0.000). After adjustment of age, sex, and other risk factors of atherosclerosis, active RA contributed the elevation of baPWV level for 2 years (P=0.032). Conclusion Active rheumatoid arthritis accelerates progression of atherosclerosis measured by baPWV.

P1-046

A case report of rheumatoid arthritis complicated with cryptogenic organizing pneumonia, having the high level of anti-citrullinated protein antibodies

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Conflict of interest: None

A 71-years-old woman was treated for rheumatoid arthritis (RA), using golimumab and methotrexate one years ago. The control of rheumatoid arthritis was good. Cough and sputum were appeared from February, 2015. Chest CT scan showed a permeation shadow mainly on a left upper lung field. Temporarily, the shadow was improved by the antibiotics in March. However, the shadow was recognized again and the disease activity of RA was worse. She was admitted to our hospital to treat. Blood tests showed CRP 6.71 mg/dl and anti-citrullinated protein antibodies (ACPA) 2098 U/ml. The last year of ACPA was 198 U/ml. Disease activity of RA was high, i.e. DAS28 5.7. We performed transbronchial lung biopsy. The pathology showed cryptogenic organizing pneumonia (COP). Her initial prednisolone (PSL) was pressured (10 mg/day) for high disease activity. After 2 weeks, her arthritis and infiltration of lung were almost improvement. When the high level of ACPA was increased in RA patients, we had better consider that COP may be complicated with RA. We speculate the link between high ACPA level and COP from our case. Generally, the treatment of COP is 0.5-1.0 mg/kg/day. We used low-dose PSL, since not only tight control of RA was best treatment but also for complicated lung disease.

P1-047

The profitable effect of DMARDs and biological products to IMT(intima-media thickness) of carotid artery in RA Remedy in preventing artery sclerosis

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Conflict of interest: None

RA is identified as the disease destructs arthral bone after proliferation of synovial membrane tissues. RA can be accompanied with other lesins outside of the joints. We can get acknowleding profitable effect of IMT in RA remedy in employment of conventional DMARDs and biological products. The subject is over 40 years old cases with RA. The mean IMT of those were 0.75mm (40s years old),0.77mm (50s years old),0.78mm (60s years old),1.0mm (70s years old),1.5mm (80s years old). The IMT remedy effect (one year period)at the treatment to RA was analized. First group was proved to have been remedied by conventional DMARDs, biological products and anti-hyperlipidemia medicine. Second group was remedied by DMARDs and biological products. Third group was proved to have been remedied by only conventional DMARDs. The first group showed 20% downing of IMT at the medial titer and 46 effective cases among 50RA cases (92%) were showed. The second group showed 14% downing of IMT at the medial titer, and 19effective cases among 23cases (82%) were showed. The third group showed 10.6% downing of IMT at the medial titer and 6effective cases. In thinking of the association of cytokines partipation in artery inflammation following artery sclerosis, these could be momentum concern.

P1-048

A case of unusual rheumatoid meningitis

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Conflict of interest: None

66-year-old woman with rheumatoid arthritis (RA) has been treated using methotrexate (since March 2014) and infliximab (since May 2014) for rheumatoid arthritis (RA). The RA treatment was successfully achieved and her neurologic history was unremarkable. She was admitted to our hospital in March 2015, because exhibiting of tonic convulsions and unconsciousness in March 2015. Brain magnetic resonance imaging (MRI) showed ticking of meninges of left frontal, temporal, and central lobe. IgG index, levels of TNF arufa alpha (1.1mg/dl) and IL6 (38.7mg/dl) was increased in her spinal fluid. The biopsy of meningesx showed vessel wall ticking of with lymphocytes and plasma cell infiltration and vessel wall ticking. The electroencephalogram (EEG) was displayed presence of slow wave. The serological markers for infection were negative. and She had diagnosed rheumatic meningitis. Methylprednisolone pulse and prednisolone (1mg/kg) was given for her and Her her symptom and laboratory data became improvementwas ameliorated. Rheumatic meningitis is a rare complication of RA. It is not clear of the Etiology of Rheumatic meningitis is unknown and treatment strategy has not been established treatment. Accumulation of cases is necessary to elucidate the etiology and establish treatment strategy.

P1-049

The efficacy of five biological agents in patients with elderly rheumatoid arthritis

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Conflict of interest: Yes

[Object] We assessed the efficacy of 5 biological agents (BIO): Infliximab (IFX), etanercept (ETN), adalimumab (ADA), tocilizumab (TCZ) and abatacept (ABT), in patients with elderly rheumatoid arthritis (ERA) aged 65 or over. [Methods] One hundred and sixty five ERA of 396 RA patients were administered BIO (IFX:18, ETN:74, ADA:19, TCZ:30, ABT:24 cases). Over the 6-months treatment period using LOCF method,

we evaluated responses to each BIO based on CDAI. [Results] There is the difference in proportion of ERA (P<0.001); IFX: 19%(18/94), ETN: 51%(74/145), ADA: 27%(19/70), TCZ: 56%(30/54), ABT: 73%(24/33). The mean level of CDAI of IFX is higher than other BIO. The mean levels of each BIO significantly decreased after administration as followed, IFX: from 25.5 to 11.6, ETN: from 21.2 to 8.0, ADA: from 18.6 to 5.5, TCZ: from 20.1 to 8.8, ABT: from 17.0 to 9.3, P<0.01, respectively. There were no significant changes of CDAI levels between BIO groups (ΔSDAI (0-6M) of IFX, ETN, ADA, TCZ and ABT is 13.6, 13.2, 13.1, 11.3 and 7.7, respectively). Remission/low disease activity rates in ERA were achieved in 11%/39%(IFX), 19%/76%(ETN), 22%/100%(ADA), 17%/64%(TCZ) and 19%/69%(ABT), respectively. [Conclusion] These data indicate that each BIO has the same effect for older RA patients.

P1-050

Biologics treatment to the latter period senior RA patients

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Conflict of interest: Yes

[The purpose] Biologics treatment for RA is carried out to highly eged patients, too. The report of biologics treatment to the latter period senior RA patients is little, and the effectivity and the safety are not clear. [Subjects and methods] The number of latter period old patients (over 74 years old) taking biologics treatment and variety of biologics were investigated in 7 rheumatism medical centers of mainly Chiba prefecture. At Chiba east hospital, background, therapeutic effect and adverse event of 24 patients were evaluated. [Result] In whole 1894 patients who take biologics, 172 patients were the latter period senior citizen (over 74 years old). 98 people received biologics after 75 years old, newly. There was a lot of abatacept, etanercept,goliumab. At chiba east hosipital, There were 16 patients that take biologics newly after 75 years old in 24 patients taking biologics. Rate of DAS28-CRP remission,HAQ remission and structural remission (Δ TSS<0.5 in year) were 85%,89% and63% respectively. SAE were mainly change with aging. [Summary] Patients taking biologics and particularly newly administrated patient increased. Effect of biologic treatment for RA was very good. Attention for adverse event with aging and infection should be necessary.

P1-051

Efficacy and safety of abatacept as monotherapy with the advanced age rheumatoid arthritis (RA) patients

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Conflict of interest: None

Objectives. To investigate the abatacept monotherapy for biologics naive advanced aged RA patients (ARA), and the effectiveness and safety of this treatment. We evaluate 32 (70 years older) ARA who performed abatacept monotherapy. The average duration of illness was 77.6 (1-521) months, the average age was 77.3 (70-91) years old. *Methods*. We evaluated the disease activity after this therapy by SDAI response at every 4-week, and we examined relations between the SDAI response and the level of RF, the ACPA. *Results*. There were 5 cases that dropped out because of invalidity and exanthema. But 27 cases were able to continue more than six months. As for remission cases of each observation point, the remission + low disease activity cases, were 5, 20 cases (19%, 74%) at 4-week, 9, 22 cases (33%, 81%) at 8-week, 12, 25 cases (44%, 93%) at 12-week, 14, 26 cases (56%, 93%) at 18-week, 16, 26 cases (59%, 96%) at 24-week. Both RF high-level group (RF>60U/ml) and ACPA high-level group (ACPA >13.5U/ml) had decreased SDAI response significantly in comparison with low level group. *Conclusions*. The abatacept monotherapy for ARA was effective and confirmed that it was safe treatment. The cases that was high in RF and ACPA, which were a poor-prognosis factors, accepted good SDAI response.

P1-052

The outcome from the elderly RA patients who were administered abatacept

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Conflict of interest: None

[Objective] Recently, biological DMARDs has been introduced to elderly rheumatoid arthritis (RA) patients with higher disease activity, and equivalent results in the continuation rate / infection incidence have been reported as compared to younger. In this study, we examined the outcome from the elderly RA patients who were administered abatacept (ABT). [Method] 22 patients of elderly RA were enrolled to examine for more than 24 weeks. [Result]Patients profiles; the average age was 76.5 ± 6.78 including 7 cases more than 80 years of age. SDAI prior administration 22.87 ± 9.61, 5 MTX combination cases, 13 bio naïve cases. Complications; 3 interstitial pneumonia, 1 primary biliary cirrhosis, 1 pulmonary alveolar proteinosis, and 1 after prosthetic joint infection. SDAI significantly improved at 24week (P=0.0004), even in 17 cases who did not receive MTX (P=0.012). Prosthetic joint infection occurred in 1 case treated with ABT and MTX, requiring hospitalization. 2 cases switched to other agents due to invalid, while 2 cases were withdrawal ABT after remission and 2 cases were extended the dosing interval. [Conclusion] ABT was effective for elderly RA patients. Prolongation of dosing interval or withdrawal of ABT can be introduced when lower disease activity was targeted.

P1-053

Efficacy and safety of biologics for elder rheumatoid arthritis

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Conflict of interest: None

Obejectives: To examine the efficacy and safety of biologics with rheumatoid arthritis patients whom the agents were prescribed.Methods: 44 patients with elderly-onset or late-onset and 17 patients with younger-onset rheumatoid arthritis have been treated with biologics (TNF-alpha inhibitors and non-TNF-alpha inhibitors). The efficacy was determined by the induction rate of remission or low-disease activity in treated patients using SDAI.Results: Basal SDAI:EORA 23±10 (TNFi 20±9, ABT 23±7, TCZ 29±12), YORA 23±11 (TNFi 21±11, ABT 18±4, TCZ 35±9. SDAI at Month 6:EORA 5±3, YORA 10±8, Efficacy at Month 6:EORA 43/64 (67%) (TNFi 60%, ABT 83%, TCZ62%), YORA 12/29 (41%) (TNFi 23%, ABT 63%, TCZ 40%). SDAI at Month 12: EORA 4±3, YORA 10±10. Efficacy at Month 12:EORA 21/64 (36%) (TNFi 20%, ABT 56%, TCZ 29%), YORA 7/29 (24%) (TNFi 23%, ABT 36%, TCZ 0%). Adverse Events:EORA 9/64 (14%) (TNFi 8%, ABT 28%, TCZ 10%), YORA 5/29 (17%) (TNFi 23%, ABT 18%, TCZ 0%). Conclusions:Biologics are effectively available for elder RA patients, and we experienced rare adverse events by careful application. Efficacy rate is generally higher in EORA than YORA cases.

P1-054

Evaluation of RA patients treated with Abatacept

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Conflict of interest: None

[Objectives]To evaluate the effect of Abatacept for patients with rheumatoid arthritis (RA), who were not be controlled with anti-TNF biologics or Tocilizumab, or who could not be treated with MTX, or who were elderly person. [Methods]Twenty-four RA patients (female 24, male 2) were evaluated. Their age was 60±11 (meanSD) and disease duration was 15±11. Ten cases were not be controlled with anti-TNF biologics or Tocilizumab. Before the treatment with Abatacept, DAS28 ESR score was 5.4±1.6, and DAS28CRP score was 4.5±1.3. Survival curve was evaluated with Kaplan-Meier method. Efficacy and safety outcomes were checked at every visit.[Results]Survival rate was 82% at 6 months, 75% at 1 year, 75% at 2 year, and 60% at 3 year. The reasons of discontinuations were as follows: lack of efficacy was 5 cases, the worse of interstitial pneumonia was 1 case, spinal cord injury due to fall down was 1 case, who could resume after 2 years interval because her spinal cord injury recovered. About disease activity, DAS28CRP with LOCF was 3.6±1.8 at 3 months. MTX could be stopped in patients who had the effects of Abatacept.[Conclusion] We have verified the effect of Abatacept in cases with RA.

P1-055

Study of treatment golimumab without MTX in elderly patients with rheumatoid arthritis.

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Conflict of interest: None

MTX is positioned as an anchor dragging in the treatment of rheumatoid arthritis. However, as a side effect of MTX, bone marrow failure, interstitial pneumonia, and infectious diseases and the like. with the increase in the number of elderly patients with rheumatoid arthritis, there are patients who can not be administered in high capacity MTX. In addition, for patients who have continued MTX long period of time, a decrease in medication compliance associated with the elderly, there remains anxiety about the safety of long-term treatment. Golimumab the efficacy and safety superior in patients without MTX in GO-MONO tests are shown. In our hospital, for patients 8 cases of rheumatoid arthritis which is performing the treatment in GLM without MTX, over 65 years of age, were studied for continuation rates and efficacy. Cases of disease activity at the start: High Disease Activity 4, Moderate Disease Activity 3, Low Disease Activity 1. Result Good response 2, Moderate response 3, No response 3. We were able to continue in the five cases in the final observation during eight cases. GLM treatment without MTX for the elderly in our hospital has been able to safely treated.

P1-056

The efficacy of Half Biologic therapies for elderly or long-term morbidity RA patients

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Conflict of interest: None

«Objectives» The use of not enough amount of biological products affects the immunogenicity and encourages the antibodies of that. However, there are several Biological products for RA which have less immunogenic. This study is The efficacy of half use of Biologic therapies for elderly patients without increasing the amount of Methotrexate (MTX) or long-term morbidity RA patients. «Methods» Seventeen patients (over 80 years or suffering from more than 20 years) has been treated by using half biological products (ETN:13 ABA:4) for more than 24 weeks (Man 4 Female 13). We evaluate the effect of Half Biologic therapies. «Results» 17 of 15 patients were keeping Low disease activity at 12week. 2 patients discontinue biologic therapies in all of the period. But the other patients were significantly improved DAS28-ESR in comparison with the previous administration and had been Low disease activity at the last observation. «Conclusion» The use of half biological products are likely to be useful for elapsed RA patients more than 20 years from the onset with in recurrent or still have not been able to maintain a low disease activity, or 80 years or older without being able to receive aggressive arthritis treatment.

P1-057

Efficacy of Certolizumab pegol therapy for Elderly Rheumatoid Arthritis Patients

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Conflict of interest: None

[Object] To evaluate the efficacy and the safety of certolizumab pegol (CZP) therapy in elderly patients (over70 years old) with rheumatoid arthritis (RA). [Method] 27 patients comprised 9 men and 18 women. Patients who discontinued CZP therapy were excluded. Mean age was 79.7 years old. 13 patients were bio-switch patients. 19 patients were treated without MTX. RA Disease activity (SDAI) and renal function (eGFR) were analyzed during 12months. [Result] Elderly RA patients showed SDAI was 20.9 and changed 8.1 at 6 months and 9.5 at 12months after CZP administration. 19 patients were treated without MTX that showed similar degree of improvement in SDAI from 20.5 to 8.9 (without MTX) and.22.3 to 11.6 (with MTX). 13 patients were bio-switch cases that showed improvement in SDAI from 20.6 to 11.7 (bio-switch) and 21.2 to 6.8 (naive). The number of elderly patients with CKD were 23 patients. eGFR was not significant changed from 57.8 to 54.6 at 6 months and 53.7 at 12months. Sustainable adverse events occurred in 3patients (infection). Another 3patients discontinued CZP therapy because of loss of efficacy and adverse events. [Conclusion] CZP therapy was efficacious in elderly patients.

P1-058

Biologic DMARD monotherapy for the treatment of elderly onset rheumatoid arthritis.

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Conflict of interest: None

[Purpose] Elderly onset rheumatoid arthritis (EORA) tends to develop physical disability rapidly and to disturb patients' QOL because of age- and treatment-related complications. Biologic DMARDs have narrower spectrum of adverse effects. Our hypothesis is that biologic monotherapy is effective and safe for EORA. [Methods] From January 2015, RA patients with the onset of 65 years or older were consecutively treated with biologic DMARD alone and carefully followed by our clinical team consisted with RA care nurses, special pharmacists and a rheumatologist. [Results] Eight patients (F 3, M 5) with mean age of 79 were enrolled. Four cases had ACPA positivity. All but one had some age-related complications. Mean period of 5 weeks after the diagnosis, they were treated with either subcutaneous abatacept in 6 or etanercept in 2. Three months after the treatment, they showed an improvement of SJC from 11 to 2.5, HAQ score from 0.19 to 0.16, RAPID3 score from 9.7 to 6.4. Five patients showed ACR50% improvement. None continued steroid or NSAID. Adverse events observed up to now were 3 cases of mild upper respiratory infection. [Conclusion] Biologic monotherapy seems effective and safe for the treatment of EORA. Long-term outcome will be carefully monitored.

P1-059

Efficacy of Tocilizumab monotherapy with elderly RA patient treated by other biologics

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Conflict of interest: None

Objective. To assess the efficacy of Tocilizumab monotherapy in elderly rheumatoid arthritis (RA) patients who had inadequate response for other biologics. Methods. Two RA patients had received Tocilizumab without methotrexate for 24 weeks. DAS28ESR, SDAI and CDAI were evaluated. Results. Case 1 patient, who was female and 71 years old, was previously treated with Infliximab, Etanercept and Abatacept, although adequate response was not obtained. After intravenous Tocilizumab therapy without methotrexate was received, DAS28ESR was decreased from 4.5 to 2.1, SDAI was decreased from 16.6 to 6.1, and CDAI was decreased from 16.0 to 6.0 at 24 weeks. Case 2 patients, who was female and 72 years old, was previously treated with Infliximab and Abatacept, although adequate response was not obtained. After subcutaneous Tocilizumab therapy without methotrexate was received, DAS28ESR was decreased from 3.4 to 2.4, SDAI was decreased from 4.4 to 2.0, and CDAI was decreased from 4.0 to 2.0 at 24 weeks.

P1-060

Clinical evaluation of abatacept and golimumab in patients with rheumatoid arthritis in our department

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Conflict of interest: None

[Objectives] To investigate the efficacy and the adherence of abatacept (ABT) or golimumab (GLM) in RA patients.[Patients]ABT/GLM; 26 (21 females, mean 63.1 yo, mean disease duration 9.7 y)/ 25 (22 females, mean 66.1 yo, mean disease duration 11.1 y), MTX; 16 (5.0 mg/w) / 16 patients (5.52 mg/w), prednisolone; 18 (mean 4.73mg/day) /12 patients (1.94mg/day). Bio-naïve: 6/11. [Methods] Efficacy of ABT and GLM was evaluated by DAS28-ESR4, CDAI and SDAI. [Results] 1) Mean DAS28 at the baseline (ABT/GLM): 5.87/5.80, CDAI 25.67/24.43, SDAI 28.46/28.60. The disease activity was significantly decreased in both groups. As time went by, the ratio of LDA + remission increased in both groups, respectively. No significant difference in both groups. 2) The adherence at 52 weeks showed about 80% in both groups and ABT was superior at 104 weeks. 3) HAQ was no difference between the base line and after the treatment in both groups, but that of Stage I+II in ABT group was significantly improved. 4) Both CRP and MMP-3 were significantly reduced in GLM group, but not in ABT group. 5) The reasons for drop-out (ABT/GLM); inadequate response 4/5, adverse events 3/6. [Conclusion] The efficacy of ABT or GLM was similar but the adherence rate of ABT was superior to GLM.

P1-061

Highly Elevated Rheumatoid Factor Is a Risk Factor for Abatacept Treatment Failure in Japanese Patients with Rheumatoid Arthritis

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Conflict of interest: None

【Object】 The aim of this study was to determine risk factors for abatacept (ABT) treatment failure in Japanese rheumatoid arthritis (RA) patients. 【Methods】 RA patients who had been treated with abatacept between October 2010 and May 2015 at our center were included. We excluded the patients with abatacept treatment for less than 24 weeks. The patients were divided into two groups in terms of clinical responsiveness at 24 weeks using disease activity score 28 C-reactive protein (DAS28-CRP). DAS28-CRP more than 2.1 was defined as treatment failure. 【Results】 Mean age (SD) of 32 patients was 64.8 years-old (12.5). 27 (84%) were female. In bivariate analyses, non-responder were more likely to be female (71.4% vs 94.4%, P value=0.14), have more tender joints (TJ) (median 4 vs 6.5, P=value 0.17), and high titer RF (35.7% vs 83.3% P=value 0.01). In multivariate analysis, adjusted odds ratio of age, female gender, number of TJ, highly elevated RF was 1.13 (95% CI 1.00 to 1.36, P value=0.05), 18.63 (95% CI 0.45 to 4042.6, P value=0.13), 1.71 (95% CI 0.97 to 4.09, P value=0.06), 14.49 (95% CI 0.98 to 622.01, P value=0.05), respectively. 【Conclusions】 Highly elevated RF is a significant risk factor for abatacept treatment failure in Japanese RA patients.

P1-062

Influence of 2-year abatacept therapy on disease activity, quality of life, prevention of joint damage and reducing of concomitant drugs in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Long-term outcome of abatacept (ABT) therapy in RA patients is lacking. The aim of this study is to investigate influence of 2-year ABT therapy on disease activity, quality of life, prevention of joint damage and reducing of concomitant drugs in patients with RA. [Methods] 35 cases were used for drug retention rate and 19 cases who continued 2-year TCZ therapy were used for detailed analysis. [Results] Mean age was 67.8yo (27 females and 8 males). Mean RA duration was 18.1 years. Rates of bio-naive was 62.9%.Drug retention rates of ABT were 82.2% at 1 year, 74.4% at 2 years, 64.1% at 3 years and 64.1% at 4 years. Although DAS28-CRP and SDAI had significantly decreased from baseline to 1-year and kept decreased from 1-year to 2-year (DAS28-CRP: 4.44/2.47/2.45, SDAI: 18.9/7.2/6.7), mHAQ had not decreased significantly (0.84/0.57/0.58). Rates (%) of concomitant PSL and MTX at baseline, 1-year and 2-year were 75.0/56.3/37.5 and 68.8/43.8/31.3,respectively. Delta-mTSS had signicantly decreased from baseline (6.6) to 30.8 during 0-1 year and to 10.1 during 1-2 year. [Conclusions] Although concomitant PSL and MTX were decreased time after time, ABT improved and kept disease activity and QOL in old RA patients with long RA duration.

P1-063

Outcomes of switching from intravenous application to subcutaneous application in Abatacept therapy for RA

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Conflict of interest: None

[Object]:Recently, a subcutaneous (SC) application form has joined in Abatacept therapy. We retrospectively investigated the clinical outcome of Abatacept therapy switched from intravenous (IV) to SC application. [Methods]:Abatacept was used for 108 patients with RA in our clinic from December 2010 to May 2015. The well followed up 58 patients were investigated. They were divided into two groups; IV application for 12 months (M) (I-I, n=43) and SC application for 6M switched from 6M IV therapy (I-S, n=15). [Results]:Mean DAS28-ESR and DAS28-CRP were evaluated before, 6 and 12M after therapy. DAS28-ESR of 58 IV treated patients successfully reduced from 4.42 to 3.27, and DAS28-CRP from 3.58 to 2.47 after 6M. DAS28-ESR of I-I group improved from 5.15 to 3.51 and DAS28-CRP reduced from 4.20 to 2.52 after 6M, and further improved DAS28-ESR to 3.49 and DAS28-CRP to 1.86 after 12M.In I-S group, DAS28-ESR improved from 4.58 to 3.01, and DAS28-CRP from 3.86 to 2.37 after 6M. After SC switch for 6M, DAS28-ESR and DAS28-CRP further improved to 2.90 and 2.12, respectively. [Conclusions]:SC group switched from IV improved DAS28-ESR and DAS28 as well as non-switched group. The present results support safe and effective switching of IV Abatacept to more convenient SC therapy.

P1-064

Two cases of rheumatoid arthritis complicated by systemic lupus erythematosus treated with abatacept

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Conflict of interest: None

We report two cases of rheumatoid arthritis (RA) complicated by systemic lupus erythematosus (SLE) treated with abatacept 【case1】A 66-year-old woman was diagnosed with RA when she was 30 years old, was treated with etanercept and prednisolone. When she was 58 years old, thrombocytopenia, positive antinuclear antibody and anti-double-stranded DNA antibody were found and she was diagnosed with SLE. Although PSL was increased 15mg/day and etanercept was discontinued, arthritis gradually exacerbation and abatacept started. 【case2】A 61-year-old woman was diagnosed with SLE and auto immune hepatitis when she was 53 years old, was treated with prednisolone. When she was 59 years old, arthritis appeared and high titer of anticitrullinated protein antibody were found. She was diagnosed with RA and tacrolimus started. Because of not improving, abatacept started. Treatment for RA complicated by SLE is controversial. We report these cases with discussion from literatures.

P1-065

Usefulness of abatacept and tacrolimus combination

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Conflict of interest: None

【the purpose】Abatacept (ABT) and tacrolimus (TAC) are often used for the patients who are difficult for the use of MTX. The combination therapy of ABT and TAC is reported less. 【Method】 22 cases are used combination therapy of ABT and TAC. 12 cases are used TAC after ABT therapy (group1). And 10 cases are used ABT after TAC therapy (group2). Evaluated in DAS28 in each group was also examined for the presence of adverse events. [Result] The average age of group1 is 74.2 years old, mean disease duration 18.4 years, was met at 1.9mg / day TAC average dose. The DAS28 was improved 4 week ~12week. The average age of group2 is 69.4 years old, mean disease duration 18.5 years, TAC average dose was in 2.1mg / day. The DAS28 was improved 4 week ~24week. The adverse events were not caused in both groups. . [Conclusion] The combination therapy of ABT and TAC was usefulness and safety.

P1-066

A case of rheumatoid arthritis(RA) with Nontuberculous mycobacteriosis(NTM) successfully treated by combination of tacrolimus and abatacept

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Conflict of interest: None

We report a case of RA with NTM. A 70year old female had been suffering from RA for 30 years. MTX and ETN was no longer used because of its side effects.She had been under treatment with mizoribin, predonisone and antituberculous chemotherapy. Hoever, she was hospitalized due to sever polyarthlaritis, vomitting and anorexia in May 2014. Chest CT revealed multiple small nodules in right lobe. DAS28CRP was 6.43, suggesting high desease activity. She was treated by 20mgs of predonisone and Tcrolimus (Tac) combined with antituberculous chemotherapy.In addition, abatacept was introduced to withdraw corticosteroid. She had been in good condition until June 25, when she complaints of left coxalgia. Xray showed dislocation of old artificial hip joint. Total hip arthroplasty was performed in July. Abatacept was introduced again 2 weeks after operation. She recovered completely, and became to be able to walk. Combination of Tac and abatacept is a useful treatment in the patient with RA complicated with NTM.

P1-067

Investigation of the trends among patients using ABT from the AORA registry

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Conflict of interest: None

[Objectives]To investigate trends among patients using ABT from the AORA registry.[Methods]Background at the initiation of treatment, treatment continuation rate, and treatment effects were investigated for a total of 55 patients (females, 81.9%; mean age at initiation of treatment, 64 years; mean duration of illness, 167 monthes; mean PSL dose, 5.7 mg; mean CRP level, 1.97 mg/dl; mean MMP-3 level, 261.1 ng/ml) given ABT who were registered before the end of July 2015. [Results]DAS28-CRP was able to be assessed at the initiation of treatment for 53 patients (mean score, 4.20). The cumulative ABT continuation rate was 83.5% and 79.8% after one and two years, respectively. ABT was continued in 48 patients (mean continuation period, 37 months). Among patients continuing ABT, the mean PSL dose had been reduced to 4.5 mg at the time of the final survey, with reductions in CRP and MMP-3 to a mean of 0.66 mg/dl and 167.3 ng/ml, respectively. DAS28-CRP decreased to a mean of 2.64, and was <2.3 in 44.4 % of patients. [Conclusion]We reported trends among patients using ABT from the AORA registry.

P1-068

Investigation of the continuation rate among patients using ETN from the AORA registry

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Conflict of interest: None

[Objectives]To investigate continuation rate among patients using ETN from the AORA registry. [Methods]Background at the initiation of treatment, treatment continuation rate, and treatment effects were investigated for a total of 280 patients (females, 82.5%; mean age at initiation of treatment, 59 years; mean duration of illness, 10.9 years; mean MTX dose, 7.15 mg; mean PSL dose, 5.5 mg; mean CRP level, 2.67 mg/dl; mean MMP-3 level, 233 ng/ml) given ETN who were registered before the end of July 2015. [Results] The cumulative ETN continuation rate was 86.8% and 63.4% after one and five years, respectively. DAS28-CRP was able to be assessed at the initiation of treatment for 218 patients (mean score, 4.55). ETN was discontinued in 97 of 277 patients; the main reasons included insufficient response (n=39), adverse events (n=21). ETN was continued in 180 of 277 patients (mean continuation period, 3.2 years). DAS28-CRP decreased to a mean of 2.70, and was <2.3 in 39%

of patients at the time of the final survey. No significant differences were observed for patient background, DAS28-CRP, MTX dose and PSL dose between cases of continuation and discontinuation. [Conclusion]We reported continuous rate among patients using ETN from the AORA registry.

P1-069

Tocilizumab and Abatacept significantly reduces the serum calcium concentration

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Conflict of interest: None

[Objectives] It has widely known that biologics suppress bone destruction. This time, we examined the effect of anti-cytokine therapy to the bone metabolism in rheumatoid arthritis (RA). [Methods] RA patients were recruited (n=48). Tocilizumab (TCZ) (n=18), Abatacept (ABT) (n=16) and TNF inhibitors (Adalimumab and Golimumab, n=14) had been administered. We examined the serum calcium and phosphorus concentration and DAS28-CRP at 0, 1, 3, 6 and12 months. [Results] In the three groups, DAS28-CRP has significantly improved since one month after the administration. In TCZ group, serum calcium concentration significantly has been reduced for six months. In ABT group, it significantly has been reduced for three months. In TNF inhibitors group, it has been decreased slightly. Serum phosphorus concentration has not been drop to a lower value in the three groups. [Conclusion] It has been known that the biologics suppress bone resorption by the means of inhibiting the T cell and inflammatory cytokines. TCZ directly inhibits IL-6 in the downstream of this mechanism. ABT directly inhibit the differentiation into osteoclasts in another route. As a result, we think that strong bone resorption suppression reduces the serum calcium concentration.

P1-070

Impact of tocilizumab on the corrected QT interval in rheumatoid arthritis patients without cardiac symptoms

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Conflict of interest: None

Objective. Patients (pts) with rheumatoid arthritis (RA) have a 2-fold higher risk of sudden death than the general population, possibly due to systemic inflammation affecting ventricular repolarization. We hypothesized that tocilizumab (TCZ) can normalize the corrected QT interval (QTc) in RA pts by reducing systemic inflammation in RA.Methods. RA pts with active disease and healthy controls were enrolled retrospectively. RA pts received TCZ once monthly for 24 weeks. electrocardiogram, clinical examination, and laboratory tests were performed at baseline, and after 24 weeks of TCZ therapy in the RA pts.Results. There were 80 RA pts and 30 age/sex-matched healthy controls.Disease activity was significantly reduced after 24 weeks. Eight pts had a prolonged QTc (>440 msec). TCZ normalized QTc in 7 pts. Baseline QTc was higher in RA pts than in controls (420.3 ± 35.8 msec vs. 411 ± 31.2 msec, p = 0.04). QTc decreased by 15.9 msec after 24 weeks (p = 0.001). Both the QTc change and baseline QTc were significantly correlated with anti-cyclic citrullinated peptide antibody (p = 0.001, p = 0.003), but not associated with other laboratory tests.Conclusion. TCZ can normalize QTc in RA patients. Our data provide further evidence of a close link between ACPA and QTc in RA.

P1-071

Effects of tocilizumab Administration in Bio-Naive and Bio-Switch Rheumatoid Arthritis Patients

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Conflict of interest: None

Aims: To investigate the clinical outcome of TCZ on the bio-naïve and bio-switch RA patients, and to clarify the appropriate indications for TCZ treatment. Methods: The retention rate, efficacy and safety of TCZ in 41 RA patients were analyzed. 15 of the patients were bio-naïve (Group N) (mean age 64.7 years) and 26 were bio-switched from othder biologics (Group S) (mean age 63.3 years). Every patiients were followed up at least 52 weeks after the start of TCZ. Results:In the group N, 86.7%, 80.0% of patients continued TCZ in 24, 52 weeks, and remission was achieved 7.1%, 33.3% in CDAI criteria of patients in 24, 52 weeks. In the group S, 73.1%, 69.2% of patients continued TCZ for 24, 52 weeks, and remission was achieved 5.3%, 11.1% of patients. The total complication rates were 60.0% in group N, 57.6% in group S. There were 8 cases (53.3%) of prolongation of the dosing interval in group N, on the other hand, 4 cases (15.3%) in group S (P=0.048). Although there were 3 cases of interrupted TCZ because those effect were not enough in group S, all cases were switched from ETN. Conclusion: TCZ for bio-switched RA patients were almost same as for bio-naive. It was suggested that TCZ treatment on early RA patients lead to prolongation of administration interval.

P1-072

Despite of early interruption of treatment with tocilizumab after remission, a patient maintains the remission:a case report

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Conflict of interest: None

A 61-year-old man was conscious of joint pains and morning stiffness from September 2014, and was admitted to orthopedics in October. Because his bloody seram level of rheumatoid factor and antibodies to cyclic citrullinated peptide were so high, he was suspected of RA and consulted to our hospital in month. His DAS28-ESR score and serum levels of C-reactive protein (CRP) and matrix metalloproteinase 3 were high too, he was treated with Methotrexate (MTX) 6mg/week and increased to 10mg/week soon. At first MTX was effective, but it became gradually poor control and the addition of prednisolone 10mg/day was no effective. In April 2015, it was too high for his RA activity that intravenous tocilizumab (TCZ) infusion was started at 560mg and secondry dosage was done in may. TCZ was effective immediately and he became the remmisson of all symptoms and normalization of CRP. However he didn't want to continue the tretment of TCZ any more, since then it was continued treatment without using TCZ. In spite of the Interruption of TCZ, his RA activity has been maintained remission and normalization of CRP later without biologics. To RA patients become remission by TCZ, the possibility that remission is continued even after the interruption of biologics at an early stage has been suggested.

P1-073

Effect of subcutaneous versus intravenous tocilizumab as a first-line biologic agent in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We evaluated effect of subcutaneous versus intravenous tocilizumab as a first-line biologic agent in patients with rheumatoid arthritis. [Method] Twenty-four biologic-naive RA patients treated with tocilizumab (TCZ) were enrolled in this study. TCZ were administered intravenously in sixteen patients (IV group) and subcutaneously (SC group)

in eight patients. Disease Activity Score 28 CRP (DAS28-CRP) and does of methotrexate were assessed at baseline and 24 weeks follow-up. [Results] DAS28-CRP was significantly decreased from 4.2 to 2.1 ($P < 0.05$) in IV group and significantly decreased from 3.9 to 1.9 ($P < 0.05$) in SC group. However, there was no significant difference in DAS28-CRP between two treatment groups. Dose of methotrexate was reduced from 8mg to 5.3mg ($P < 0.05$) in IV group and 9.8mg to 6.3mg ($P < 0.05$) in SC group. [Conclusion] This study suggested that subcutaneous TCZ treatment is as effective as intravenous TCZ treatment in the first-line biologic agent for RA.

P1-074

Analysis on efficacy of Tofacinib (TOF) based on usage of MTX and number of biologics usage ~ Sweet Cohort ~

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Conflict of interest: None

Objectives: According to TOF guideline ruled by PMS, TOF should not be administered to patients who cannot tolerate MTX. However, at clinical practice, there are cases of patients who cannot control disease activity with other biologics or MTX. Here, we report efficacy analysis of TOF at clinical practice. Method: Among 34 patients treated with TOF between 2014/1 and 2015/7, 26 patients whose treatment duration lasted at least 24 weeks was analyzed on DAS28-ESR and continuation rate and compared by MTX usage and number of biologics use (low 1~2 vs high 3~7). Result: Overall continuation rate is 88.5% and 100% with MTX and 85.7% without MTX. There was no significant difference in DAS28 regardless of MTX usage. Continuation rate for low bio group is 100% and 76.9% for high bio group with some trend ($P = 0.07$). Low bio group showed a significant difference on DAS28 at week 12 and 24 as compared to high bio group. Discussion: Due to better continuation rate, TOF seems better to be combined with MTX even if MTX dose is lower than 8mg. Low bio group showed improved efficacy as compared to high bio group, this might indicate treatment strategy of TOF as a third line biologics

P1-075

Efficacy and safety of tofacitinib treatment in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To evaluate the efficacy and safety of tofacitinib (TOF) treatment in RA.Method; 25 patients with RA who were treated with TOF were enrolled. Clinical disease activity as DAS 28-ESR, DAS28-CRP, SDAI and CDAI were assessed during of TOF treatment. Result: 22 patients (88%) had been treated with biologics prior to TOF. 12 patients (48%) received concomitant MTX with mean dose of 8.3mg/week. The mean DAS28-ESR score decreased from 5.57 to 3.99 at 24 weeks. 21 patients had been observed over 1 year and efficacy of TOF continued in these patients for 1 year. In the concomitant MTX (+) and (-), DAS28-ESR score decreased from 5.77 to 3.65, from 5.38 to 4.31, respectively. 3 patients discontinued TOF during 6 months. All reason of discontinuation is lack of efficacy. Patients with a high titer of anti-CCP antibody (>100U/ml) showed good response as compared with those in low titer group. Conclusion: Even in the previous biologics treatment, without concomitant MTX, TOF treatment was effective in RA. Long term observation and analysis of baseline characteristics in larger study are needed to find RA patients who are “suitable” for TOF.

P1-076

Consideration of the optimum amount of Golimumab seen from a patient background

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Conflict of interest: None

【Purpose】We retrospective examined investigation Golimumab 72 cases we were able to follow-up over 52 weeks this time,and the proper use of 50 mg and 100 mg in the real clinical. 【Method】We maked 72 examples the subject. The gender was 10 examples of man and 62 examples of lady, the average age was 59 years old, and an average disease duration was 13.6 years. An average of DAS28-CRP before prescription was 4.0. MTX in use rate was 83.3%. Examination item investigated DAS28-CRP,persistency rate and safety of each group. 【Result】1)It is seemed that Golimumab is basically combined with MTX from the effectiveness and persistence rate of Golimumab.2) The weight participated in the optimum amount of Golimumab closely. 3) It was Bio-Naive case light in the weight that the effect can be expected in 50 mg of Golimumab relatively, but increase to 100 mg seemed desirable promptly in the case for which the effect is insufficient during a follow-up. 4) It was seemed that Bio-Switch case and Bio-Naive case heavy in the weight is required 100 mg of Golimumab. 【Conclusion】It is relatively early determined whether Golimumab is valid, and it is seemed that Golimumab is biologic DMARDs expected long term effect if the effect is an expected.

P1-077

Analysis of patients with rheumatoid arthritis (RA) who were treated with golimumab (GLM) more than 52 weeks

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Conflict of interest: Yes

Purpose: To clarify the long term use of GLM in RA. **Methods**: GLM was used in 96 patients (M12, F82). Among them, we analyzed 51 patients (M5, F 48) who were treated more than 52 weeks. **Results**:21 patients (21.9%) stopped GLM before 52 weeks. Mean age was 65.2 YO (38-82), 17 patients were in their sixties, 19 were in seventies and 4 were in eighties. There were 24 patients in Bio-naïve group (50mg 91.7, 100mg 8.3%), MTX7.2mg/W (0-12, 3 without MTX), and DAS28 4.40 (1.85-4.61). There were 27 patients in Bio-switch group (50mg 55.6, 100mg 44.4%), MTX5.2mg/W (0-14, 5 without MTX), DAS28 4.42 (1.85-6.54). One patient in Bio-naïve and 2 patients in Bio-switch group dropped out due to inefficacy. We lost 5 patients due to transfer. As a result, 86.3% of the patients continued GLM after 52 weeks. In Bio-naïve group, DAS 28 changed from 4.40±1.01 to 3.19 ±1.27 ($p<0.001$), and in Bio-switch group, DAS 28 changed from 4.42±1.02 to 3.10±1.27 ($p<0.001$) **Conclusion**: If we avoided to loose patients at the induction phase, we would be able to continue GLM in elderly patients or patients without MTX effectively and safely regardless of prior biologics usage. Lack of immunogenicity of GLM might contribute long term efficacy.

P1-078

Utility of Golimumab for therapy of rheumatoid arthritis without metotrexate

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Conflict of interest: Yes

The treatment of anti-TNF antibody for the treatment of rheumatoid arthritis is recommended in combination with MTX. However, in clinically, many cases should not be used to MTX, anti-TNF antibody non combination of MTX also considered an important treatment option. From 39 cases out of Golimumab 70 patients who introduced in the property was a non-MTX combination, and were compared with 31 cases in which combined with the MTX. As a result, the difference in efficacy and safety by the presence or absence of MTX combination was not observed, and continuation rates was 85%, 84% respectively. Here, it is examined the usefulness of Golimumab during MTX non-combination.

P1-079

Biologics induced eosinophilia: one aspect of immunogenicity and preventive measures by Golimumab

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Conflict of interest: None

Immunogenicity of biologic agents attracts attention as a problem concerning efficacy and safety. We report a patient with RA who developed repetitively eosinophilia during Infliximab (IFX), Adalimumab (ADA) and Tocilizumab (TCZ), and was successfully managed by Golimumab (GLM). A 43-year-old woman was diagonosed with RA 15 years ago. Although she was initially treated with corticosteroid and methotrexate, active polyarthritis persisted. In 2004, IFX was started with an adequate response. After three years, she developed eosinophilia (300-1800/μl). In 2011, urticarial and skin itching appeared during IFX infusion. After discontinuation of IFX, eosinophil count and skin symptoms improved. As polyarthritis deteriorated, ADA was started in 2012. After 4th injection, eosinophil count increased markedly (1300-4800/μl), and skin rash and severe itching appeared. Following the cessation of ADA, eosinophil count and skin symptoms improved. In 2013, TCZ was administrated. After 3rd infusion, eosinophil and skin symptoms reappeared. Moreover, serum level of TCZ-specific IgE antibody was elevated (6.64 UA/ml). TCZ was withdrawn, and eosilophilia and skin involvements disappeared. GLM was started in May 2015. GLM led to remission in RA without severe eosinophilia and skin symptoms.

P1-080

Improvement Factor of Activities of Daily Living in Patients with Rheumatoid Arthritis Treated by Golimumab

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Conflict of interest: None

[Objectives] The aim of this study was to clarify the improvement factor of ADL in patients with Rheumatoid Arthritis (RA) treatmed by Golimumab (GLM).[Methods]We studied 44 patients (male; 4, female; 40) with RA that we could evaluate by HAQ-DI for 6 months after giving GLM in the hospitals of GRN. Patients with RA were 63 years old on average and had mean disease duration of 10 years. 73% of patients used MTX concomitantly, 8.6mg/week on average and 39% of patients used PSL, 4.4mg/day on average. 32 patients took GLM 50mg/4weeks, and 12 patients took GLM 100mg/4weeks. Patients underwent serum marker (CRP, ESR, MMP-3), disease activity score (DAS28-ESR, SDAI, CDAI) and HAQ-DI at pre-administration, 1 month, 3 months, 6 months.[Results]Serum markers except for CRP at 3 months improved in every points compared to before administration. Disease activity score except for CDAI at 1 months improved. Improvement factor of HAQ-DI at 1 month was disease duration. [Conclusion]RA patients taking GLM yielded improvement in their ADL early. But their ADL was not better in patients with long duration of RA.

P1-081

Use experience of golimumab in our department

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Conflict of interest: None

OBJECTIVE: Evaluate the safety and efficacy and treatment persistency rates of golimumab (GLM) for RA patients in daily practice.We also investigate background of the patients with methotrexate (MTX) who need dose escalation of GLM. METHODS: We intended for 20 RA patients receiving GLM in our clinic and evaluated safety, efficacy, and treatment persistency rates. We also analyze the characteristics of the patients at baseline who require dose-escalation of golimumab from 50 mg to 100 mg despite of combination with MTX.RESULTS: Treatment persistency rates at week 48 were 61%.The EULAR good response rate at 12 week was 56%. The DAS28-ESR remission rate at 48 week was about 50%, low disease activity rate was 62.5%. Serious adverse event was not found without 1 patient with PCP. There were no significant differences in disease duration, dose of MTX between dose escalation regimen group and continuation of the 50-mg regimen group. However dose escalation regimen group showed higher disease activity at baseline.CONCLUSIONS: High efficacy and high persistency rate were obtained by GLM treatment for RA patients. Earlier dose escalation of GLM or 100 mg of GLM as an initial dose should be consider even with MTX for the treatment of patient with high disease activity.

P1-082

Certolizumab Pegol in Treating Rheumatoid Arthritis Patients with Mono-/ Oligo-synovitis Resistant to Prior TNF-α Inhibitors

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Conflict of interest: None

Objectives. To examine the effect of treatment with certolizumab pegol (CZP) of rheumatoid arthritis (RA) patients with persistent mono- or oligosynovitis by prior TNF-α inhibitors. Methods and Patients. Six patients (38.5±14.8 years old) were in a moderate/ low activity, or a remission of RA, however, they sustained inflammatory mono-/oligo-arthritis after treatment with prior various TNF inhibitors (GLM 2, ETN 2, IFX 2, ADA 1). They were then switched to CZP and observed in a serial ultrasonography. Results. The observed positive power Doppler signals in the joint have disappeared promptly (grade 2→0) and the patients were able to retain remission in the long term (DAS28-CRP 2.80±0.56, NTJ 1.8, NSJ 1.8 → DAS28 1.55±0.30, NTJ 0.2, NJS 0.4). The treatment of CZP to the refractory mono-/oligo-arthritis of inflammatory synovitis in RA is possibly effective. Conclusion. The cases suggest that it may be as-

sociated with the feature of CZP with effective penetration into the site of inflammation.

P1-083

Assessment of the effectiveness of certolizumab pegol in patients with rheumatoid arthritis in daily practice

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Conflict of interest: None

【Objectives】To assess the effectiveness of the certolizumab pegol (CZP) in patients with rheumatoid arthritis (RA) in daily practice. 【Methods】We retrospectively analyzed RA patients who started CZP between June 2013 and October 2015. We assessed Disease Activity Score 28-CRP (DAS28-CRP), SDAI, CDAI and treatment continuation rate. Risk factors associated with time to discontinuation of CZP were determined with proportional hazard analysis. 【Results】We analyzed 23 patients. DAS28-CRP, SDAI and CDAI at baseline were 3.79, 19.23, and 17.56, respectively. These activity scare at week 24 significantly improved to 2.81, 10.56 and 9.39 ($p<0.05$, respectively). Treatment continuation rate at week 24 was 79.6%, and at week 52 was 68.6%. None factors such as treatment at baseline, previous use of biologic agents, or disease activity at baseline was not associated with discontinuation of CZP. 【Conclusions】CZP is effective in patients with RA in daily practice. CZP was mostly well tolerated.

P1-084

Clinical effect of certolizumab pegol in patients with rheumatoid arthritis from data registered in the Akita Orthopedic Group on Rheumatoid Arthritis (AORA)

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Conflict of interest: None

[Objectives] To analyze the efficacy of certolizumab pegol (CZP) in patients with rheumatoid arthritis (RA). [Patients and Methods] CZP was used in 23 patients with RA treated at the Akita orthopedic group on rheumatoid arthritis (AORA) from 2013. Seventeen patients who were followed up for at least 24 weeks of treatment with CZP, were included in this study. We evaluated persistence rate, DAS28-CRP, SDAI, CDAI and reasons for discontinuing at 24 weeks. [Results] The patient characteristics were as follows: there were 3 males and 14 females, mean age was 60.0 years and mean disease duration was 13.1 years. Seven patients were biologics-naïve, while 10 were biologics-switched. Fourteen patients (82%) were administered continuously in 24 weeks. At 0, 4, 12 and 24 weeks after initiation, the mean DAS28-CRP were respectively 4.34, 3.51, 3.48 and 3.30. The mean CDAI were respectively 20.0, 13.1, 12.2 and 11.4. The mean SDAI were respectively 22.2, 14.6, 13.3 and 12.8. The reasons for discontinuing were insufficient effect in all 3 cases and all of them were biologics-switched case. [Conclusion] These data suggest that CZP improve disease activity at 4 weeks after initiation and could become an option for the treatment of patients with RA.

P1-085

Retention rate of etanercept treatment in our hospital

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Conflict of interest: None

Purpose: The retention rates of treatment with etanercept (ETA) were evaluated in our institution. **Methods**: A total of 90 patients who started ETA therapy were evaluated. **Results**: Twenty-one patients had received at least one biological agent before ETA therapy. Sixty-nine patients received monotherapy. Treatment retention rates were 80.2%, 73.9%, 68.7%, and 55.2% at years 1, 2, 3, and 5, respectively. A total of 4 adverse events occurred. Analysis of patients by factors possibly affecting retention rates revealed no significant differences by patient characteristics. **Discussion**: We conclude that ETA is a beneficial drug in our hospital.

P1-086

Selection of RA treatment for patients who cannot use MTX ~ From TBCR~

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Conflict of interest: None

Objective MTX is well known as the golden standard and anchor drugs in RA medication therapy, however up to 30% patients are withdrawed by some reasons,mainly adverse reactions due to toxicity.So It is important to know which drugs should be selected for that patients who discontinued MTX medication. Methods 226 RA patients who discontinued MTX and then administrated IGU or first biologics (ETN, ADA, TCZ, ABT, GOL, CER, TOF) in TBCR from February 2011 were investigated in the point of their backgrounds, drug retention rates and disease activities. Result 226 patients (IGU 58 patients, ETN 32 patients, ADA 8 patients, TCZ 17 patients, ABT 88 patients, GOL 14 patients, CER 7 patients, TOF 2 patients) were enrolled. The average ages of patients using IGU, ETN, ADA, TCZ, ABT, GOL, CER, TOF were 70 years, 56 years, 59 years, 56 years, 69 years, 66 years, 73 years, 74 years old respectively. The DAS28ESR were 5.1, 4.9, 4.8, 4.9, 5.4, 5.9, 6.0, 5.1 respectively. The drug retention rate of IGU was 70% at 52 weeks, that of ETN was 81%, ADA 71%, TCZ 93%, ABT 88%, GOL 90%, CER 86%, TOF 100%. Conclusion All drugs including biologics had relatively good drug retention rates in the treatment for patients who discontinued MTX.

P1-087

Biologics:more than ten years of experience

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Conflict of interest: None

【Objective】We analized RA patients treated with biologics for more

than 10 years. 【Object and Methods】80 patients started biologics from 2003-2005. Average age: 58.9 y. o., 19 males and 61 females, disease period 11.6 years, stage 3.26, class 2.25. 【Results】53 patients were treated with IFX as naïve. 20 patients (37.7%) continued IFX until Oct. 2015 and 11 patients switched to other biologics (ETN 7 cases, TCZ 3 cases, ABT 1 case). Totally 31 patients continued biologics. The complication to quit IFX was severe pneumonia, glomerular nephritis and heart disease. 27 patients were treated with ETN as naïve. 6 patients (22.2%) continued ETN for more than 10 years. 7 patients switched to other biologics and totally 13 patients continued biologics. The complication to quit ETN was pneumonia, tongue cancer and lung cancer. 44 patients (average age: 56.2 y. o., 8 males and 36 females, disease period 12.3 years, stage 3.34, class 2.13) continued biologics for more than 10 years include switching biologics. mHAQ score was 4.6 on an average. After starting biologics 16 patients had surgery, 7 out of 20 patients in IFX, 2 out of 6 cases in ETN, 7 cases in mix biologics. No difference was found among the biologics. We also discussed DAS28 ESR and radiological evaluation.

P1-088

Analysis of RA patients' problems relating to self-injecting of biologics

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Conflict of interest: None

[Object] There were some problems realized in the clinic with some patients' ability to self-inject. The backgrounds of RA patients' problems to self-inject biologics were studied. [Methods] A group of 84 RA patients were studied by how difficult it was to self-inject biologics. Of these 84 patients, 38 patients were able to easily self-inject within 8 weeks (Easy group), 29 patients were able to self-inject after 8 weeks (Difficult group) and 17 patients found it impossible to self-inject (Impossible group). The backgrounds of the three groups were compared and the reasons were analyzed. [Results] Within the Impossible group we found coaching and guidance was often delayed along with little to no help and understanding from family members. As for the reasons for difficulty for self-injecting we find that delayed guidance, hand disability, living alone, dementia and the lack of social services being the most prevailing. [Conclusions] Many medical workers may lack the knowledge about the necessary social services required for self-treatment. Some problems may be possible to solve by an early involvement in coaching the patient with self-injection. Adequate information and help from a social worker may be necessary.

P1-089

Analysis of factors that impact the QOL in rheumatoid arthritis patients with biologic therapy

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Conflict of interest: Yes

Objective: This study aimed to assess the QOL of rheumatoid arthritis (RA) patients with biologic therapy. Methods: Our subject population comprised 404 RA patients, for whom we assessed parameters that could potentially affect the EQ-5D score, as follows: age, gender, disease duration, BMI, tender joint count, swollen joint count, CRP, pain, patient global assessment, physician global assessment, DAS28-CRP, HAQ, and HADS. Pearson's correlation coefficients were calculated between each indicator. Stepwise multiple regression analysis was performed using the EQ-5D score. Results: We obtained the following values for the assessed parameters: age, 61.0±14.1 years; patient global assessment, 2.6±2.2 cm; DAS-28, 2.8±1.1; HAQ, 0.57±0.64; HADS, 0.73±0.20; and EQ-5D score, 0.73±0.20. The adjusted coefficient of determination was 0.64 (significant at the 1% level). Standardized partial regression coefficients were as follows: HAQ, -0.53; patient global assessment, -0.15; HADS, -0.14; DAS28-CRP, -0.11; age, -0.079; and BMI, 0.065 (all significant at the 5% level). Conclusion: The QOL of RA patients with biologic therapy is influenced by physical dysfunction, global assessment, anxiety, depression, and disease activity.

P1-090

The comparison of treatment effect between anti TNF and non-anti TNF agents on rheumatoid arthritis using propensity score matching

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Conflict of interest: None

Background: The selection of biological agents about treatment of RA is controversial. We compared the treatment effect between anti-TNF (αTNF) and non-αTNF on bio-naïve RA. Methods: The relevant data were derived from the registry dataset of Nagoya University named TBCR. Biologics were classified into 2 groups, αTNF including Adalimumab, Certolizumab, Etanercept, Golimumab, and Infliximab or non-αTNF, Abatacept and Tocilizumab. The baseline characteristics including sex, body weight, age, disease duration, MTX dose and DAS28ESR at pre-treatment were approximated reciprocally using propensity score matching. Conditional logistic regression analysis was performed with EULAR response criteria of good as primary endpoint. Result: Both groups had 143 patients respectively with homologous baseline characteristics. The female proportion, mean body weight, age, disease duration, MTX dose and DAS28ESR at pre-treatment of αTNF and non-αTNF were 79/79 %, 53/53 kg, 59/60 aged, 9.9/9.1 years, 5.3/5.1 mg/week, and 5.1/5.0 respectively. The treatment effect of non-αTNF was better than that of αTNF with odds ratio of 1.89 (95% confidence interval: 1.02-3.48; $p<0.05$). Conclusion: This study suggests the treatment effect of non-αTNF is superior to that of αTNF in bio-naïve RA patients.

P1-091

Efficacy and safety of infliximab-BS for Bio-naïve RA patients

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Conflict of interest: None

Infliximab Biosimilar®(IFX-BS®) is the first biosimilar introduced in Japan, Nov, 2014. IFX-BS is gradually being used for rheumatoid arthritis and inflammatory bowel disease. In its preclinical studies, the transmembrane TNF-expressing T cell line established by our laboratory was used by the pharmaceutical company for CDC, ADCC and apoptosis activities. IFX-BS and innovator IFX (Remicade®) have shown the similar effects concerning these effects on TNF-expressing (TNF-producing) cells. Based on these data, Pharmaceutical and Medical Devices Agency (PMDA) advises pharmaceutical companies to demonstrate CDC, ADCC and apoptosis activities for anti-TNF BSs being developed after the first IFX-BS, which should be comparable to the innovator anti-TNF agent. In the present study, we administered IFX-BS® to the bio-naïve patients with rheumatoid arthritis and show the efficacy and safety.

P1-092

Risk factors for the Exacerbation of Interstitial Lung Disease (ILD) after Administration of bDMARDS in RA Patients with Pre-existing ILD

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Conflict of interest: None

ILD associated with RA is a big concern particularly in Japanese patients. We tried to find risk factors for the exacerbation of ILD during the treatment with bDMARDS. Subjects were 93 patients with RA (mean age 63) associated with ILD who were administrated with various bDMARDS. Chest X-ray film was taken at least every 3 months. Chest CT scan was done before and every yearly. The severity of ILD was graded into 4, namely grade 0 to grade 3. The mean observation period was 23.9 months (range 2 - 90 months). MTX and PSL were under use at the introduction of bDMARD in 61 % and in 85 %, respectively. Exacerbation of ILD was recognized in 15 patients (16 %), with the mean administration period of 6.5 months (2 - 14 months). The bDMARDS at the time of ILD exacerbation ware ABT in 1, ADA in 1, ETN in 8, and IFX in 5, respectively. Discriminant analysis was done incorporating 19 variables such as kind of bDMARDS, age, gender, duration of bDMADS administration, ILD pattern, ILD grade, dose of MTX and PSL, KL-6 value, DAS28ESR, and others, and only 1 significant risk factor (TNF-inhibitors) was extracted. Odds ratio of ILD exacerbation for TNF-inhibitors was 10. We should be cautious for the exacerbation of ILD when TNF-inhibitors were administrated.

P1-093

Continuous tocilizumab, anti-IL6 receptor antibody, therapy for rheumatoid arthritis in patients with active tuberculosis reactivated during tocilizumab medication

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Conflict of interest: None

We reported that successful continuous tocilizumab, anti-IL6 receptor antibody, therapy for rheumatoid arthritis in patients with active tuberculosis reactivated during tocilizumab medication.

P1-094

Case report for emergence of bullous pemphigoid in a rheumatoid arthritis patient treated with adalimumab

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Conflict of interest: None

Bullous pemphigoid is autoimmune bleb caused by autoantibodies against epidermal basal antigen (BP180 and BP230). There are limited numbers of reports about bullous pemphigoid, only 3 reports upon adalimumab (ADA) and no report on rheumatoid arthritis (RA). Here we report a rare case of bullous pemphigoid upon ADA treatment of RA. 75 years old female RA patient have been treated with methotrexate (MTX) since 2010/7. Since WBC counts dropped at MTX 6mg/week, MTX reduced to 4mg/week and ADA started concomitantly. Disease activity is stably managed upon switching MTX to tacrolimus, however, bleb emerged at lower limbs and many of those acutely appeared by the time to see the doctor. Skin biopsy revealed bleb formation at basement membrane zone and inflammatory infiltrate including eosinophil as well as at capillary vessels in corium, leading to diagnosis of bullous pemphigoid. As 30mg/day prednisolone (PSL) started, bleb gradually improved and PSL was papered to 1mg/day. Meanwhile, joint pain got worsens and disease activity increased, tofatinib was started and resulted in stable control of RA and discontinuation of PSL. We consider the immunological mechanism of these so-called paradoxical reaction under anti-TNF agents.

P1-095

A case of successful use of biologics to treat rheumatoid arthritis on hemodialysis

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Conflict of interest: None

A 57-years-old man is undergoing hemodialysis from about 15 years ago. He was diagnosed with rheumatoid arhriris due to pain in the joints in both hands and wrists and elevation of the rheumatoid factor and CRP. He received leukocytapheresis,but the effect was insufficient. Because his rheumatoid arthritis disease activity was high, he was administered abatacept,but infusion reaction was appeared after abatacept use. He was treated with golimumab (100mg,every 4 weeks)with favourable response.

P1-096

The case report of successful pregnancy and childbirth in a rheumatoid arthritis patient changed MTX to etanercept

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Conflict of interest: None

The patient was a 35-year-old woman. At age 32, the patient was diagnosed with rheumatoid arthritis (RA) presenting with swelling and tenderness of bilateral wrist, metacarpophalangeal joints (MP), and proximal interphalangeal joints (PIP), increasing C-reactive protein (CRP) levels, high levels of anti-cyclic citrullinated petide antibody and rheumatoid factor. The patient was administered 8mg/week of methotrexate (MTX), and at three months after, achieved favorable RA control. However, because the patient wished to conceive, MTX was discontinued and the patient was treated with 50mg/dose of etanercept alone. After the patient was confirmed to be a pregnant, administration of etanercept was continued for treating of RA during pregnancy and RA was favorable controlled. The patient was gave birth to a baby successfully, and the Apgar score of baby was favorable. After three months of childbirth, etanercept was discontinued and the patinet was retreated with MTX.

P1-097

Experience with biologics for rheumatoid arthritis(RA) of maintenance dialysis patients in our hospital

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Conflict of interest: None

【Objective】Biologics is considered to suppress disease activity in RA of maintenance dialysis patients. Here we report 7 cases using biologics in RA patients with maintenance dialysis for chronic renal failure. 【Methods】We evaluated the efficacy of the 7 cases that started using biologics in RA patients in dialysis, and the harmful, such as infectious disease. 【Result】Biologics introduced at the time of the average age: 64.3 years old, 5 males and 2 females, mean disease duration:20 years. Types of biologics at the time of introduction are Etanercept (ETN): 3 cases, Tocilizumab (TCZ): 3 cases, and Abatacept (ABT):1 case. 3 cases out of 7 cases are repeatedly hospitalized due to infectious diseases, of which 1 case have died because of the infection. Administration interruption due to adverse events in all cases is seen, but the persistence rate is 100%. 【Conclusion】With respect to biologics of maintenance dialysis patients, TCZ (for amyloidosis), ETN (for short half-life), ABT (for consideration of the infection prophylaxis) are selected. After the adverse event occurs, to suppress the disease activity, biologics is continued.

P1-098

Genome-wide association studies in Japanese patients with rheumatoid arthritis (RA) on anti-Tumor Necrosis Factor (TNF) response: analysis considering effectiveness at two time-points after initiation

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Conflict of interest: None

Objective: GWAS in patients with RA on anti-TNF response have been done mostly in Caucasians and little overlaps in findings were found across studies. Our aim was to identify genetic markers in Japanese patients associated with anti-TNF response at two time-points after TNF inhibitor (TNFi) initiation. *Methods:* 487 Japanese RA patients having had TNFi were recruited. 1,133,484 SNPs were genotyped and additional SNPs were imputed. Using change in DAS28 scores between baseline and 3 months, and 3 months and 6 months as the response phenotype, a GWAS was conducted to accommodate the repeated measures of the outcome, adjusting for baseline values of DAS28, time since their initiation, type of TNF inhibitors and concomitant MTX. *Results:* A total of 4,253,138 SNPs passed quality thresholds for analysis. Suggestive evidence of association ($p<1x10^{-6}$) with ΔDAS28 was observed at 3 chromosomal regions (6q15: rs284515, $p=6.6x10^{-7}$, 6q27: rs75908454, $p=6.3x10^{-7}$ and 10q25.3: rs1679568, $p=8.1x10^{-7}$). Potential candidate genes include MAP3K7 (6q15), a key player in TNFα-mediated inflammatory signaling, GFRA1 (10q25.3) whose association was already reported and WDR27 (6q27). *Conclusion:* 3 SNPs were identified for TNFi effectiveness among Japanese RA patients.

P1-099

Why baseline blood ADAMTS5 can predict the efficacy of infliximab or adalimumab?

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Conflict of interest: Yes

Objective. We have reported that high and low level of ADAMTS5 mRNA could predict the efficacy of infliximab (IFX) and adalimumab (ADA), respectively. In this paper, we investigate the discrepancy of ADAMTS5 level for the prediction between these anti-TNFa biologics. **Methods.** Baseline ADAMTS5 mRNA was quantified using real-time PCR using peripheral whole blood. **Results.** In 100 RA patients treated with IFX, TJC, SJC, and DAS28 after 14 weeks' treatment were significantly lower in Low-ADAMTS5 (< 1.2 Index) group (0.56 ± 0.64, 1.28 ± 1.70, 2.54 ± 1.15) than in High-ADAMTS5 group (2.51 ± 0.37, 2.77 ± 2.71, 3.84 ± 1.41). HAQ and serum Rf after 14 weeks' treatment were not different. On the other hand in 56 patients treated with ADA, DAS28, HAQ, and Rf after 20 weeks' treatment were significantly lower in High-ADAMTS5 (> 1.7 Index) group (3.13 ± 1.26 and 0.54 ± 0.57, 50.0%) than in Low-ADAMTS5 group (3.93 ± 1.33, 1.16 ± 0.70, 82.8%). TJC and SCJ after 20 weeks' treatment were not different. **Conclusion.** IFX should be effective due to low ADAMTS5 with less cartilage destruction while ADA can be successful estimated by HAQ improvement for patients with low Rf level associated with high ADAMTS5, despite of cartilage destruction.

P1-100

Validation of algorithms using genome-wide SNP analysis for prediction of responder (R) or non-responder (NR) for tocilizumab (TCZ)-treated RA patients using multiple medical cohorts

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Conflict of interest: None

Object: Achievement of responder in TCZ treatment is currently one of the most important matters in RA treatment. However, there is no method for prediction of efficacy of TCZ. In this study, we validated the third cohort sample by using the first and second cohort algorithms. **Methods:** The first cohort included 71 RA patients, the second, 68 patients, and the third, 17 patients, for a total of 156 patients from eight hospitals in different regions of Japan. R or NR was determined by CDAI around 24-30 weeks after the initiation of treatment. We selected 10 SNPs associated with TCZ-R or NR which were common in both analyses of the first and second cohort ($p < 0.05$). We scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs, and then examined relationships between R and NR, and the total score in the third cohort. **Results:** The SNP algorithms can predict R or NR with more than 70% accuracy in the third cohort samples. **Conclusion:** These highly accurate algorithms using SNP analysis may be useful in the prediction of remission or low disease activity before treatment with TCZ.

P1-101

14-3-3η could be a predictor for efficacy of tocilizumab in rheumatoid arthritis

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Conflict of interest: None

【**Purpose**】14-3-3η is a member of a family of cytoplasmic molecular chaperone proteins. The clinical usefulness of 14-3-3η is being extensively studied to include prediction of RA in arthralgia subjects and efficacy of drugs used to treat RA. In this study, we investigated the association between serum 14-3-3η levels and disease activity index in RA patients. 【**Methods**】Serum 14-3-3η were measured in 41 Japanese patients with RA before and 3, 6, and 12 months after the treatment with tocilizumab. 【**Results**】Twenty-eight of 41 (68.3%) were 14-3-3η-positive (Median: 1.85 ng/mL) at pre-treatment. Compared with group of 14-3-3η-negative patients (< 0.19 ng/mL), the group with positive 14-3-3η had significantly more severe disease scores (DAS28-ESR [5.3 vs. 4.5, p=0.0550] and CDAI [25.4 vs. 20.0, p=0.0463], respectively). In analyses using EULAR response criteria, serum 14-3-3η levels were significantly lower in good responder than patients who didn't achieve adequate response at 3 months (0.37 vs. 1.76 ng/mL, p=0.0261). 【**Conclusion**】Serum 14-3-3η levels may reflect the disease activities and be useful as a biomarker for predicting efficacy of tocilizumab in RA patients.

P1-102

The effect of serum oxidative stress and biological antioxidant potential with tocilizumab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives]The aim of this study is to evaluate the effect of tocilizumab on serum reactive oxidative stress and biological antioxidant potential with tocilizumab (TCZ) in patients with rheumatoid arthritis (RA). **[Methods]**17 RA patients,who were treated with TCZ more than 3months,were registered. The mean age was 53 years old. The mean disease duration was 12.1years. The level of Diacron-reactive oxygen metabolites (dROMs) and biological antioxidant potential (BAP) were compared before with 3 and 6months after TCZ administration. Further the total of dROMs and BAP were statistically compared about the correlation with other serum biomarkers. **[Results]**Significant difference of the dROMs was detected between the post administration of TCZ and the prior administration of TCZ, as same as other serum biomarkers and DAS28. ($p<0.05$) Significant difference, positive correlations was detected between dROMs and other serum biomarkers and DAS28. ($p<0.01$) However no significant dufference was detected between BAP and other serum biomarkers including dROMs,and DAS28. **[Conclusions]**These data suggest that dROMs, in conjunction with other serum biomarkers

and DAS28 may be used as a surrogate biomarker to evaluate the disease activity of RA.

P1-103

Analysis of podoplanin expression in rheumatoid arthritis using a novel anti-podoplanin monoclonal antibody

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Conflict of interest: None

Introduction: Podoplanin (PDPN), a platelet aggregation-inducing factor, is a selective marker of lymphatic endothelium and also involved in tumor metastasis and invasion. Expression of PDPN has been reported in many tumors including osteosarcoma, malignant brain tumor, lung cancer, esophagus cancer, mesotheliomas, and osteosarcoma. PDPN expression has also reported in synovial tissue of rheumatoid arthritis (RA) patients. In this study, we had established novel monoclonal antibody (Mab) and compared with NZ-1 in immunohistochemistry (IHC) which used synovial tissues obtained from RA patients. Methods: We first established a novel anti-PDPN mAb, LpMab-7, by immunizing mice with LN229/hPDPN. To determine the epitope of LpMab-7, ELISA, Western blotting and flow cytometry were performed. Tissue specimens from 8 RA patients were used for IHC using LpMab-7 and NZ-1. Results: The epitope of LpMab-7 was identified as Arg79-Leu83 of human PDPN using ELISA, Western-blot, and flow cytometry. Using IHC analysis, LpMab-7 showed high reactivity against deep lining layer of RA synovial tissues compared with NZ-1. Discussion: LpMab-7 was shown to be more sensitive than NZ-1 in IHC analysis, suggesting that LpMab-7 has advantage for detecting PDPN localization in synovial tissue of RA.

P1-104

Serum levels of ROM (reactive oxygen metabolities) at 12 weeks during treatment with biologic agents are associated with the remission at 52 weeks

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Conflict of interest: None

【Objectives】We have shown that serum levels of reactive oxygen metabolities (ROM) were associated with CRP and DAS28 in patients with RA and reduced temporally by the treatment with biologic agents (BAs). However, its clinical significance as a biomarker has not been elucidated. 【Methods】Forty-four biologic -naïve RA patients (mean age: 60.0±13.2 y.o., disease duration: 8.23±11.5 y) were included in this study. Association between serum levels of ROM, CRP, MMP3 and HAQ at 12 weeks during treatment with BAs and the remission of DAS28-ESR, CDAI, SDAI and Boorean at 52 weeks was investigated. 【Results】All of ROM, CRP, MMP3 and HAQ significantly reduced at 12 weeks after administration of BAs (535±129 to 343±94.6, 2.63±3.16 to 0.252±0.575, 313±327 to 113±79.0 and 0.861±0.690 to 0.378±0.601, respectively). ROM, CRP and HAQ at 12 weeks in a DAS-remission group at 52 weeks were significantly lower than the non-remission group. ROM and HAQ at 12 weeks in a CDAI-, SDAI- and Boorean-remission group at 52 weeks were also significantly lower than each non-remission group ($P<0.05$). 【Conclusion】Serum levels of ROM at 12 weeks during treatment with BAs were significantly lower in a DAS-, CDAI-, SDAI- and Boorean-remission group at 52 weeks than each non-remission group.

P1-105

HAQ at starting biologic agents is a risk factor associated with radiographic progression of large joint damage: results of 1 to 3-years follow up

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Conflict of interest: None

【Objectives】We have shown that in RA patients treated with biologic agents, radiographic progression of large joint damage (RPD) is expected to be increased when Larsen grade is III or higher (Mod Rheumatol 2015). However, relationship between patients' background characteristics and RPD has not been elucidated. 【Methods】Eighty-eight patients receiving biologic agents (BAs) for 1 to 3-years were included in this study. The mean age at starting BAs was 62.9 year-old, and the mean disease duration was 11.7 years. A total of 400 joints including shoulder, elbow, hip, knee, and ankle was evaluated whether there was RPD or not by comparing X-rays before and after the treatment. 【Results】DAS28-ESR was significantly improved from 4.82 to 2.26 after the treatment. RPD was found in 16 patients (18%) and 21 joints (5.3%). Among patients' background characteristics including age, height, weight, BMI, stage, disease duration, MTX dose, GCs dose, CRP, MMP3, DAS28-ESR and HAQ, a logistic regression analysis showed that HAQ was an independent risk factor for RPD (Odds ratio = 2.965). 【Conclusion】HAQ at starting BAs was a risk factor for RPD in the therapeutic period of 3-years. Since RPD further decreases ADL of the patients, improvement of HAQ in early therapeutic periods is required.

P1-106

Relationship between effectiveness and serum MMP-3 levels in RA patients treated with biological agents

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Conflict of interest: None

【Objects】We previously reported that serum MMP-3 was elevated in patients with active RA, and decreased after treatment. The aim is to clarifiy a relationship between effectiveness of biorogics treatment and serum MMP-3. 【Method】MMP-3 was serially measured for 132 outpatients treated with several kinds of biologics including IFX (30 patients), ETN (15), TCZ (20), ADA (20), ABT (32), and GLM (15). The patients were divided into responders (good) and non-responders (moderate+none) according to the EULAR Response Criteria 24 weeks after the treatment. 【Result】Serum MMP-3 levels were significantly decreased from 4 weeks after treatment and continued to decrease until 48 weeks ($p<0.0001$) in both responders and non-responders. However, degree of decrease in serum MMP-3 was significantly greater in the responders than the non-responders. Analysis for each biologics revealed significant decrease only in the responders for the patients treated with IFX, ETN, TCZ, and ADA. MMP-3 was significantly decreased in both responders and non-responders for patients with ABT.【Conclusions】Serum MMP-3 levels were significantly decreased by biologics treatment, especially in responders. However, the change in MMP-3 levels after treatment was various among patients with different biologics.

P1-107

Analysis of serum peptide profiles of relapsing polychondritis

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Conflict of interest: None

[Objective] To explore serum peptides which are biomarker candidates and associated with the pathophysiology of relapsing polychondritis (RP). [Methods] Serum samples were obtained from 14 RP patients and 14 healthy control subjects (HC). Peptides were extracted by weak cation exchange. Ion intensity of peptides was comprehensively measured by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. [Results] 87 serum peptides were detected. In RP group, 10 peptides showed more than 1.2-fold ion intensity than in HC group ($p<0.05$). Sim-

ilarly, 9 and 5 peptides showed more than 1.5-fold and 2.0-fold ion intensity in the RP group than in the HC group, respectively ($p<0.05$). Conversely, 12 peptides showed less than 1/1.2-fold ion intensity than HC group ($p<0.05$). 4 and 1 peptides showed less than 1/1.5-fold and 1/2.0-fold ion intensity in the RP group than in the HC group, respectively ($p<0.05$). The RP group was accurately discriminated from the HC group by multivariate analysis using ion intensity of all the 87 peptides and selected 22 peptides. [Conclusion] Serum peptide profiles of RP were different from those of HC. 22 peptides, ion intensity of which discriminated RP from HC, are biomarker candidates of RP and may be associated with the pathophysiology of RP.

P1-108

Current state of rheumatoid arthritis treatment: Kaplan-Meier survival analysis of patients in a database

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Conflict of interest: None

Objectives: Rheumatoid arthritis (RA) treatments have problems in terms of efficiency, adverse effects, and secondary failure. We evaluated the current state of RA treatment to obtain a long-term planning of the therapy. **Methods**: Data on 1078 patients from our RA database made in January 2006 were examined, such as onset age, complications, and dose and duration of methotrexate (MTX) and biologics. Using Kaplan-Meier curves, the reason for stopping drugs was determined. **Results**: The MTX use rate was 80%; the persistency rate was 6.3 year, 75%; 20 years, 50% [4337 person-time]. After discontinuation, MTX was changed to biologics or other drugs in most patients. Patient preference was the main reason for discontinuation, followed by hepatic dysfunction. In all, 49% of the patients with hepatic dysfunction continued MTX after dose reduction to 3.1 mg. The persistency rate of the seven biologics was highest in etanercept (6 year, 75%), but with no significant differences among drugs. Biologics were changed mainly for secondary failure. **Conclusion**: Control of RA was more manageable in the longer term with MTX than with biologics, perhaps due to improved MTX usage in the recent years. After secondary failure of biologics, RA control can be attained by changing drugs appropriately.

P1-109

The risk factor of infection in rheumatoid arthritis(RA) patients treated with biological drugs(BIO)

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Conflict of interest: None

【object】We examined the risk of infection for RA with BIO. 【methods】We retrospectively examined RA with BIO in Apr.2014 to Oct.2015. All these patients were undergone echocardiography,abdominal echo,plain CT,and esophago-gastro-duodenoscopy.“Infection” was the infectious disease that was necessary to stop BIO.The established risk factors and their backgrounds at the starting point were analyzed by univariate and multivariate methods. 【results】64 cases were analyzed (14 males and 50 females,average age;67.4,range;26-90 y.o,average disease duration;7.4 years.Steinbrocker-stage:I=27,II=16,III=8,IV=13).they were treated with Abatacept in16 cases,Certolizumab in 18,Etanercept in 8,Golimumab in 3,Tocilizumab in 7,Tofacitinib in 2.The frequency of “Infection” was 13.2 per 100 person-years.These “infection” were including 4 of bacterial pneumonia,2 of herpes zoster,and 1 of panniculitis.They all were improved completely. Both of univariate and multivariate analysis revealed that the usage of predonisolone (PSL) and low titer of serum IgG were significant risk factors and that lymphopenia,low albuminemia,and disease activity were not. 【conclusions】Infectious risk in RA with BIO was reconfirmed as usage of PSL and low IgG.We will continue to analyze data for safe treatment RA with BIO.

P1-110

The investigation of patients treated with Infliximab (IFX) in Akita Registry in 2015

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Conflict of interest: None

Purpose: To investigate the patients treated with IFX who registered with the Akita Orthopedic group on Rheumatoid Arthritis (AORA).Methods: Two thousand and twenty-one patients were registered with AORA in 2015. Of these, 139 patients were treated with IFX who comprised the subjects of this study.Results: The patient characteristics were follows: there were 26 males and 113 females, the mean age was 58 year and the mean disease duration was 123 months. The DAS28ESR could be calculated in 99 patients, and the mean was 4.84 (REM:2, LDA:10, MDA:47, HDA:40). The mean CRP of 130 parities was 2.30 mg/dl, and the mean MMP3 of 98 patients was 262 ng/ml. One hundred and thirty-four patients had been prescribed methotrexate (MTX) with a mean dose of 7.0mg, and 96 patients had been prescribed prednisolone (PSL) with a mean dose of 5.6mg. Four patients were administrated IFX as a second biologics. Forty patients could continue IFX treatment during the investigation with a mean duration of 38 months. In DAS28ESR, MDA and HDA which accounted for 90% at the start were decreased. On the other hand, REM and LDA were increased, and were accounted 60% at the investigation. Ninety-nine patients could not continue IFX treatment, because of a decreasing effect, lung disease, and so on.

P1-111

Clinical efficacy and safety in patients with rheumatoid arthritis of Certolizumab Pegol in our hospital

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Conflict of interest: None

[Objective] To evaluate efficacy and safety of certolizumab pegol (CZP) with rheumatoid arthritis (RA) patients in our hospital. **[Methods]** Two clinical trials, concomitant MTX and without MTX studies were conducted until March 2013 in Japan, subsequently we evaluated efficacy and safety in RA patients of CZP in our hospital. **[Results]** Twenty-three patients (7 males, 16 females), average age at start of administration was 48.6 yrs old, duration of RA was 5.8 yrs, 8 patients (34%) were administered prednisolone, 14 patients (61%) were administered MTX, proportion of prior biologics 9 (39%), pretreatment mean DAS28-ESR and SDAI were 5.25, 27.7, respectively. After 12 months mean values fell to 3.07, 8.3, respectively ($p<0.01$), 13 patients (56.5%) achived low disease activity (LDA) including remission of 9 patients (8 discontinued admin-

istration of CZP, 6 maintaining Bio-free after 1 year). **[Conclusion]** After 1 year to administration of CZP, 56.5% of 23 patients achived LDA, CZP is efficacious regardless of use of con-MTX or Bio-switch in our hospital.

P1-112

Correlation between the value of RF and anti-CCP antibody and the efficacy of Adalimumab and Golimumab

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Conflict of interest: None

[Object] To study the correlation between the value of RF and anti-CCP antibody and the efficacy of ADA40mg and GLM100mg. [Methods] Among RA patients which has begun prescription in 2009-14 in our hospital and has passed for more than 52 weeks, 27 cases of ADA 40 mg medication and 29 cases of GLM 100 mg medication were investigated. They were divided two group. One is double high group to the cutoff value as RF:55U/ml and anti-CCP antibody:100U/ml. In the other group either or both of them are below the cutoff value. Among each two groups of ADA and GLM, ⊿DAS, ⊿SDAI, ⊿TSS and ⊿HAQ are analyzed 52 weeks later by the LOCF method. [Result] In the other group, ⊿DAS of ADA/GLM100 are -1.28/-1.53 and ⊿SDAI of ADA/GLM100 are -9.70/-7.78, without the significant differences. In double high group, ⊿DAS of ADA/GLM100 were indicated -0.29/-1.93 (p:0.018) and ⊿SDAI admitted -3.88/-12.65 (p:0.039) with the significant differences. [Conclusions] When even both of RF and anti-CCP antibody are high value, by the enough amount of TNF inhibitor there is a possibility that the validity is obtained.

P1-113

Result of multicenter clinical study for Adalimumab initiation within 3 months after MTX administration -DARUMA study-

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Conflict of interest: None

【Background and Objective】Adalimumab (ADA) can be administrated for patients who are DMARDs naïve in August, 2012 in Japan. Nevertheless few patients who can be administrated for ADA in combination with methotrexate (MTX), so evidence which is in accordance with clinical practice is needed. 【Patients and Method 】In Gunma Rheumatoid Arthritis Network (GRN), multicenter study was conducted and examined efficacy and safety for ADA initiation within 3 months after MTX administration. 【Result】We analyzed 32 cases. Ave. age 58.2 years old, Ave. disease duration 2.8 years, Combination other than MTX 3 cases (9.4%), PSL combined 16 cases (50%), Ave. Dose of PSL 5.1mg/day, Ave. MTX dose 8.5mg/w, Ave. duration for MTX monotherapy 5.4weeks. Significant decrease was observed on DAS28CRP 4 weeks after ADA administration (P<0.001) and similar result was maintained until 52weeks. As for MMP-3 there is no difference between both groups after 4 weeks, but significant decrease was observed after 12 weeks (P<0.005), similar result was maintained until 52weeks. Retention rate was 75% in 52 weeks and 8 discontinued ADA. 【Conclusion】ADA initiation within 3 months after MTX administration is effective for high efficacy.

P1-114

How we selected bDMARDS when we administrate bDMARDS for the first time for patients with RA

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Conflict of interest: None

We retrospectively analyzed what factors influenced the selection of the first bDMARDS. Patients were 229 patients with RA, 54 males and 175 females with the mean age of 62 years (range 18 - 85 years). bDMARDS selected as the first one were as follows; ABT in 30, ADA in 12, ETN in 116, GLM in 2, IFX in 33, and TCZ in 36, respectively. On analysis, we slightly modified the groups. ETN group was divided into 2, 25mg/week (ETN25) and 50mg/week (ETN50), and anti-TNF antibodies (ADA, GLM and IFX) were grouped into one (aTNF-ab). Ten variables were incorporated in the discriminant analysis and 7 variables were extracted as significant factors influencing the selection of bDMARDS. The order of coefficients in size is as follows: age > DAS28ESR > > dose of MTX = stage > dose of PSL > ILD grade >> ACPA titer, which means that the selection of bDMARDS was greatly influenced by age and DAS28ESR. Advanced age preferred ABT and ETN25, and high DAS28ESR preferred ETN50, TCZ and aTNF-ab. At the final observations, DAS28ESR did not show significant differences among bDMRDS. We conclude that selecting bDMARDS mainly taking age and DAS28ESR into consideration is suitable.

P1-115

Long-term follow-up of treatment with biologics in patients with rheumatoid arthritis in our hospital

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Conflict of interest: None

[Purpose] In this study, the long term follow-up of the patients who were started biologics before 2007 for rheumatoid arthritis in our hospital was investigated. [Materials and Methods] Thirteen patients (2 males and 11 females) were studied. The average disease duration of rheumatoid arthritis until the prescription of biologics was 11 years four months. The average age of the patients was 63.3 years. The average DSA-28 (CRP) score at the time of new prescription of biologics was 5.62. Infliximab or Etanercept is the first biologics for these patients. [Results] One patient was dead, and one patient did not visit our hospital. Remaining 11 cases survived and were following it up. A serious side effect included one pneumonia. All cases who continue biologics, maintained low disease activity. As for the number of the use drugs of the biologics, five cases were given one drug, three two drugs, four three drugs and one four drugs. Even though 12 orthopedic operations were carried out before prescription of biologics, only one patient received orthopedic operation after administration of biologics. [Conclusion] The patients who continue biologics, maintained low disease activity. The most causes of the interruption of biologics were a respiratory disease.

P1-116

Long-term efficacy, safety, and retention rate of abatacept for rheumatoid arthritis: Kagoshima Abatacept Registry

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Conflict of interest: None

Objective. This study aimed to assess the two-year efficacy, safety, and retention rate of abatacept (ABT) for RA. Methods. One hundred twenty-nine patients who had received first treatment with ABT more than two years previously were analyzed. Results. The mean age and mean disease duration were 60.6 and 11.0 years, respectively. The mean

DAS28-CRP at baseline was 4.32, and it decreased to 3.24 at 24 months. The retention rates at 12 and 24 months were 86.0% and 63.1%, respectively. None of the differences in retention rate stratified by age, disease duration, stage, class, RF, ACPA, ILD, COPD, MTX, and line of treatment were statistically significant. When stratified by DAS28-CRP at 3 months, the cumulative incidence (CI) of discontinuation due to inadequate response was significantly higher in the moderate-to-high disease activity group than in the remission-to-low group (p=0.00707). When stratified by body weight, CI of discontinuation due to adverse events (AEs) was significantly higher in the <40 kg group than in the ≥40 kg group (p=0.0056). Conclusion. Treatment responsiveness at 3 months was associated with long-term retention rate of ABT in RA patients. Caution should be exercised when treating underweight patients because of a higher incidence of AEs.

P1-117

Exploring the current state of rheumatoid arthritis by using a novel assessment measure (joint index vector): A multicenter observational study based on the *NinJa* (National database of rheumatic diseases by IR-Net in JAPAN)

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Conflict of interest: None

Background: Joint index vector, Vji is a novel assessment measure for RA. Although Vji does not have other factors such as CRP and VAS, its scalar (|Vji|) is correlated with SDAI.**Aim:** To explore the current state of RA by using Vji.**Methods:** Joint index (JI) of upper/large (UL), upper/small (US), lower/large (LL), and lower/small (LS) was defined as previously described[1]. Vji (x, y, z) for 15,023 patients registered in *NinJa* database was calculated as $x = JI_{UL} + JI_{US}$, $y = JI_{LL} + JI_{LS}$, and $z = JI_{UL} + JI_{LL} - JI_{US} - JI_{LS}$.**Results:** The longer the disease duration was, the closer the mean vector moved toward the Z axis. |Vji| was inversely correlated with Boolean remission rate (R2=0.99). Compared to the mean vector of all the patients, the mean vector of MTX user was small and close to the XY plane; however, the vector of biologics user was large and close to the Z axis, that indicates biologics were chosen on polyarticular cases involved more with large joints.**Conclusion:** Joint index vector is a useful tool for exploring the current state of RA visually. Computer analysis can reduce the burden of complicated calculation for a large database such as *Ninja*.
Reference: 1. Nishiyama S, et al. Rheumatol Int. 2012:32;2569-71

P1-118

Cost-effectiveness analysis of DMARDs and biologics therapy (annual report from Ninja 2014)-NHI price revision has a certain efficacy for the cost of DMARDs

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Conflict of interest: None

[Objectives] To evaluate the balance between the clinical effects of recent anti-rheumatic treatment and its cost [Method] The Data from RA patients registered in the large cohort database *(NinJa*) in 2002-2014 was analyzed. They included clinical indices and dosage of DMARDs. The annual cost-effectiveness calculated from them. [Results] All averages of clinical indices were decreasing constantly. The annual cost of DMARDs was about 490,000 yen / patient in 2014, 10,000 yen higher than the cost in 2013. The rate of the cost of biologics was 74.9% and decreased slightly. Usage rates of ABT and TCZ, whose prices are cheaper than other biologics, increased constantly. [Conclusion] NHI price revision leaded to the stop of increase of the DMARDs' cost in 2012 and 2014. Accordingly, the cost-effectiveness of DMARDs therapy was improving. However, its effect was temporary in 2012. Therefore, we must ascertain the effect of price revision by the careful observation of the cost for several years.

P1-119

Progression of atherosclerosis in patients with systemic lupus erythematosus

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Conflict of interest: None

[Object] We conducted a longitudinal cohort study to clarify relevant clinical factors for the progression of atherosclerosis in patients with SLE. [Methods] SLE patients received echographies of carotid arteries at interval of 2yrs or more, were enrolled. A mean of the bilateral intimal carotid artery media thickness (mIMT) was measured. [Results] 32 patients (29, female) were recruited. The medians of age, disease duration, total prednisolone dosage (tPSL), and daily prednisolone dosage (mPSL) were 60 y/o, 25 yr, 57 g and 13.7 mg/day, respectively. At the baseline, mIMT was significantly correlated with age, levels of HbA1c, but not with tPSL. An annual progression of mIMT (ΔIMT) was positively correlated with SLEDAI scores at the baseline (bSLEDAI) (p=0.01). A multivariate regression analysis showed that bSLEDAI (B=0.011) as a positive, mPSL (B=-0.05) as a negative contribution factor for ΔIMT. [Conclusion] These results suggested that a progression of atherosclerosis in SLE patients was mainly determined with the high disease activities, but glucocorticoid therapy might be protective.

P1-120

Efficacy of Lunaber ULD for joint pain appearing in 20~49 years old female

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Conflict of interest: None

(object) There are many causes of joint pain in young females, including systemic rheumatic disease, psychosomia, and premenstrual syndrome. HRT is considered by some to be an effective treatment for undifferentiated arthralgia in postmenopausal women. In this study, the efficacy of Lunabell ULD in this patient group was investigated. (Methods) Nineteen females with a mean age of 40 (24~48) complaining of dysmenorrhea, malaise, morning stiffness and joint pain were enrolled and prescribed Lunabell ULD. Clinical and laboratory tests included simplified menopausal index, patient Visual Analogue Scale (VAS), levels of estradiol and follicle stimulating hormone (FSH). (Results) Of the 19 patients, ten experienced ongoing joint pain after 24 weeks of follow up. Of those with ongoing pain, eight reported 50% improvement of their joint pain (42.1%) with Lunabell. Two patients developed RA during the trial, and one developed Sjogren's syndrome. Three patients under the care of psychosomatic internal medical specialists were able to reduce the dose of their psychoactive medication after receiving Lunabell ULD. (Discussion) Monophasic Lunabell ULD may be effective treatment for undifferentiated arthralgia in pre- and peri-menopausal women.

P1-135

Examination of the optimal dose of tacrolimus in systemic lupus erythematosus

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Conflict of interest: None

[Objectives]To examine optimal blood concentration of tacrolimus

(TAC) in systemic lupus erythematosus (SLE) retrospectively. [Methods]31 patients were treated with prednisolone and TAC, but not with other immunosuppressant. Observation period was six months after TAC start. The improvement of SLE defined it as SLEDAI-2K ≥4. [Results] Regarding patient background, 25 patients were female, and the median values were as follows: age, 37 years (15-69); C3 at pretreatment, 58 mg/dl (27-121); anti-ds-DNA antibody, 26.3 IU/ml (3.32-7012); SLEDAI-2K, 13 (1-45); initial dosage of prednisolone, 45 mg/day (10-90); TAC dosage, 3 mg/day (1-5); and TAC trough level, 4.3 ng/ml (1.3-10.0) TAC dose correlated with improvement of the number of the platelets, C3, the titer of anti-dsDNA-Ab and SLEDAI-2K. An ROC analysis was conducted to determine the effective cut-off values of the TAC trough level most suitable for improvement of SLE. The value that maximized the area under the ROC curve was 7.7 ng/ml (sensitivity: 100%, specificity: 43%). The improvement of SLEDAI-2K was significantly higher in patients with a TAC trough level ≥7.7 ng/ml than in those with a score of < 7.7 ng/ml ($P < 0.029$). [Conclusion]The possibility that a TAC trough level ≥7.7ng/ml were useful was suggested.

P1-136

The effectiveness on skin manifestations of hydroxychloroquine for cutaneouslupus erythematosus and systemic lupus erythematosus patients

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Conflict of interest: Yes

[Purpose] The effectiveness on skin manifestations of hydroxychloroquine (HCQ) for cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus patients (SLE) and its predictive factors were examined. [Methods] 2 CLE and 7 SLE patients who were treated with HCQ were enrolled. 7 of them were female. The mean age at the start was 41.3 years old. The mean disease duration was 7.6 years. The change of skin manifestations were evaluated with Cutaneous LE Disease Area and Severity Index (CLASI). We defined 'delta CLASI activity ratio (d-CLASIAR)' as determined by the change of CLASI activity score divided by CLASI activity score at the start. The correlation between d-CLASIAR with physical and laboratory results were examined. [RESULTS] CLASI activity scores were (13.3±6.0, n=9) at the baseline, (9.8±3.6, n=9) at 3 months, (10.6±6.5 n=5) at 6 months, and (8.5±3.4, n=4) at a year. d-CLASIAR showed a positive correlation with serum concentration of LDH at the baseline (p=0.02) and a negative correlation with eosinophil counts of blood at the baseline (p=0.02). [CONCLUSION] HCQ improved CLASI activity score of CLE and SLE. The improvement of skin manifestations could be predicted by serum LDH concentration or blood eosinophil count.

P1-137

The efficacy and the long-term prognosis of rituximab for refractory thrombotic microangiopathy associated with connective tissue diseases (CTD-TMA)

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Conflict of interest: None

[Objectives]It has been described that B cell has important roles in connective tissue disease (CTD). Rituximab (RTX) is widely known as effective for patients with several autoimmune hematological disorders. Thrombotic microangiopathy (TMA) is developed in CTD occasionally. CTD-TMA with normal activity of ADAMTS-13 is often resistant for plasma exchange conducted for thrombotic thrombocytopenic purpura as a first-line treatment. [Methods]We investigated the patient's characteristics and the efficacy and the long-term prognosis of RTX treatment in 7 refractory CTD-TMA patients between 2006 and 2015. We defined complete response (CR) as platelet counts $>150\times10^9$ /l for more than 3 consecutive days. We considered CR continued more than 30 days after RTX treatment as remission. [Results]No abnormality of ADAMTS-13 activity was observed 6 patients. The thrombocytopenia was improved immediately within 2-3 weeks after the initiation of RTX. 6 patients could achieve CR. They who achieved CR all have sustained long-term remission by only first RTX administration. [Conclusion]We suggest that RTX treatment has efficacy with high response rate and long-term remission for the refractory CTD-TMA patients. Moreover, RTX treatment can be the first-line treatment for CTD-TMA.

P1-138

Analysis of the new onset cases of SLE treated by steroids and double filtration plasmapheresis

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Conflict of interest: None

【Purpose】 Sometimes DFPP is used for SLE patients with the high tighter autoantibody or the other connective tissue diseases. In this study, we analyzed the usefulness of DFPP.【Method】 We analyzed the 22 new onset cases with SLE. The 7 cases of those were treated by steroids and DFPP. We compared it about the blood test data and treatment regimens in the DFPP group and the non-DFPP group.【Result】 There were recognized a lot of the other connective tissue diseases complicated with SLE in the DFPP group ($p<0.05$). Although we did not recognize the statistical significant difference, there was no reccurense case in the DFPP group.【Conclusion】 The rate of decline of anti-DNA antibody was similar to the non-DFPP group in the DFPP group. However, the recurrence case did not exist in the DFPP group, and the combination effect was suggested.

P1-139

Clinical characteristics and prognosis of lupus nephritis

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Conflict of interest: None

[Objectives] Lupus nephritis is one of organ dysfunction in systemic lupus erythematosus, and have various characteristics and prognosis. The aim of this study was to compare the background of lupus nephritis. [Methods] 35 patients (5 men and 30 women) who had biopsy-proven lupus nephritis were enrolled in this study. We retrospectively discussed clinical characteristics of these patients. [Results] The median age at the time of renal biopsy was 31. The distribution of the histological classes of lupus nephritis was followed; 1 was class I, 2 were class II, 10 were class III, 15 were class IV, 3 were class V, and 4 were class III/IV + V. Complete renal response occurred in 22 patients, and partial renal response occurred 10. Renal flare was observed in 9 patients. In patients of class III, IV, and III/IV + V, 9 of them had received only corticosteroids, 20 of them had received any immunosuppressant in combination with corticosteroids (Mizoribine and Tacrolimus used frequently). Renal flare of class III occurred less frequently than class IV. [Conclusions] Class III had trend toward good prognosis compared to class IV. Mizoribine and Tacrolimus had potential of therapeutic agent.

P1-140

Activation status of mucosal-associated invariant T cells reflects disease activity and pathology of systemic lupus erythematosus

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Conflict of interest: None

Background: Mucosal-associated invariant T (MAIT) cells are innate lymphocytes that are restricted by the MHC-related molecule-1 (MR1) and express a semi-invariant TCRα chain: Vα7.2-Jα33 in humans. MAIT cells constitute about 5% of peripheral blood abT cells. This study aimed to investigate their involvement in in systemic lupus erythematous (SLE). **Methods:** The activation status of MAIT cells was assessed by the expression of CD69. Jurkat cells expressing invariant Vα7.2-Jα33 TCR (Vα7.2-Jurkat cells) or human MAIT cells were co-cultured with B cells or monocytes in the presence of MR1 ligand, ant the expression of CD69 on Vα7.2-Jurkat or MAIT cells were evaluated. Peripheral blood mononuclear cells were cultured in the presence of various cytokines, and CD69 expression on MAIT cells was analyzed. **Results:** The CD69 expression levels on MAIT cells correlated with disease activity. Lupus monocytes exhibited increased ability to induce MAIT cell activation. MAIT cells were activated by cytokines including IFNα, IL-15, and IL-12 plus IL-18. **Conclusions:** The activated status of MAIT cells reflects the disease activity of SLE. The capacity of lupus monocytes to activate MAIT cells and elevated cytokine levels may contribute to the hyperactivated status of MAIT cells in SLE cells.

P1-141

Lupus nephritis treatment result of mycophenolate mofetil (MMF)

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Conflict of interest: None

Purpose: We performed kidney biopsy and administered mycophenolate mofetil (MMF) to the patients with class 4 lupus nephritis (LN) in conformity with guidelines of ACR (2012). Because there was still little announcement of the LN treatment result of the MMF in our country, we investigated the results in our hospital. Methods: The patients who had administered MMF in our department by July 2015 were tallied. We extracted the patients who received MMF for the purpose of LN treatment and investigated urinalysis views and the changes of blood albumin level. Results: 46 SLE patients have received MMF. In 31 cases, MMF was started for LN treatment, but 4 cases were omitted from the study because of data insufficiency. In the remaining 27 cases, 25 have presented increase of albumin level within 6 months, and 15 have reached the normal value of albumin within 1 year. 13 have reached negative or the degree of plus/minus in urine protein qualitative test within 1 year. There were 6 cancellation cases, and their reason were as following; remission 1, patient's hope 1, suicide 1, leukocytopenia 1, diarrhea 1, and lack of effect 1. Conclusions: Because they were used high dose of steroid, they were not effect of MMF alone, but MMF with steroid showed high curative effect for LN.

P1-142

The effects of remission criteria and evaluation timing on remission rates and outcome prediction

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Conflict of interest: None

Objective: To investigate the effects of remission criteria and time of evaluation on the remission rates and accuracy of outcome prediction. **Methods:** Thirty lupus nephritis (LN) patients were treated with combination therapy of mizoribine, tacrolimus, and prednisolone, and then retrospectively evaluated. Three renal factors (proteinuria, renal function, and urine sediment) at 2, 4, 6, and 12 months were used as the remission criteria. Because there were no patient deaths, nor any end stage renal dysfunction, we used relapse and insufficient dosage reduction of prednisolone as alternative evaluation outcomes. **Results**: Of the 18 remission criteria that combined three renal factors, significant differences in the remission rates (3.3-76.7%) were observed. The remission rate was reduced by approximately 10% after adding urinary sediment analysis. Although the remission rate continued to increase at periods up to 12 months, the treatment outcome was predictable at month four. Unfortunately, the ideal criteria for determining remission were not able to be determined from this study. **Conclusion**: LN remission rates vary depending on the remission criteria and the period of evaluation. Remission rates reached a maximum at 12 months, but could be predicted after a much shorter time.

P1-143

Three patients with lupus myelitis

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Conflict of interest: None

Case 1. A 31-year-old woman with SLE was admitted for bladder rupture. She had suffered from fever, voiding difficulty and weakness of lower limbs for 3 weeks. Neurological examination showed weakness of lower extremities. The results of anti-Sm and anti-Ro antibody were positive, with negative results of anti-aquaporin 4, anti-dsDNA and antiphospholipids antiody (aPL). Her conditions responded to immunosuppressive therapy, and she gained her feet with sticks, with self-catheterization for urination. Case 2. A 24-year-old woman with SLE was admitted for headache and fever. Within several days, she had voiding difficulty and paresthesia of lower limbs, and became paraplegia. The results of anti-dsDNA and aPL were positive, with negative results of anti-RNP, anti-Ro and anti-aquaporin 4 antibody. She never improved with the therapy, leading to paraplegia and catheter-dependence. Case 3. A 32-year-old woman was admitted for voiding difficulty and gait disturbance, appearing the same day. The next day, she became paraplegia. Laboratory data showed thrombocytopenia, and positive results of ANA and aPL. Her conditions never responded to the therapy. Myelitis is estimated to affect 1-2% of SLE patients. We discuss mechanism of the complication with a role of lupus-specific antibodies.

P1-144

Leucine-rich alpha-2 glycoprotein (LRG) as a possible urinary marker for lupus nephritis

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Conflict of interest: None

【Background】Lupus nephritis (LN) is a serious complication of SLE and its accurate evaluation is dependent on renal biopsy. A search for other non-invasive methods such as urinalysis is warranted. Recently, we identified a novel acute phase protein, LRG, whose expression is induced at the site of inflammation by various inflammatory cytokines. 【Object】 To investigate whether LRG can be a new urinary biomarker of LN. 【Method】We analyzed about the relationship between urinary LRG levels and pathological diagnosis of LN. We also analyzed NZ B/W F1 mice, a lupus model, to study the mechanism of LRG expression in LN. 【Result】Urinary LRG levels were higher in patients with LN than in those without LN. In NZ B/W F1 mice with LN-like alteration, LRG expression was significantly upregulated in kidney compared with control B6 mice. Immunohistochemically, LRG was observed in renal tubular epithelia of NZ B/W F1 mice. Additionally, macrophage infiltration and IL-1beta production was detectable around of the tubule of NZ B/W F1 mice. In vitro, LRG expression and secretion was induced by IL-1beta in PTEC of NZ B/W F1. 【conclusion】Urinary LRG may be useful as a

marker of LN, which reflect the active inflammation of LN.

P1-145

Profiles of cell surface proteins of PBMCs from patients with SLE

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Conflict of interest: None

[Object] Patients with SLE show diverse clinical manifestations and laboratory findings. A single marker for the diagnosis of SLE would be useful if exists. We here tried to find such a diagnostic marker from cell surface proteins of peripheral blood mononuclear cells (PBMCs). [Methods] PBMCs, prepared from 5 SLE patients and 5 healthy controls (HC), were subjected to cell surface-proteomics. Protein spots which showed more than ±2.5-fold difference in the SLE group compared to the HC group were identified by mass spectrometry. We here focused on proteinase 3 (PR3) among them. PR3 on the surface of the lymphocytes and monocytes were detected by flow cytometry. [Results] Forty-four protein spots which showed more than ±2.5-fold intensity difference between the SLE and HC groups. Seventeen out of the 44 protein spots were identified. The proportion of PR3-positive monocytes was higher in 2 SLE patients than in 2 healthy controls tested until now. [Conclusions] Cell surface protein profiles of PBMCs in SLE were greatly different from those in the healthy condition. Further analyses are needed to clarify whether the identified differently expressed proteins such as PR3 are a single diagnostic marker for SLE and whether the proteins are involved in the pathophysiology of SLE.

P1-146

Oxidative stress marker d-ROMs and BAP in patients with systemic lupus erythematosus

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Conflict of interest: None

[Object] In late years the study on oxidative stress is done much in various fields, but there is not many it in the collagenosis region. In this report, we weigh patients with SLE and the healthy subject against d-ROMs and BAP for an index of the oxidative stress, and examine the significance. [Methods] An oxidative stress degree (Reactive Oxygen Metabolites, d-ROMs) and the antioxidant power (Biological Antioxidant Potential, BAP) of 20 patients with SLE that was under the medical treatment in this hospital were measured. The measurement was carried out with the serum of the patients using F.R.E.E. (Free Radical Elective Evaluator) made in Dacron.We measured ten normal controls similarly and weighed it. [Results] In SLE group, d-ROMs was an average of 683±213 U.CARR, BAP were an average of 4268±978 μM. Whereas, in the normal control, d-ROMs was an average of 323±100 U.CARR and BAP was an average of 2697±257 μM. A significant difference was found in both indexes between both groups. [Conclusions]Patients with SLE had high oxidative stress degree in comparison with the normal control, and the antioxidant power was in a high state.We evaluate these changes by the activity of the SLE and will consider the clinical significance in future.

P1-147

Clinical features of systemic lupus erythematosus with lupus nephritis in Kochi Medical School

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Conflict of interest: None

[Objectives] Our goal is to assess the clinical features of SLE with LN in Kochi Prefecture. [METHODS] 30 patients with SLE who had been admitted to our hospital and undergone renal biopsy from 2009 to 2014 were enrolled. We assess the correlation among clinical characteristics, laboratory data, and pathohistological findings. [RESULTS] Female were 25 (83.3%). Mean age was 43.6 years old. According to ISN/RPS classification, I, II, III, IV, III+V, and IV+V were 2, 1, 9, 3, 8 and 7 cases, respectively. Laboratory data on admission showed that average values were as follows; Alb 3.4mg/dL, Cr 0.89 mg/dL, BUN 17.4 mg/dL, CRP 0.49 mg/dL, Hb 11.2 g/dL, WBC 5860/mm^3, dsDNA Ab 55.7 IU/mL, CH50 36.9 CH50/mL, C3 75.2 mg/mL, C4 14.7 mg/mL, proteinuria 2.4 g/gCr. Incidence of other antibodies were as follows; Sm Ab:10, RNP Ab:15, Cardiolipin Ab:1, MPO-ANCA:5, PR3-ANCA:1. Intensive therapies included mPSL pulse therapy (53.3%), IVCY (23.3%) and IVIG (10.0%), following oral PSL (average dose was 33.1 mg daily). After 1 year, 27 patients had complete remission, and 3 had incomplete remission. [CONCLUSIONS] Our date suggests that it might be useful to evaluate an organ disorder degree by renal pathohistology findings for the improvement of SLE patients' progrosis.

P1-148

Study of 24 cases diagnosed with lupus nephritis in renal biopsy

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Conflict of interest: None

【Objective & method】In our hospital patient database,we extracted the 24 people who confirmed diagnosis of lupus nephritis in renal biopsy. And we were examined such as immunological background, treatment methods, and therapeutic effect retrospectively. 【Conclusion】The average age of onset of lupus nephritis (24 cases) was 27 years old. And typeIII is 3 (12.5%), typeIV is 12 (50%), typeV is 9 (37.5%), the type I and II was 0 people. The average onset period from SLE was 2.9 years. Recurrence rate was 29.1%. We examined the risk factors of nephritis recurrence, there was no significant difference in antibody type (anti-dsDNA-antibody,anti-Sm-antibody,anti-SSA-antibody,anti-RNP-antibody),C3 titre, and titre of maximum proteinuria. Remission induction therapy was high dose PSL in all cases. And type of immunosuppressive agent was cyclophosphamide (71%), tacrolimus (8%), cyclosporine (8%), and PSL alone (13%). By remission induction therapy, SLEDAI,C3, and ds-DNA antibody were improved with a significant difference at 12 weeks. Occult blood was improved at 52 weeks. In tacrolimus group, proteinuria was reduced in 52 weeks. (UP/Cr:2.7→1 p=0.024). Interestingly, in one case who had high proteinuria over 10 years, tacrolimus beginning had remarkable effect immediately.

P1-149

Examination of features of interstitial pneumonia with systemic lupus erythematosus

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Conflict of interest: None

We examined the clinical and radiological features of interstitial pneumonia (IP) with systemic lupus erythematosus (SLE). Subjects included 17 SLE-IP patients (15 women, median age 63 years). About half of patients had systemic sclerosis (SSc), 3 had Sjögren syndrome, 2 had mixed connective tissue disease, and 1 had rheumatoid arthritis associated with SLE (some patients had multiple conditions). Raynaud's phenomenon was observed in 64%, arthritis in 64%, and renal involvement in 44%. Speckled type of antinuclear antibody (Ab) was observed in 82% of patients, anti-RNP-Ab in 76%, and anti-Scl-70-Ab in 1 patient, and anti-CCP-Ab in 1 patient, respectively. The median KL-6, %FVC, and %DLco were 316 (131-795) mg/dl, 87.4 (60.7-132.6) %, and 51.6 (23.5-57) %, respectively. Respiratory function test's results were not significantly changed between diagnosed IP to present. The characteristics of

SLE-IP were elderly age, chronic progression, and presence features of other collagen diseases. HRCT of the chest had features of pulmonary lesions of collagen diseases associated with SLE.

P1-150

A case of SLE-associated protein-losing gastroenteropathy (PLGE) accompanied by high serum levels of VEGF

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Conflict of interest: None

【Case】58 years old woman. She had abdominal distention 2 month prior to admission and had dyspnea in the decubitus position 1 month prior to admission. She presented to a hospital and was admitted. On admission, systemic edema and pleural effusion and ascites were noted. Blood tests showed low levels of total protein and albumin and complement. ANA, anti-Sm antibody and anti-RNP antibody were positive, anti-ds-DNA antibody was negative. Serum levels of VEGF is very high (682 pg/mL). Scintigraphy showed protein loss from the stomach, small intestine and ascending colon. We diagnosed the patient with SLE-associated protein-losing gastroenteropathy (PLGE). We started 50mg per day of oral prednisolone (0.8 mg/kg/day). After 3weeks from starting steroid therapy, her serum total protein and albumin and complement were not improved. At that time, Serum levels of VEGF remained high (267 pg/mL). We added cyclophosphamide pulse and plasma exchange. They improved her condition. 【Conclusion】Cases of SLE-associated PLGE accompanied by high serum levels of VEGF are rare. High serum levels of VEGF may cause resistant to therapy of this case.

P1-151

Successful treatment of diffuse alveolar hemorrhage in systemic lupus erythematosus with combination therapy of plasmapheresis, intravenous cyclophosphamide and oral tacrolimus

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Conflict of interest: None

Diffuse alveolar haemorrhage (DAH) is a rare but life-threatening complication of systemic lupus erythematosus (SLE). Despite immunosuppressive treatments, an early mortality rate of 20-50% is reported in the literature. We describe a 48-year-old man with SLE complicated by alveolar hemorrhage. The patient presented fever, hemolytic anemia, thrombopenia, proteinuria, antinuclear antibody-positive, anti-dsDNA antibody-positive and polyarthralgia. He was diagnosed as SLE. Although oral steroid therapy has been started, he suddenly developed new pulmonary infiltrates, decline in hemoglobin, hemoptysis, dyspnea, hypoxia, and he was diagnosed as alveolar hemorrhage. After intravenous methylprednisolon pulse therapy (1000 mg/day) for 3 days, treatment with plasmapheresis (PE) and intravenous cyclophosphamide (IVCY) was initiated. His chest X-ray showed prompt but temporary improvement. DAH was relapsed soon. Oral tacrolimus was administered in addition to PE, monthly IVCY and steroid therapy. The combination therapy markedly improved DAH and other SLE states without relapse. Our experience suggests that the prompt initiation of combination therapy of PE, IVCY and oral tacrolimus should be considered for SLE patients with life-threating alveolar hemorrhage.

P1-152

A case of NPSLE with radiculopathy which was difficult to diagnose

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Conflict of interest: None

The patient is 31 years old female with SLE complicated with lupus nephritis IIIA.She complained of numbness of lips, hands and feet on admission, but cerebrospinal fluid and MRI of brain and spinal cord showed no feature of abnormalities. However after starting treatment with PSL 50 mg/day, she complained of muscle weakness and loss of sensation of whole body. Her symptoms progressed in spite of mPSL pulse and became bed ridden. Repeated lumbar puncture and nerve conduction studies eventually revealed increased IgG index and IL-6, delay of F wave and peripheral nerve conduction velocity. According to these results, we conclude that radiculopathy was the main clinical condition in this case. Her symptoms improved significantly after treatment of cyclophosphamide (IVCY). There have been few case reports about NPSLE with radiculopathy so far, so we discuss this case with some literature review.

P1-153

An case of juvenile male SLE which developed acute for cryoglobulinemia during follow for pericarditis, steroid-resistant hemophagocytic syndrome

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Conflict of interest: None

[case] 19 years, man [the history] He was introduced for serum cryoglobulin positive, SS-A antibody positive in 2008. I was followed up without meeting the SLE diagnostic criteria. Lassitude, leg edema, Raynaud symptom develop from about the winter of 2014. I accepted thrombopenia from March, 2015 and to be hospitalized because accepted heart expansion in May. [progress]I diagnose SLE and started treatment in PSL1mg/kg. Because he was improved, I reduced PSL two weeks after start of therapy.I doubted a merger of Hemophagocytic lymphohistiocytosis (HLH) because CRP13.7mg/dl, ferritin 1327ng/ml and fever, cytopenia and I accepted hepatosplenomegaly in CT. I enforced bone marrow aspiration, but the image did not accept it. I gave steroid pulse therapy, but the fever and the cytopenia lasted. After strongly doubting HLH, and repeating bone marrow aspiration, I confirmed a blood corpuscle ingurgitation image. The effect was temporary and got remission in what I added it to steroid pulse therapy of four times in total every two weeks, and cyclosporine added though I gave steroid pulse therapy. [consideration] There are few case reports of juvenile male SLE which assumed HLH a first symptom and reports it in conjunction with consideration from literatures.

P1-154

Severe heart failure as the initial manifestation of systemic lupus erythematosus : 2 case reports

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Conflict of interest: None

Cardiac involvement is rare as the initial manifestation in systemic lupus erythematosus (SLE). We describe 2 cases of severe heart failure as the initial manifestation in SLE.Case 1: 16-year-old female presented high fever, appetite loss, and severe dyspnea. Echocardiography indicated massive pericardial effusion and severe diffuse hypokinesis. According to the significant laboratory findings, existence of nephritis and mucosal ulcer, the diagnosis of SLE was established. Under the intensive care of circulation system by pericardiocentesis and the intra-aortic balloon pump (IABP) assist, high dose of prednisone (PSL) was administrated. She was dramatically improved. Case 2: 42-year-old female indicated anasarca and nocturnal dyspnea. Echocardiography showed severe dif-

fuse hypokinesis. The diagnosis of SLE was performed according to the existence of pleuritis, nephritis, and significant laboratory findings. She was treated with high dose of PSL under the intensive support by IABP and artificial respirator. Ultimately, she achieved complete recovery from heart failure. In conclusion, SLE may be a cause of acute heart failure in young individuals. Therefore, it is necessary to perform immediate diagnosis and treatment for achieving favorable outcome.

P1-155

Outcome of mycophenolate mofetil treatment for resistant or relapsing lupus nephritis

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Conflict of interest: None

[Object] The aim of the present study is to evaluate the outcome of MMF treatment for resistant or relapsing LN. [Methods] We performed a retrospective study of the 4 LN cases who received MMF. Baseline characteristics of 4 LN were age:44.5±12.1 years,the details of 4 LN:{incipient LN:1 IVG (A/C)+V type,relapsing LN:3[2:IVG (A/C)+V type,1:IVG (A/C) type]},SLEDAI:19.5±4.1, C4:10±2.3 (mg/dl),Cr:1.1±0.3 (mg/dl),albumin:2.2±0.5 (g/dl),urine protein:9.5±8.8 (g/g·Cr). All cases developed nephrotic syndrome. All cases have received some immunosuppressants (CY,TAC,CyA,MZR), but they have failed treatment or recurred LN. [Results] All cases received MMF (1750±289mg)[2:PSL+MMF,2;PSL+TAC+MMF]. After 6 months from treatment of MMF, complete remission:1,incomplete remission type1:2,incomplete remission type2:1. [Conclusions] MMF was effective all cases in remission induction and maintenance therapy of refractory LN. MMF was effective against cases that conventional treatment was ineffective. In the future,MMF can become the key drug of the LN treatment in Japan.

P1-156

Systemic Lupus Erythematosus with Thrombotic Microangiopathy due to Antiphospholipid Syndrome

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Conflict of interest: None

42 y.o. man. He was diagnosed as SLE at 13 y. o. At 29 y.o., large amount of proteinuria was found and renal biopsy was perfomed, diagosed as lupus nephritis IV (G) + V (A/C). Immunosuppressive therapy was started. Renal function and the platelet count were gradually decreasing. When he was 35 y.o., he had a stroke (visual loss). anti PL antibody had been detected, so we diagnosed as APS. At the same time, he reached at end-stage of renal disease, hemodialysis was started. After platelet count was recoverd by warfarinization, kidney transplantation was performed when he was 36 y.o.. 2 years after the transplatation, he was admitted because of AKI, forth kidney biopsy was performed, which showed TMA. IF and EM showed no deposition in the glomeruli. We concluded TMA was caused by APS. We want to share the various pathological changes about APS.

P1-157

A case report: recurrent lupus nephritis during pregnancy with survival of both mother and child

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Conflict of interest: None

Pregnancy is associated with the increase risk of SLE flares. Here, we report a case of lupus nephritis (LN) flare triggered by pregnancy and its recovery. When she developed polyarthritis, facial erythema, leukopenia and proteinuria, she was diagnosed as SLE at the age of 26. Renal biopsy revealed a pathologic diagnosis of the LN typeV+II(ISN/RPS). She was treated by prednisolone (PSL) of 1 mg/kg and tacrolimus. PSL was tapered to 6 mg/day and her symptoms were under control for about 4 years. After the first pregnancy at the age of 35, her proteinuria gradually increased, which was regarded as LN flare, and she was admitted. We used a 3-day pulse methylprednisolone (mPSL) 1 g/day and subsequent intravenous PSL 1 mg/kg, yet proteinuria was not improved. She also developed hypertension, elevation of hepatic enzymes, and reduction of platelets. As we diagnosed with Hemolysis Elevated Liver enzymes Low Platelets syndrome (HELLP syndrome). She delivered a baby by Caesarean section at 24 weeks. After delivery, her condition was improved with mPSL and mycophenolate mofetil administration. Even if SLE patients maintain a deep remission, there is a possibility of relapse, therefore we should carefully follow up the pregnant patients with SLE.

P1-158

A case of systemic lupus erythematous successfully treated with intravenous gammaglobulin for sever neutropenia

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Conflict of interest: None

A 35-year old woman admitted to our hospital suffered from submucosal hemorrhage with low grade fever, general fatigue and Reynoue phenomenon. She was diagnosed as systemic erythematous (SLE) from findings of positive of anti-nuclear antibody, hypo-component, leukocytopenia (neutropenia) and thrombocytopenia. She was treated with 40mg prednisolone daily. Although her symptom was improving rapidly and her thrombocytopenia was slightly improved, her neutropenia was not improved. Because she was complicated by bipolar disorder, we could not treated her with high dose of methylprednisolone (mPSL). She was treated with add on tacolimus, but her neutropenia was not improved. She was treated with intravenous gammaglobulin (IVIG). Her neutropenia was rapidly improved and her dosage of steroid could taper to a maintenance dosage without flare-up of disease activity and leukocytopenia. However mild neutropenia is common findings in SLE, only 5% of SLE patients reportedly have moderate to severe neutropenia (<1000 or <500 neutrophils, respectively). Usually, leukocytopenia in SLE can be successfully treated by only steroid. We consider that IVIG is one of the useful therapy for SLE who can't be treated with mPSL pulse therapy because of complications such as psychiatric disorder etc.

P1-159

A case of systemic lupus erythematosus complicated with bilateral ureteral stenoses

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Conflict of interest: None

A 61-year-old female was referred to our hospital with complaints of renal dysfunction (Cre 1.24 mg/dL). Laboratory tests showed increased CRP (3.14 mg/dl). Imaging tests revealed right hydronephrosis, left kidney atrophy and bilateral ureteral stenoses of unknown origin. Because her renal dysfunction got worse (Cre 1.63 mg/dL), ureteral stents were placed in bilateral ureters, resulting in the improvement of her renal func-

tion. She was diagnosed as having systemic lupus erythematosus (SLE) by photosensitivity, arthritis, lymphopenia and anti-cardiolipin antibody positivity. Prednisolone 30mg/day was started. Then, arthritis and CRP improved rapidly. Moreover, bilateral ureteral stenoses improved and we removed ureteral stents one by one. Persistent ureteral stenoses could lead to irreversible renal failure secondary to chronic hydronephrosis. Despite being rare, we should consider SLE as a differential diagnosis when a patient has ureteral stenosis, since immunosuppressive therapy could be effective as observed in our case.

P1-160

A patient with severe systemic lupus erythematosus : It was difficult to discriminate between steroid psychosis and central nervous system lupus

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Conflict of interest: Yes

[Case] A 16-year old man [Past history] none [Present illness] He was pointed out his proteinuria and hematuria at the medical examination. He also had high grade fever, arthralgia and erythema of cheeks since one month ago. So he was introduced and admitted to our hospital. [diagnosis] systemic lupus erythematosus [clinical courses] He had oral ulcers, blood disorders, renal involvement, antinuclear antibodies, immunologic phenomena, malar rash and alveolar hemorrhage. So he was diagnosed with systemic lupus eruthematosus. He was treated with steroid pulse therapy and 60mg of prednisolone. After treatment, he had sleeplessness, restless and loss of speech. He entered asylum and treated with antipsychotic agent. His disease activity was still high, and he was also diagnosed lupus colitis. So he was treated second steroid pulse therapy, four times of plasma exchange and two times of intravenous cyclophosphamide. After these therapies, his disease activity was decreased. His psychic symptoms were improved according to decrease of predonisolone. [consideration] This man had severe systemic lupus erythematosus. And it was difficult to discriminate between steroid psychosis and central nervous system lupus. We report this case with our considerations of literatures.

P1-161

A case of small lymphocytic lymphoma(SLL) that meet the diagnostic criteria for systemic lupus erythematous (SLE)

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Conflict of interest: None

A 78-year-old-woman was admitted to our hospital because of dyspnea on exertion (DOE). Abnormal shadows on her chest X-ray film pointed out 10 years ago. Three month before admission, she begun having DOE. Bilateral exudative pleural effusion was detected, she was referred to our hospital. The results of blood test on admission included ANA x5120 (H), ds-DNA Ab 235IU/ml, lymphopenia (510/μl), and hypocomplementemia (C3 69mg/dl, C4 6mg/dl), meeting the SLICC criteria (Petri M et al. Arthritis Rheum 64 (8):2677-2686, 2012). Whole body CT showed no abnormality except bilateral pleuritis and pulmonary infiltrations. Lung biopsy by VATS showed lymphocytes and plasma cells infiltrating to pleura, interlobular septa and bronchovascular bundles. These cells were CD5 (+), CD23 (+/-), CD79a (+), CD20 (+), CD10 (-), CD138 (+/-), Cycling D1 (-), and k/λ 4.2, indicating the diagnosis of SLL. Her symptom and pulmonary infiltration were ameliorated with 25mg of PSL. 【discussion】 Association of SLL and autoimmune diseases, especially with AIHA or ITP has been described (Kate Hodgson et al. hematological 2011; 96 (5)). As far as we could search, there have been 6 SLL (or CLL: chronic lymphocytic leukemia) cases with lupus including our patient, suggesting some common pathogenesis for both diseases.

P1-162

A case of systemic lupus erythematosus with intra-abdominal arteriorrhagia

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Conflict of interest: None

A 43 years old man had given PSL for systemic lupus erythematosus (SLE) from 12 years old, but stopped treatment by oneself from X-2 year. Facial edema and urine protein were pointed out by local doctor. Laboratory data showed leukopenia, positively antinuclear antibody and anti ds-DNA antibody. Following increased PSL, he developed choledocholithiasis and pancreatitis. Pancreatitis was relieved, whereas lupus enteritis and hydrothorax were developed. After steroid pulse therapy, he had given PSL 60mg. However these symptoms were not relieved, he treated with PSL 80mg intravenously. Thereafter, he developed melena and false aneurysms of gastroduodenal artery were detected by contrast enhanced CT. We carried out hemostasis by transcatheter arterial embolization (TAE), but pancreatitis was developed. Continuous regional arterial infusion and plasma exchange were started. Serological manifestations of SLE and hydrothorax retention were improved. Although 4 times of repetition of bleeding into gastrointestinal tract, we carried out hemostasis by TAE. Pancreatic pseudocyst was developed, and state of acute pancreatitis was relieved. He was making satisfactory progress to date. This was a rare case of SLE with intra-abdominal arteriorrhagia.

P1-163

A case of catastrophic antiphospholipid syndrome with systemic lupus erythematous developing persistent candidemia and CMV pneumonitis

Akira Jibatake, Tamao Nakashita, Yuto Hamada, Kotaro Matsumoto, Shinji Motojima
Kameda Medical Center

Conflict of interest: None

A case of catastrophic antiphospholipid syndrome with systemic lupus erythematous developing persistent candidemia and CMV pneumonitis Rheumatology and Allergy department, Kameda medical center ○Akira Jibatake, Tamao Nakashita, Yuto Hamada, Koutaro Matsumoto, Shinji Motojima Introduction:catastrophic antiphospholipid syndrome with systemic lupus erhthematous is only 1 percent of antiphospholipid syndrome which half of the cases are complicated with systemic lupus erythematous Case: the patients is a 45 years old femal who developed lupus nephritis when she was 14 years old. she received steroid and anticoagulant agent as she has NP-SLE and antiphospholipid syndrome. as her renal function deterioted, she was refered to our hospital and hospitalized with the congestive heart failure. with her new ischemic stroke and deep venous thrombolism, skin uclers, the catastrophic antiphospholipid syndrome was suspected. steroid and plasma exchange were begun but her persistent candidemia and CMV infection couldnt be controlled. at autopsy, new ischemic infartion of brain, spleen and kidney was found. Conclusion:CAPS can present with multiple embolism in a short term and a poor prognosis.

P1-164

The case of SLE onset following pr otein-losing enteropathy after the medical interruption

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Conflict of interest: None

[Case] 24 years old woman. She received abortion in pregnancy ten weeksA half year later, she presented anasarca, low proteinemia, and was diagnosed as protein-losing enteropathy (PLE) by Tc-99m albumin scintigraphy, but not as SLE. Furthermore, the becoming an intermittent fever, leukopenia, lymphopenia, anti dsDNA seroconversion, we had a diagnosis of SLE, and Lupus nephritis 4-S (A/C), a half year later. [Discussion] The pregnancy often causes the onset and flare up of SLE because of the immune and neuroendocrine changes.But the most is experienced after the 2nd pregnancy trimester, as the result of immunostimulation with the rising estrogen levels. We report the rare case that the medical interruption may have affected the PLE, SLE onset in early gestation.

P1-165

A case of longitudinally extensive transverse myelitis (LETM) associated with systemic lupus erythematosus (SLE) occurred soon after influenza type A virus infection

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Conflict of interest: None

【Case】A 32-years-old woman visited our hospital complaining a fever and a weakness in her legs. She had a 22-years history of SLE that included neuropsychiatric involvement. A test for influenza type A virus was positive and laninamivir was administrated. After a half day, she was admitted to the hospital due to development of paraplegia, sensory disturbance in a lower half of the trunk and lower extremities, and urinary retention. Magnetic resonance imaging showed high intense signal in the cervical to lumbar spinal cord on STIR. Cerebrospinal fluid analysis showed hypercellularity and high levels of protein and interleukin-6. Blood examination revealed increased level of anti-dsDNA antibody and decreased level of CH50. Anti-aquaporin 4 antibody was negative. She was diagnosed as having LETM associated with SLE, and treated with corticosteroids, plasma exchanges, intravenous immunoglobulin and cyclophosphamide. The motor and sensory function was recovered, but the bladder sphincter function remained impaired. 【Discussion】LETM, defined as myelitis affecting more than 3 spinal segments, is a rare but important complication of SLE that requires prompt diagnosis and treatment. In our case, influenza virus infection may affect the development of LETM.

P1-166

Efficacy of first-line disease modifying therapies in systemic sclerosis (SSc): experiences in a routine clinical setting

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Conflict of interest: None

Objective To evaluate the efficacy of first-line disease modifying therapies in SSc. ***Methods*** We enrolled 18 consecutive patients who were diagnosed as having SSc between 2011 and 2015 and received first-line disease modifying therapies. Modified Rodnan Total Skin Score (MRSS) and percent-predicted forced vital capacity (%FVC) were serially monitored. We also evaluated drug adherence rates, safety, and outcome. ***Results*** Eleven patients received cyclophosphamide followed by azathioprine (CY group), and 7 patients tocilizumab (TCZ group). The demographics showed TCZ group had more diffuse cutaneous SSc (dcSSc) and higher MRSS. CY was targeted to early dcSSc in 5 and to interstitial lung disease (ILD) in 7, and TCZ was targeted to early dcSSc in all. MRSS improved by more than 5 scores, a clinically meaningful change, in one of CY group and 4 of TCZ group, while worsened in one of each group. %FVC was stable in both groups. One year adherence rates were 100% and thereafter one in CY group and two in TCZ group discontinued the treatments. Although one patient developed bacterial pneumonia in each group, treatments were able to resume. ***Conclusion*** CY and TCZ as first-line disease modifying therapies were well-tolerated. Both treatments might inhibit progression of skin thickness and ILD.

P1-167

Tocilizumab for diffuse-cutaneous systemic sclerosis (dcSSc): report of the three cases

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Conflict of interest: None

[Background]The efficacy of tocilizumab (TCZ) to skin fibrosis, arthritis and interstitial lung disease due to systemic sclerosis has been reported recently. [Methods]Retrospective assessment of the clinical data of the 3 dcSSc patients treated with TCZ. [Results]Two of the 3 patients were female, and all patients showed positive anti-neutrophil antibody. The disease specific antibody was anti-RNA polymerase III/anti-Scl-70/not detected, and the disease duration form the onset of Raynaud's phenomenon was 1/10/4 years, respectively. In the former 2 cases, oligoarthritis were noted, and their arthritis improved to remission after TCZ initiation. The last case had polyarthritis and her CDAI was 23.7 before TCZ, which improved to 7.6 at week 12 and 1 at week 24. Their modified Rodnan Skin Score at baseline/week 12/week 24 were 17/16/16, 46/46/NA, 12/11/8, and serum CRP level were 0.3/0.3/0.3, 0.5/0.3/NA, 1.5/0.3/0.3, respectively. All patients had interstitial lung disease at the baseline, although their pulmonary function test and chest CT did not change significantly. No significant adverse events were noted. [Conclusion]TCZ was effective for arthritis of dcSSc with CRP elevation. The effect to skin manifestation was minimal, which may be due to long disease duration.

P1-168

Pursuit of better timing for the treatment of interstitial lung disease (ILD) associated with systemic sclerosis (SSc)

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Conflict of interest: None

[Objective] Interstitial lung disease (ILD) is an important organ involvement strongly associated with morbidity and mortality in SSc. Although cyclophosphamide is with proven efficacy, the optimal timing for starting treatment is still unclear. The purpose of this study is to elucidate the better timing for the treatment of patients with SSc-ILD, considering the extent of ILD. [Method] Twenty patients with SSc-ILD treated with immunosuppressive agents from 2003 to 2015 were involved, and stratified as extensive (ED) or limited disease (LD) based on the disease extent over 20% or less using CT scan, respectively. Short-term response was evaluated by the difference of %FVC before and after the treatment. Results of pulmonary function test and other clinical parameters were retrospectively collected from medical record, and compared between the groups. [Result] Eleven patients were stratified as ED and 9 as LD. Improvement of %FVC was significant in LD than ED (6.77±5.76 vs -1.34±7.64 %, p=0.04). Baseline %FVC was higher (87.4±13.0 vs 67.7±17.2%, p=0.02) and disease duration was shorter in LD (10.6±21.9 vs 41.3±34.9 months, p=0.01). [Conclusion] Earlier intervention for SSc-ILD might lead to better clinical response for the treatment and to achieve better prognosis.

P1-169

Successful treatment of medium-sized vasculitis complicating in systemic sclerosis utilizing immunosuppressive agent: two cases report

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Conflict of interest: None

[case 1] A 77-year-old woman had Raynaud phenomenon and finger swelling since January 2015. For interstitial pneumonia and a digital ulcer, prednisolone (PSL) 20mg was started. She had anti-centromere antibody positivity, and diagnosed as limited cutaneous systemic sclerosis (lcSSc). CT angiography (CTA) showed bilateral ulnar artery narrowing and occlusion without collateral circulation. Treatment with PSL 30mg and intravenous cyclophosphamide (IVCY) resulted in an improvement of both signs, symptoms and ulnar blood flow detected by CTA. [case 2] A 71-year-old woman had sclerodactyly and anti-centromere antibody positive since 2014. Diffuse cutaneous SSc was diagnosed. Because of a skin ulcer developed at the right toe, she admitted to our hospital. MR angiography revealed the occlusion of an anterior tibial artery, fibular artery and posterior tibial artery without collateral circulation. The occluded posterior tibial artery was reopened and the skin temperature rose using combination treatment of PSL 45mg and IVCY. [clinical significance] The SSc related medium-sized vasculitis in response to immunosuppressive therapy is rare in literatures, but an important complication.

P1-170

Efficacy of combination therapy of prednisolone(PSL) and tacrolimus(TAC) for systemic sclerosis with progressive interstitial pneumonitis

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Conflict of interest: None

[Objectives] To evaluate the efficacy of combination therapy of PSL and TAC for systemic sclerosis with progressive interstitial pneumonitis (SSc-IP). [Methods] Out of 157 patients with SSc-IP in our hospital between 2002 and 2014, we retrospectively analyzed 11 patients with progressive SSc-IP treated with combination therapy of PSL and TAC. [Results] The median age was 59 (42-77). 10 patients were female, and 7 patients dc-SSc. Anti-Scl-70 antibody was positive in 7 patients, anti-RNP antibody was positive in 1, and all patients were negative for anti-centoromere antibody. At the starting of the treatment, KL-6 was 909 (305-3,206) U/ml, Hugh-Jones classificationI/II/III/IV were 2/6/2/1 cases, respectively. SpO_2(room air) 97 (95-98)%, %FVC 82.9 (55.2-110.1)%, and %DLCO 47.4 (9.7-64.4)%. The initial dose of PSL was 15 (0-45)mg/day. The dose of TAC was 2.5 (1.0-8.0)mg/day with blood concentration of 7.95 (2.3-13.6)ng/ml. One year after the treatment, respiratory symptoms were improved in 3 patents, and had no changes in 8. The adverse events were 1 case of cytomegaloviral infection, 2 cases of renal disorder, 2 cases of impaired glucose tolerance. [Conclusion]These results suggest combination therapy of PSL and TAC for progressive SSc-IP was effective and well tolerated.

P1-171

Effective Immunosuppressive therapy in severe pulmonary hypertension with systemic sclerosis: two case reports

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Conflict of interest: None

Pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc) is extremely critical and little effective therapy has been reported until now. In contrast, some cases of PAH with systemic lupus erythematosus (SLE) or other connective tissue disease (CTD) response to the immunosuppressive therapy. We report two cases of pulmonary hypertension (PH) associated with overlap syndrome of SSc and the other CTD received the effective immunosuppressive therapy. <case1>A 61-year-old woman with sclerodactylia for thirty years was diagnosed with PAH overlapped with SSc and SLE last year. Vasodilators were not effective, but corticosteroid (CS) and cyclophosphamide (CY) improved pulmonary arterial pressure (PAP). Steroid psychosis prevented her from continuing the treatment, and she died 4 month later. <case2> A 72-year-old woman complaining of dyspnea on exertion over seven years diagnosed with idiopathic PAH three years ago, but vasodilators were not effective. She was diagnosed with SSc and Sjogren's syndrome two years ago and additional therapy of CS and intravenous CY improved PAP. She died from deteriorating right cardiac failure about two years later. In conclusion, Immunosuppressive therapy might be effective for PH associated with SSc if any other CTD overlapped.

P1-172

Efficacy and safety of bosentan for refractory digital ulcers related to systemic sclerosis

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Conflict of interest: None

[Objectives]The aims of our study were to evaluate the efficacy and safety of bosentan on digital ulcers (DU). [Methods] A retrospective single center study was performed in 10 patients with severe DU who were treated with bosentan,from August 2008 to August 2015. [Results]The study included 10 patients (mean age 56.2 years, 8 female, 2 male, 9 diffuse cutaneous SSc, mean disease duration 10.5 years). The mean duration from the diagnosis of SSc or MCTD to the start of bosentan was 7.9 years. Mean final dose of bosentan was 125 mg. 6 patients were complicated with pulumonary fibrosis. 6 patients treated with oral corticosteroid. 2 patients combined with oral cyclophosphamide and 1 patient combined with azathioprine. 1 patient, bosentan was discontinued because of pancytopenia. In 6 patients,multiple DU healed by the treatment of bosentan. In 3 patiants, the pain decreased and no new lesion bone developed. [Conclusion]These results suggest that bosentan is an effective and safe treatment for refractory DU related to SSc or MCTD.

P1-173

Treatment for refractory Raynaud's syndrome lead to finger necrosis

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Conflict of interest: None

Raynaud's phenomenon is a major symptom of rheumatic diseases such as scleroderma and SLE. We treat this symptom with Guidance avoiding the cold and non smoking, and with vasodilators such as Ca channel antagonists, α1 blockers and so on. However, in severe cases, fingers and toes may lead to necrosis despite these treatments. We perform surgical treatment for for pain relief and preservation of fingers and toes in these case. We report several cases with some considerations.

P1-174

Hemodynamics in connective tissue diseases patients with borderline pulmonary pressure: comparison with those with normal pulmonary pressure

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Conflict of interest: None

[Object] Borderline mPAP is not well characterized. We retrospectively studied 14 CTD patients with borderline mPAP and 23 with normal mPAP who was suspected to have PH. [Methods] They performed exercise echocardiography and right heart catheterization. [Result] SSc (9/16 patients), SLE (2/1), MCTD (2/2), systemic vasculitis (1/0) were included in CTD patients with borderline mPAP/normal mPAP. Mean age (SD) was 60.6 (16.0) / 59.0 (19.1). TRPG (SD) was higher in patients with borderline mPAP [33.5 (6.4) mmHg] than normal mPAP [29.2 (6.0) mmHg](P = 0.0656). Higher value of pulmonary vascular resistance

(PVR) was observed in patients with borderline mPAP compared with those with normal mPAP (P = 0.0098). Value of PAWP was higher in patients with borderline mPAP [12 (3.5) mmHg] than those with normal mPAP [7 (2.8) mmHg](P <0.0001). Negative correlation of PAWP and PVR was observed among borderline mPAP patients (r^2 = 0.78, P <0.0001) suggesting post-capillary as well as pre-capillary disease were included in this patient population. [Conclusion] Borderline mPAP was considered to be a phase of transition from normal hemodynamic condition to PH. Introduction of pulmonary vasodilators, without an appropriate devaluation, should be avoided in this patient population.

P1-175

Analysis of clinical features in systemic sclerosis sine scleroderma with renal crisis

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Conflict of interest: None

Systemic sclerosis sine scleroderma (ssSSc) is characterized by severe organ involvements with fibrosis, but there are absence of the characteristic skin symptoms. Therefore, early diagnosis and treatment is very difficult. Here, we investigated clinical findings of ssSSc with hypertension scleroderma renal crisis. 6 patients with hypertension scleroderma renal crisis (0 male and 6 female) were admitted to our hospital after 1990. Among 6 SSC patients, 2 cases were ssSSC with renal crisis. It showed Raynaud's phenomenon in one case. Anti-nuclear antibody and anti-centromere antibody were positive, and anti-scl-70 antibody and MPO-ANCA were negative in both cases. The anti-RNA polymerase III antibody was positive in one case. Though this case got good pressure control with Ca antagonists and ACE inhibitor, renal function had progressed end-stage renal disease. This case didn't have a risk factor of hypertension scleroderma renal crisis, which were diffuse cutaneous sclerosis and rapidly progressive cutaneous sclerosis. These results indicated that it is important to measure the anti-RNA polymerase III antibody in hypertension with Raynaud's phenomenon cases, and we should consider the possibility of a sine scleroderma.

P1-176

Left heart disease as common manifestation in systemic sclerosis with pulmonary hypertension

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Conflict of interest: None

[Objective] We investigated the frequency of left heart disease (LHD) in SSc carrying pulmonary hypertension (PH). [Patients] We analyzed 37 SSc patients who underwent right heart cathetelization from 2006 to 2011. Potential LHD were evaluated by electrocardiography, echocardiography, scintigraphy, and MRI among PH patients with PAWP >15mmHg or PVR <3 Wood units (WU). [Results] Of the 37 patients (12 diffuse), 14 had PH (4 PAH / 10 PVH including 2 combined PAH /PVH). The 10 PVH patients had PAWP >15mmHg (n = 5) or PVR <3 WU (n = 5). All of the 5 patients with PVR <3 WU had PAWP <15mmHg. The PVH patients had autoantibodies to centromere (n = 2), Scl-70 (n = 3), RNAP III (n = 1), RNP (n = 2), SSA (n = 2). 9/10 had at least one abnormality associated with LHD by electrocardiography (n = 7), echocardiography (n = 6), scintigraphy (n = 1), or MRI (n = 1). Electrocardiography findings included left ventricular hypertrophy (n = 3), LA overload (n = 4), and negative T in V5/V6 (n = 1). Left diastolic dysfunction was suspected by echocardiography in 6 patients [LAVI >25 (n = 4), E/E' >15 (n = 2), LA diameter >4cm (n = 5)]. [Conclusion] More than 2/3 of the SSc-PH patients had LHD. The method to evaluate the impact of this abnormality on pulmonary arterial pressure needs to be established.

P1-177

Radiographic findings in hand X-ray in patients with systemic sclerosis

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Conflict of interest: None

[Purpose] To elucidate the characteristic findings of hand X-ray in patients with systemic sclerosis (SSc). [Methods] Forty-four patients with SSc and without rheumatoid arthritis were included in the study. Two directional hand X-ray was used to evaluate articular changes. We retrospectively collected clinical parameters from medical records, and association between the X-ray findings and clinical features was examined by Pearson's chi-square test. [Results] 44 patients (17 dcSSc and 27 lcSSc) were included. Mean age was 67.4 ± 36.4 years, 82% were female and the disease duration was 15.3 ± 21.7 years. In X-ray findings, acroosteolysis (29%) and erosive hand osteoarthritis (EHOA) (13%) was observed. EHOA changes was observed more frequently in lcSSc than dcSSc (22% versus 0%, p=0.036). In contrast, acroosteolysis tended to be more common in dcSSc than lcSSc. While EHOA changes were associated with digital tip ulcer, acroosteolysis was with digital pitting scar. [Conclusion] Characteristics of X-ray findings in patients with SSc were acroosteolysis and EHOA changes. These findings associate with types and clinical characteristics of SSc. These findings suggest that difference of the findings might reflect the pathogenesis of each patient with SSc.

P1-178

Clinical features of limited cutaneous systemic scleroderma with anti-centromere antibody

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Conflict of interest: None

[Objectives] Our goal was to study the prevalence of organ damages of lcSSc with anti-centromere antibody. [METHODS] 52 lcSSc patients who had hospitalized in our outpatient clinic from 2012 to 2015 were enrolled. We assess the correlation between the clinical characteristics and data. [RESULTS] Female were 48 (92.3%). Mean age was 67.4 years old. Clinical characteristics; Incidence of Raynaud phenomenon and sclerodactylia were 84.6 and 100.0%. Organ damages; interstitial pneumonia, pulmonary hypertension, PBC, Sjogren syndrome, Hashimoto's disease, CKD were 23.1, 25.0, 50.0, 13.5, 20.0 and 42.3%, respectively. Laboratory data; BNP was 81.7±17.3 pg/mL, KL-6 was 271.0±30.9 U/mL, Cr was 0.72±0.04 mg/dl. Incidence of antibodys; anti-SS-A Ab was 53.8%, anti-SS-BAb was 9.6%, anti-TPOAb was 18.2%, anti-TG Ab was 7.3%, M2 Ab was 34.7%, anti-dsDNA Ab was 8.0%, CCPAb was 5.0%, and anti-RNPAb was 9.8%. BNP as a biomarker for pulmonary hypertension had correlation to age, DBP, Alb, Ca, FT3, duration from onset. [CONCLUSIONS] The results of our study suggested that the prognosis of pulmonary hypertension could be associated with the prognosis of interstitial pneumonia and malabsorption, and this entity might include multiple autoimmune diseases.

P1-179

HLA-DQB1 **Alleles Associated with Anti-Centromere Antibody-Positive Systemic Sclerosis in Japanese: A Predisposing Role for **03:02*** **and **05:01*** **and a Protective Role for **03:01***

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Conflict of interest: Yes

Background: Several studies on associations between human leukocyte antigen (HLA) allele frequencies and susceptibility to systemic sclerosis (SSc) have been reported. Anti-centromere antibodies (ACA) and anti-topoisomerase antibodies (ATA) are found in SSc patients. Interstitial lung disease (ILD) is also frequent in SSc. Here, we sought to identify *HLA* alleles predisposing to SSc in Japanese, and explored their associations with SSc phenotypes including the presence of autoantibodies and ILD. *Methods:* Associations of HLA class II alleles in Japanese SSc patients were analyzed. *Results: DRB1*10:01* was associated with SSc (*P*=0.0009, *Pc*=0.0245, odds ratio [OR] 29.72, 95% confidence interval [CI] 1.66-531.38). There was a significant association between *DQB1*03:02* and *DQB1*05:01* and susceptibility to SSc with ACA (*P*=0.0011, *Pc*=0.0157, OR 2.56, 95%CI 1.47-4.45, and *P*=0.0014, *Pc*=0.0191, OR 3.19, 95%CI 1.61-6.33, respectively). The presence of *DQB1*03:01* was negatively associated with SSc with ACA (*P*=0.0004, *Pc*=0.0061, OR 0.20, 95%CI 0.07-0.57). An association with susceptibility to ILD in SSc was found for the DR6 serological group (*P*=0.0074, OR 3.25, 95%CI 1.36-7.73). *Conclusion:* This study identified both positive and negative associations of *HLA* class II alleles with Japanese SSc.

P1-180

Clinical features of systemic sclerosis (SSc) with Japanese patients

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Conflict of interest: None

[Objective] To investigate the clinical features of SSc in Japanese patients. [Methods] We studied patients with SSc who visited our clinic between January and April 2014. Clinical and laboratory data were collected from their medical records. [Results] A total of 351 patients with 328 females (93.4%) and 23 males (6.6%) were enrolled. Among these patients, 135 patients (38.5%) had diffuse cutaneous type (dc SSc) and 208 patients (55.8%) had limited cutaneous type (lc SSc). Interstitial lung disease (ILD) was present in 59% and 26%, pulmonary hypertension (PH) was present in 9% and 7%, and scleroderma renal crisis (SRC) was present in 6% and 3% of dc SSc and lc SSc patients, respectively. Digital ulcer (DU), ILD, gastrointestinal (GI) involvement and arthritis were higher in dc SSc patients. The frequency of anti-Scl-70 antibody (Ab) and anti-RNA polymeraseIII(RNAPIII) Ab were higher in dc SSc patients. In contrast, the frequency of anticentromere Ab (ACA) was higher in lc SSc patients. ILD was present in 75% of anti-Scl-70 Ab positive patients. SRC was higher in anti- RNAPIII Ab positive patients. [Conclusion] To classify into disease subsets and to measure autoantibodies may be useful to predict clinical features.

P1-181

A case of anti-RNA polymerase III antibody positive scleroderma that was complicated with a thymic carcinoma

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Conflict of interest: None

The case is a 61 years old woman. She was aware of Raynaud's phenomenon without the medical history that should mention specially than before. An anterior mediastinum tumor was detected with hemolytic anemia, thrombocytopenia, and acute renal failure. Detailed analysis of the ANA showed significant increase in anti-RNA polymerase III antibody, and it was recognized that a series of clinical condition was the TMA secondary to the scleroderma renal crisis. After diagnosis, we added ARB to a calcium channel blocker, and performed three times of plasmapheresis. The blood test findings are improved. After surgery of thymic carcinoma resection, symptoms and antibody titer decreased.Here, we report a case of scleroderma following thymic carcinoma with anti-RNA polymerase III antibody.

P1-182

A case report of systemic sclerosis complicated with pure red cell anemia

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Conflict of interest: None

Objective: Reasons of Secondary pure red cell anemia are variable such as tumor, infection and autoimmune disease. We experienced a case of systemic sclerosis (SSC) complicated with pure red cell anemia (PRCA) which is difficult to differentiate diagnosis and improve. Present illness: 61 years old lady who was diagnosed of SSC complicated with interstitial pneumonitis and pulmonary hypertension. She visited hospital because was getting worse of fatigue and dyspnea, and admitted hospital emergency in 30th July in 2015. Progress after admission: Leukocyte and thrombocyte count were normal but erythrocyte and reticulocyte decreased and hemoglobin was 5.7g/dl. Digestive bleeding was a negative decision and enforcement of bone marrow puncture suggested PRCA. We stopped doubtful drugs, administered ganciclovir therapy because cytomegalovirus DNA was positive and increased quantity of steroid combined with cyclosporine. Therapy effect was not definite. We continue admission therapy continuing blood transfusion when necessary. Consideration: The case of SSC complicated with pure PRCA is a rare occurrence. We will report continuance progression, and report with literature about relationship with autoimmune disease and the method of the differential diagnosis.

P1-183

A case of overlap syndrome(Systemic sclerosis and systemic lupus erythematosus) with progressive gangrene of fingers

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Conflict of interest: None

A case of overlap syndrome (Systemic sclerosis and systemic lupus erythematosus) with progressive digital gangrene A 58-year-old female presented with progressive digital gangrene. Her sister died of systemic lupus erythematosus (SLE), and her brother is suspected of Systemic sclerosis (Scc). She noticed contracture of her fingers a year before, her fingers hurt two months before, and they got gangrene a month before. Her blood test showed ANA ×2560 anti-Scl70 antibody 176.5U/ml anatidsDNA antibody 57U/ml antiSSA antibody1200< anti-SSBantibody290<. She was diagnosed as Scc. We treated with PGE1, anti thrombin drug, PDE5 inhibitor, and Ca blocker, but not only the gegrine didn't get better,

but also she had pericardial and pleural effusion and ascites.We thought she also has SLE, and treated with steroid, tacrolimus, and IVCY. During the medication she had severe pneumonia,and her right sum got gangrene in several days.Soon after that the progression of digital gangrene stopped and effusion also disappeared. She was discharged from hospital after 108days. Her gogrene fingers droped out by themselves in a year after she left hospital.

P1-184

A case of the scleroderma which was diagnosed with pneumatosis cystoides intestinalis and chronic intestinal pseudo-obstruction, and got remission

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Conflict of interest: None

Case; A 49-year-old woman with several months history of nausea, vomiting and abdominal distention developed watery diarrhea, which resulted in her weight loss. Because of ascites on echography she was referred to our department. X-rays and CT scan showed abdominal free air, pneumatosis and ileus without mechanical obstruction in intestines, which suggested chronic intestinal pseudo-obstruction (CIPO) with pneumatosis cystoides intestinalis (PCI). She also had Raynaud's phenomenon, puffy fingers and abnormal nailfold capillaries. Skin biopsy showed accumulation of collagen fibers. We diagnosed the secondary CIPO following systemic sclerosis (SSc). With fasting therapy using total parenteral nutrition her symptoms resolved for three months, whereas they recurred and intestinal dilatation deteriorated several months later. After treatment with metronidazole, her abdominal symptoms improved and intestinal dilatation disappeared. With weight gain she has remained asymptomatic. Conclusion; Most of clinical aspects in CIPO is unproven. Although about 16 % of the cases in CIPO is reported to be followed by the SSc, the treatment of the CIPO itself is not established. In this case we report that we diagnosed the SSc with PCI and CIPO, and succeeded in remission.

P1-185

The outcome of 95 patients with vasculitis syndrome

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Conflict of interest: None

[Objectives] We assessed the outcome of 95 patients with vasculitis syndrome.[Methods] We retrospectively analyzed 43 patients with Microscopic Polyangiitis (MPA), 7 with Granulomatosis with Polyangiitis (GPA), 20 with Eosinophilic Granulomatosis with Polyangiitis (EGPA), 4 with Polyarteritis Nodosa (PN), 11 with Rheumatoid Vasculitis (RV), 7 with Giant Cell Arteritis (GCA) and 3 with Takayasu's Arteritis, who were diagnosed at this hospital, from 2004 to 2015. [Results] The mean age of all patients was 67.0 years old. The median follow-up was 53 months. At the end of observation period, all patients keep vasculitis in remission. Total mortality of vasculitis syndrome was 22.1%, and the one of MPA was 30.2%. 51.6% of patients with vasculitis syndrome, and 65.1% of MPA, quitted attending to this hospital as outpatients due to ADL decline or death.[Conclusion] More than half of the patients with vasculitis syndrome quitted attending to this hospital as outpatients at this hospital. We considered their advanced age onset, sequelae of Vasculitis and adverse reaction of immunosuppressant as the reason.

P1-186

Muscle biopsy in small vasculitis

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Conflict of interest: None

【OBJECTIVE】For the purpose of proving the usefullness of muscle biopsy in small vasculitis syndrome. 【METHODS】We picked up the cases from data base of all our inpatients from April 2014 to October 2015. We analyzed their clinical information including results of biopsy. 【RESULTS】In this term, we treated 19 new patients with small vasculitis (final diagnosis:13 microscopic polyangitis;MPA, 3 GPA, and 3 EGPA). 17 cases were performed biopsies and 9 of them were biopsied thier muscles (1 teres minor and 8 gastrocnemius). All 9 cases had positve MPO-ANCA and had not any major organ disease nor surrogate marker. 6 cases had histopathological findings of vasculitis but the other 3, who were diagnosed clinically as MPA. All cases recovered without any complications of biopsy. 【DISCUSSION】We couldn't established relationship between the focal manifestations and the pathological findings. As a gastrocnemial biopsy is less-invasive, it may be more valuable in a case with positive MPO-ANCA for the diagnosis without specific manifestations of ANCA associated vasculitis. We'll intend to investigate more cases and consider a difference from biopsy proven cases and clinically diagnosed. 【CONCLUSION】We report our investigation of small vasculitis performed biopsies in our hospital.

P1-187

Analysis of clinical features in elderly patients with ANCA-associated vasculitis: 30 years single center experience

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Conflict of interest: None

【Object】 ANCA-associated vasculitis (AAV) is found in elderly patients commonly, but theclinical features are not well examined. Thus, we retrospectively analyzed the clinical database of the113 patients with AAV who were admitted to our hospital at age ≧70years for the last 30 years. 【Methods】We divided the AAV patients into 3 groups according to the periods, which were PeriodI: 1984-1993, PeriodII: 1994-2003 and PeriodIII:2004-2013, and compared the clinical features among them. 【Results】 Comparison among different periods show an increasing tendency of age of onset, and a downward trend of BVAS scores, serum Cr concentrations, rate of RPGN, and frequency of relapses and mortality. Almost all patients used glucocorticoids for remission induction, but immunosuppressive therapy were used in 0% periodI, 11% periodII and 28% periodIII. At the relapse, glucocorticoids therapy alone was 70%. Recently, immunosuppressive therapy was used in 60% and Rituximab was used in 10 % after relapse. 【Conclusion】These results showed that AAV is good tend among elderly patients recently. But, we should evaluate the efficacy and safety of treatment.

P1-188

Clinical study on ANCA -associated vasculitis(AAV)

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Conflict of interest: None

【Objective】 We examined the clinical features, the relationship between detection of anti-neutrophil cytoplasmic antibodies (ANCA) and organ damages in AAV. 【Subjects and methods】 We retrospectively examined 62 patients who were admitted at our hospital during 2009-2015 for microscopic polyangitis (MPA), granulomatosis with polyangitis (GPA), or eosinophilic granulomatosis with polyangitis (EGPA). 【Results】 ANCA was positive in all MPA patients; in 9 of 10 GPA patients (1 unknown); and in 8 of 15 EGPA patients. Among EGPA patients, there was a higher tendency to develop pulmonary lesions in those who were ANCA-positive compared with those who were ANCA-negative (63% vs. 14%, respectively). The 5-year survival rates of patients with GPA, EGPA, and MPA were 100%, 88.9%, and 76.5%, respectively. Pulmonary lesions were seen in 7 of 9 patients who died; the cause of death in 8 patients was lung-related infection. 【Discussion and conclusion】 In

EGPA, pulmonary lesions were seen more often in ANCA-positive patients than in ANCA-negative patients.Furthermore pulmonary lesions may vitally affect prognosis through infectious complications.

P1-189

Evaluation of remission criteria in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in RemIT-JAV-RPGN, a nationwide, prospective, inception cohort study

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Conflict of interest: None

[Objective] To evaluate remission criteria using the Birmingham Vasculitis Activity Score (BVAS) in patients with AAV registered in remission induction therapy in Japanese patients with AAV and rapidly progressive glomerulonephritis (RemIT-JAV-RPGN) [Methods] Of 321 patients (28 with EGPA, 53 with GPA, 198 with MPA/RLV, and 42 who were unclassifiable) registered in RemIT-JAV-RPGN, 319 patients with follow-up data were included in this study. We analyzed remission, survival, and renal survival rates for 6 months and identified organs with active disease at 6 month in patients who did not achieve remission. We defined remission as BVAS of 0 on two occasions at least 1 month apart. [Results] By 6 months, 260 patients (82%) achieved remission. Of 15 deaths (14 MPA and 1 GPA) (4.7%), causes of death were vasculitis itself (n=3), infection (n=7), and others (n=5). Twenty nine (9.1%) ESRDs developed (25 MPA, 2 GPA, and 2 unclassifiable). In 29 patients who did not achieve remission and were followed up for 6 months, new or worse symptoms of BVAS were reported for renal (n=18, 62%), neurological (n=4, 14%), respiratory (n=3, 10%), cardiovascular (n=2, 7%), and ENT symptoms (n=1, 4%). [Conclusion] Activity of vasculitis in kidney may be difficult to evaluate in current BVAS system.

P1-190

The clinical features and prognosis in patients with ANCA-assoicated vasculitis

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Conflict of interest: None

[Object] The treatment of ANCA-associated vasculitis (AAV) has been changing since the rituximab (RTX) became available. This study was conducted to investigate the clinical features and the prognosis of the AAV patients. [Methods] The AAV patient's data from January 2002 through March 2015 were analyzed retrospectively. [Result] Twenty-five patients had microscopic polyangitis (MPA), 15 patients had granulomatosis with polyangitis (GPA) and 6 patients had eosinophilic granulomatosis with polyangitis (EGPA). Patients with GPA were scattered in a range of about 8 years younger populations than the patients with MPA. Five of 15 GPA patients were treated with rituximab. There were more refractory or relapsing cases in GPA which needed RTX treatment than MPA. Recently, the Otitis Media with ANCA associated vasculitis (OMAAV), the subtype of GPA, has been increased. The OMAAV are characterized to have symptoms limited to upper airway lesions, and 4 OMAAV patients among GPA cases were also identified in this study. All of them were MPO-ANCA weak-positive or both MPO-ANCA and PR3-ANCA negative. [Conclusion] It is suggested that the treatment of MPA with RTX should be considered carefully and that the establishment of therapies for limited types of GPA are necessary in the future.

P1-191

Analysis of anti-myeloperoxidase antibody-positive patients

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Conflict of interest: None

[Objective] To analyze the symptoms, treatments and prognoses of anti-myeloperoxidase antibody (MPO-ANCA)-positive patients. [Method] We retrospectively analyzed 20 patients who had been measured MPO-ANCA more than two times and had one or more positive results from 2000 to September 2015. [Results] Twenty MPO-ANCA-positive patients (MPO-ANCA$^+$) included eight microscopic polyangiitis (MPA), two systemic lupus erythematosus (SLE), and ten MPO-ANCA$^+$ who were not diagnosed as MPA nor SLE but suspected as ANCA-associated vasculitis (AAV). Most common symptom was pyrexia (63% of MPA, 0% of SLE, and 60% of AAV). Anti-double strand DNA antibody were frequently detected (three out of four MPA, two out of two SLE, and two out of six AAV). Nineteen patients received glucocorticoid therapy. High-dose intravenous methylpredonisolone were administered to one MPA and one AAV. The doses of predonisolone of each group were not statistically different (28.6 mg/day of MPA, 38.5 mg/day of SLE, and 34.8 md/day of AAV). The death rates were not statistically different (50% of MPA, 0% of SLE, and 10% of AAV). [Conclusion] Half of MPO-ANCA+ were diagnosed as AAV. Almost all MPO-ANCA$^+$ received glucocorticoid therapy. The death rate of MPA may be higher than that of AVV.

P1-192

Study of prognosis of microscopic polyangiitis in our hospital

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Conflict of interest: None

<Objective>Prognosis of MPA considered to be improved by advance of treatment, so we examined prognosis of MPA.<Method>We extracted 34 patients of MPA who are first hospitalization treatment that diagnosis in our hospital from 2005 to 2015. We used MPA diagnostic criteria of Japan, and diagnosed 25 pt as definite, 9 patients as probable. No patient diagnosed as probable patients changed diagnosis during the course. 34 patients were investigated and analyzed.<Result>Of the 34 patients, 25 were diagnosed as definite and 9 as probable. 24 were female. average of age at diagnosis of MPA was 68.8. Of the 34 patients, 18 patients were mild, and 16 patients were severe. 5 patients died and the average of survival was 36 month. Their cause of death were infection in 3 patients, and organ dysfunction in a patients. There was no difference in average dose of steroid that was 0.8 mg/kg with severe and mild. Usage rate of cyclophosphamide was 69% and 39%, inclined to be more of severe. <Conclusion>Our results demonstrated that early mortality was decreased, there is possibility that combination therapy of immunosuppressive agents in early stage have improved the prognosis. But there is no change in the long term, so we need further measures against the merger of infection.

P1-193

Clinical features of MPO-ANCA associated vasculitis with glomerulonephritis in Kochi Medical School

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Conflict of interest: None

[Objectives] Our goal is to assess the clinical features of MPO-ANCA associated vasculitis with glomerulonephritis in Kochi Prefecture. [METHODS] 13 patients with MPO-ANCA associated vasculitis who had been admitted to our hospital and undergone renal biopsy from 2008 to 2014 were enrolled. We assess the correlation among clinical characteristics, laboratory data, and pathohistological findings. [RESULTS] Female were 7 (53.8%). Mean age was 73.8 years old. According to Watt's algorism, EGPA, GPA and MPA patients were 3 (23.1%), 3 (23.1%), and 7 (53.8%), respectively. Pathohistological classification of renal biopsy were as follows; sclerotic (7.2%), focal (69.2%), crescentic (15.4%), and mixed (7.2%). Laboratory data on admission showed that average values were as follows; Cr 2.1 ±0.4mg/dL, CRP 7.4±1.7 mg/dL, MPO-ANCA 202.7±74.3 IU/mL and proteinuria 1094.9±213.4 mg/gCr. Intensive therapies included mPSL pulse therapy (76.9%), IVCY (30.8%) and IVIG (15.4%), following oral PSL. [CONCLUSIONS] Our date suggests that patients might be elder than previous reports. Patients who received renal biopsy might have mild and early histological changes. We considered that physicians should take into account the effect of infection and disease activitiy to duration of hospitalization.

P1-194

Clinical and histological predictors of renal outcome and life prognosis in ANCA-associated vasculitis

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Conflict of interest: None

ANCA-associated vasculitis (AAV) sometimes progresses rapidly and is life-threatening. Therefore it is required to diagnose and treat quickly. Therapeutic strategy is determined on the basis of clinical severity score, which is provided by age, the serum creatinine level, disease feature such as renal-limited or systemic vasculitis, and the value of CRP. The characteristics of Japanese AAV patients are that the elderly are affected predominantly, and MPO-ANCA-associated vasculitis and microscopic polyangiitis (MPA) are common. The elderly patients with decreased residual organ function have poor prognoses, and have greater risk of adverse effect and treatment-related death. Prognosis is a particularly important when the disease is aggressive, and effective but potentially toxic immunosuppressive treatment has to be performed. The aim of the present retrospective study is to characterize prognostic subgroup in order to identify clinical, histological and therapeutic factors that could represent prognostic factors. Therefore, we investigated the histological and clinical severity of 23 patients underwent renal biopsy, which are consisted of 20 MPA (10 systemic, 10 renal-limited) and 3 granulomatosis with polyangiitis (GPA). Here we report their renal-outcome and life prognosis.

P1-195

Oxidative modification of myeloperoxidase in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides

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Conflict of interest: None

[Objectives] Alteration of post-translational modifications of myeloperoxidase (MPO) was examined in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. [Methods] Proteins were extracted from peripheral blood polymorphonuclear cells (PMN) obtained from 5 MPO-ANCA-positive patients with ANCA-associated vasculitides and 5 healthy donors. MPO was detected by 2-dimensional western blot (2D-WB). [Results] Heavy and light chains of MPO from healthy donors were detected respectively as multiple protein spots. The proportion of heavy chain spots that showed higher isoelectric points (pI) and heavier molecular weights than its theoretical values (p*I* 9.4, 53kDa) was higher in the MPO-ANCA-positive group than in the healthy group ($p<0.01$). Treatment of healthy donor-derived PMN proteins with reactive oxygen species (ROS) provided similar 2D-WB results to those of the MPO-ANCA-positive group and increased kynurenine and hydroxykynurenine formation. In 1D-WB results, dityrosine bands indicating oxidative modification were detected in PMN proteins from MPO-ANCA-positive patients and ROS-treated ones from healthy donors. [Conclusion] MPO was oxidatively modified in MPO-ANCA-positive patients. This modification may participate in the production of MPO-ANCA.

P1-196

Clinical features of eight patients with Eosinophilic granulomatous with polyangitis in our hospital

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Conflict of interest: None

We assessed clinical features of eight patients with eosinophilic granulomatous with polyangitis between 2009 and 2015. They consisted of five males and three females, median age at diagnosis was 67-year-old, and five were diagnosed with definite and the rest were probable on the basis of EGPA criteria. They had leg pain and numbness, eruption, abdominal pain and diarrhea at initial visit and main affected organs were nerve, gastrointestinal tract and skin. At diagnosis median eosinophil counts was 10657/μl, median IgE was 1273U/ml, and MPO-ANCA positive was only two. Some of them had elevated LDH, sIL2R and TM. We underwent biopsy from gastrointestinal tract, skin and nerve and got following biopsy findings; necrotizing vasculitis 3, leukocytoclastic vasculitis 3, granulation 2 and eosinophilic infiltration 2. All of them treated with prednisolone, using pulse therapy for five patients. About FFS two of them were 3 and one was 4 and seven patients were under treatment. We report and consider our cases on basis of literature.

P1-197

Five cases of ANCA-associated vasculitis treated with Rituximab therapy

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Conflict of interest: None

【Objectives】In the treatment of ANCA-associated vasculitis (AAV), Rituximab (RTX) is considered when the disease is refractory to Cyclophosphamide and corticosteroids. So far, only a few case studies have been reported in Japan. Here, we investigated the efficacy of RTX in Japanese AAV patients.【Methods】We collected newly diagnosed AAV patients and AAV patients with relapse who hospitalized in our department from April 2014 to June 2015. RTX at a dose of 375 mg/m^2/week was administered for 4 weeks with corticosteroids. We reviewed the clinical condition, Birmingham vasculitis activity score (BVAS), efficacy and adverse events.【Results】Five patients were enrolled in this study (2 newly diagnosed, 3 relapsed). Relapsed patients suffered from hearing loss, pe-

ripheral neuropathy, and nephritis. Four in five cases completed the RTX administration for 4 times. One patient developed deep vein thrombosis after the second RTX administration. After RTX therapy, BVAS, ANCAs and the dose of corticosteroids decreased in all cases. Adverse events occurred in 3 patients: deep vein thrombosis, bacterial pneumonia and pulmonary tuberculosis.【Conclusion】RTX seems to be a good therapeutic choice, however, further studies are needed to elucidate the efficacy and adverse events.

P1-198

Two cases of relapsing granulomatosis with polyangiits successfully treated with rituximab

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Conflict of interest: None

[Case-1] A 75-year-old woman admitted our hospital because of right sudden hearing loss. MRI scans showed a soft tissue occupying her right antrum of mastoid, and MPO-ANCA was positive. She was diagnosed as granulomatosis with polyangiits (GPA). She was treated with dexamethasone, prednisolone (PSL) and cyclophosphamide (CY), but the disease relapsed several times. Two years later from the diagnosis, rituximab (RTX) of 500 mg was administered once weekly for consecutive 4 weeks, followed by the single administration 2 times every 6 months. She is now in remission with PSL of 5 mg/day. [Case-2] A 63-year-old woman admitted our department because of her right hearing loss. MPO-ANCA was positive. We firstly treated with PSL, but 4 months later, severe pain around her right auricle developed. CT scan showed a tumor like leision at paraepipharynx, we diagnosed with GPA. We could induce her to remission with CY, but the disease relapsed again within a 1.5 years. RTX of 500 mg/day was administered as the same regimen of Case-1. She is now in remission with PSL of 5 mg/day. [Conclusion] RTX is outstandingly efficient for relapsing GPA.

P1-199

A case of microscopic polyangiitis with refractory hypertrophic pachymeningitis successfully treated with rituximab

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Conflict of interest: None

A 74-year-old woman presented to our hospital with fever and numbness in both legs in 2011. Laboratory data revealed elevated C-reactive protein (CRP) (10.6mg/dl) and myeloperoxidase anti-neutrophil cytoplasmic autoantibody positive (181.0IU/mL). She was diagnosed as microscopic polyangiitis (MPA), according to the Ministry of Health and Welfare criteria. In 2013, she complained of visual impairment and headache, and magnetic resonance imaging (MRI) revealed hypertrophic pachymeningitis. she was treated with oral prednisolone 40 mg daily, high-dose methylprednisolone therapy, azathioprine, ciclosporin, cyclophosphamide pulse therapy (500mg/body four times), infliximab (3mg-5mg/kg five times), methotrexate, and so on, with no apparent improvement in the symptom. In 2014, MRI revealed exacerbation of subdural hygroma and hypertrophic pachymeningitis. She was treated with rituximab (375mg/m2/week four times), subsequently her symptom was promptly improved, and MRI showed improvement of subdural hygroma and hypertrophic pachymeningitis. In conclusion, we report a case of microscopic polyangiitis with refractory hypertrophic pachymeningitis successfully treated with rituximab.

P1-200

Otitis Media with ANCA-Associated Vasculitis that required rituximab therapy

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Conflict of interest: None

Case Report: A 61-year-old man was referred to otolaryngology of our hospital because of rapidly progressive hearing loss of both ears. CT scan showed soft shadow occupying middle ear and serum MPO-ANCA was positive. He was diagnosed as Otitis Media with ANCA-Associated Vasculitis (OMAAV) and treated with high dose predonisolone (PSL) and oral cyclophosphamide, which improved his hearing condition. Two month later, when PSL was ceased, right facial paralysis was developed. PSL of 100mg was given, but 2weeks later, he presented left facial paralysis. PSL was increased, but, his hearing loss was worsened to deaf and referred to our department. Based on the diagnosed of systemic ANCA-associated vasculitis affecting middle and inner ear, facial nerves, he was treated with steroid pulse therapy and rituximab (365mg/m2 x4), which improved his hearing condition well. Discussion: OMAAV was a recently proposed concept of ANCA-associated vasculitis by otolaryngologists. The concept is important for early diagnosis of ANCA-associated vasculitis. However, some of OMAAV are systemic vasculitis and refractory. Thus, cooperation of rheumatologists with otolaryngologists is required for management of OMAAV.

P1-201

A Case of Otitis Media with ANCA-Associated Vasculitis (OMAAV)

Mai Sorachi, Masao Tamura, Aki Nishioka, Kazuyuki Tsuboi, Kota Azuma, Chie Ogita, Yuichi Yokoyama, Takeo Abe, Momo Maruoka, Tetsuya Furukawa, Takahiro Yoshikawa, Takuya Hino, Atsushi Saito, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Shinichiro Tsunoda, Kiyoshi Matsui, Hajime Sano
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Conflict of interest: None

A 68-year-old-woman presented right hearing loss. She was treated with antibiotics, however her symptom did not improved. Then low-grade fever continued. Although right myringotomy was enforced, hearing loss progressed, it showed bilateral mixed hearing loss at hearing test. Both sides myringotomy was enforced, but the right is not recognized the waste solution for adhesions, left showed a large amount of leachate. On the head CT, it showed soft tissue on both sides intratympanic. She consulted with the otorhinolaryngologist in our hospital because of left hearing loss. ANCA-associated Vasculitis Syndrome was suspected because serum level of myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) elevated (76.4EU). She admitted to our hospital She was clinically diagnosed with granulomatopic polyangitis (GPA). It reported the effectiveness of the RTX for the Otolaryngologic Manifestations of GPA. She was treated with prednisolone and RTX. Left hearing was improved up to 42.5dB from 67.5dB, but right was not improved. We consider that early diagnosis and early treatment are important, because it is usually difficult to recover from the deafness in OMAAV. We report with some literature review.

P1-202

Elderly-onset MPO-ANCA positive granulomatosis with polyangiitis successfully treated with rituximab

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Conflict of interest: None

A 80-year-old woman presented with slight fever and cough from May, 2014. Elevated serum CRP level and a nodular lesion in her left lung on chest CT were found by an internist. She was referred to our hospital. She was diagnosed with granulomatosis with polyangiitis (GPA) because of respiratory symptoms, mononeuritis multiplex, elevated serum

CRP level, positive finding for MPO-ANCA 193 U/mL and Granuloma on biopsy of TBLB (BVAS 9/63). She was treated with prednisone (PSL) 60 mg/day and rituximab (RTX) (375 mg/m^2×4 times). The dose of PSL was swiftly decreased without suffering a relapse. Azathioprine (AZP) was additionally administered. Titer of the MPO-ANCA was finally decreased to 9.4U/mL (BVAS 3/63). Pulmonary polygranulomatosis were gradually improved on chest CT. At 16 months after the initial RTX treatment, she continues to remission without any adverse effects including infection. Early intervention of RTX therapy may an effective and new therapeutic approach for the treatment of elderly onset or refractory GPA.

P1-203

A case report of refractory EGPA which lead to death in spite of intensive treatments including rituximab

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Conflict of interest: None

A 38 year old man with early diagnosis of asthma 8 years before arrived to our neurology department complaining of 3 week history of fever and progressive foot numbness. He had eosinophilia, positive MPO-ANCA, high IgE, mononeuritis multiplex which lead to diagnosis of EGPA. Three courses of dexamethasone pulse therapy gave scarce change in fever and progression of numbness, and was readmitted to rheumatology department. Intensive treatment including intravenous immunoglobulin, rituximab, cyclosporine, cyclophosphamide was given which only improved MPO-ANCA and eosinophilia. Meanwhile, the low grade fever remained and the numbness progressed to upper and lower limb motor disturbance. Four months after admission, he had acute worsening of liver and heart function and died due to heart failure. EGPA is generally reported to have good response against steroid. As for refractory EGPA, there are many case reports that showed effectiveness of particular treatments including rituximab. Meanwhile, there are no case report of EGPA that showed scarce response against such intensive treatments which finally lead to death as in this case. We report this rare case with some literature review.

P1-204

A case of refractory Granulomatosis with Polyangitis

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Conflict of interest: None

[Introduction] It has been reported that Rituximab was administerd to many refractory Granulomatosis with Polyangitis (GPA) cases since January, 2013. But there are still few case reports about Rituximab readministration. [Case Report] A 25 years old man. His fever was elevated from December, 2010. He received antibiotic treatments as a lung abscess in nearby doctors, but his symptom did not improve, and he was refered to our hospital. The PR3-ANCA was positive, and GPA was diagnosed because of PR3-ANCA positivity and multiple pulmonary nodules. Otherwise he received a steroid pulse therapy, following predonisolone 60mg, intra venous cyclophosphamide pulse therapy (IVCY), oral cyclophosphamide therapy, oral methotrexate therapy, and intra venous infliximab therapy, his disease repeated the recurrences. A pulmonary nodule lesions recurred in March, 2013, he was received the first rituximab therapy. Six months later, he was received the second rituximab therapy, because of the sinusitis and the pulmonary nodules exacerbation. Ten months later from the second rituximab therapy, he was received the third rituximab therapy because of the sinusitis.

P1-205

A space-occupying lesion in the carotid space leading to acute-onset dysphagia; a rare intracranial involvement of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

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Conflict of interest: None

Case 1. A 37-year-old man presented with acute-onset dysphagia and headache. The tongue deviation to the left was observed. MRI revealed gadolinium (Gd)-enhanced space-occupying lesions (SOL) in the left carotid space but no signs of hypertrophic pachymeneingitis (HP). Proteinase 3-ANCA was positive, but any other findings of granulomatosis with polyangiitis (GPA) were not seen. Steroids improved dysphagia as well as fading of Gd-enhancing effect in the SOL. During steroid tapering, he developed nasal obstruction, epistaxis and headache, and was finally diagnosed as having GPA. He was treated with Steroids, cyclophosphamide, and rituximab with salient improvement. ***Case 2.*** A 68-year-old woman with otitis media with ANCA-associated vasculitis, which was diagnosed by otitis media refractory to antibiotics and tympanostomy and positive myloperoxidase-ANCA, presented with acute-onset dysphagia during steroid tapering. Uvula deviation to the right and the loss of pharyngeal reflex were seen. MRI revealed Gd-enhanced SOL in the left carotid space but no signs of HP. Steroids improved dysphagia as well as reducing the size of SOL. ***Conclusion.*** In the various diagnosis of a SOL in the carotid space, intracranial involvement associated with ANCA-associated vasculitis should be included.

P1-206

Jugular foramen syndrome as a suspected cause of MPO-ANCA associated hypertrophic pachymeningitis

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Conflict of interest: None

We report a 70-year-old man presenting a jugular foramen syndrome as a suspected cause of myeloperoxidase-specific anti-neutrophil cytoplasmic antibody (MPO-ANCA) associated hypertrophic pachymeningitis (HP). He has a history of headache and fever with high values of CRP; 27 mg/dl and MPO-ANCA; 88.5 U/mL. The Magnetic resonance imaging (MRI) showed the thickening of the dura mater with an enhancement of the left cerebellar tentorium supported the diagnosis of MPO-ANCA associated HP. Therapy with oral prednisolone (PSL) 20mg daily corrected the laboratory abnormalities and improve clinical features. Three years later, when he was treated with an oral PSL 10mg daily and mizoribine 100mg daily as a maintenance therapy, he developed headache, facial palsy, dysarthria, and dysphagia. MRI demonstrated an abnormal enhancement around the left jugular foramen without the enhancement of left cerebella tentorium. He was diagnosed as having MPO-ANCA associated HP based on MRI de novo findings. He responded well to the treatment with steroid pulse therapy, followed by oral PSL 40mg daily and intravenous cyclophosphamide pulse therapy. MRI revealed the improvement of abnormal thickening of jugular foramen. We should keep in mind that ANCA-associated vasculitis may induce the nerve compression.

P1-207

A 46 year-old woman representing ulcerative colitis and PR3-ANCA associated hypertrophic pachymeningitis

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Conflict of interest: None

A 46 year-old woman with history of ulcerative colitis admits for bilateral temporal headache and fever. On Examination, tender superficial temporal arteries are palpable without jaw claudication. CRP level is as high as 14.89 mg/dL and the finding of cerebrospinal fluid is non-specific. She admits our hospital for further investigation. Laboratory fidings show PR3-ANCA positive, and C-ANCA is positive by the fluorescent antibody technique. Contrast-enhanced MRI shows diffuse thickness in

meningis and she is diagnosed as PR3-ANCA associated pachymeningitis. On the other hand, she complains abdominal pain, diarrhea and hemafecia. Colon fiberscopy shows ulcers in whole colon including terminal ileum which suggests the exacerbation of ulcerative colitis. 60mg/day of prednisolone improves her headache as well as abdominal pain. [Clinical significance] We should consider of not only granulomatosis with polyangitis but also inflammatory bowel disease such as ulcerative colitis and pachymeningitis in case of PR3-ANCA positive.

P1-208

Subarachnoid hemorrhage and right coronary artery lesion in eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

A 48-year-old woman was admitted to our hospital with an 8-month history of numbness, edema, purpura in both legs, allergic rhinitis, and polyarthritis. Mononeuritis multiplex, purpura, and hypereosinophilia were observed, and necrotizing vasculitis was revealed in skin biopsy. Thus, she was diagnosed with EGPA. The patient was treated with 1 mg/kg/day of prednisolone, and her leg edema and hypereosinophilia gradually improved. However, she exhibited sudden onset of headache on the 8th day of hospitalization. Head CT showed diffuse SAH. An emergent digital DSA showed no abnormal vascular aneurysm. Electrocardiogram showed bradycardia and negative T waves in leads I and aVL. Cardiac ultrasonography showed hypokinesis in the inferoposterior wall, and right coronary artery lesion was suspected due to vasculitis of EGPA. Additional treatment with IVCY and IVIG were administered. Further complication of the cerebral vascular lesions was not observed, and heart wall motion improved dramatically. On the 42nd day of hospitalization, eosinocytes increased and relapse of EPGA was suspected. Additional treatment with 4 courses of rituximab (375 mg/m^2) was initiated, followed by improvement of EPGA, and the patient was discharged on the 74th day of hospitalization.

P1-209

Histone methylation profiling in peripheral white blood cells of Behcet's disease

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Conflict of interest: None

Objectives Although a line of evidence has suggested genetic contributions to Behcet's disease (BD), non-genetic factors, like epigenetics, may play pivotal roles in the pathogenesis as well. We examined the histone modifications of peripheral white blood cells (WBCs) in BD. **Methods** Peripheral WBCs were obtained from 28 patients with BD and 16 healthy controls (HC). Peripheral WBCs were classified as below: CD4+T cells, CD8+T cells, γδT cells, neutrophils, Tregs, and B cells. All samples were analyzed with a fluorescence-activated cell sorting. **Results** MFI levels of H3K27me3, a suppression marker, in BD were low in CD4+T cells, CD8+T cells and γδT cells, and high in neutrophils. MFI levels of H3K4me3, an activation marker, in BD were low in CD4+T cells, CD8+T cells, γδT cells and Tregs. H3K4me3/H3K27me3 MFI ratio of BD was low in neutrophils and Tregs, and high in γδT cells. H3K27me3 MFI of active BD were significantly lower in γδT cells than that of inactive BD. H3K4me3/H3K27me3 MFI ratio of active BD was significantly higher in γδT cells than that of inactive BD. **Conclusion** Aberrant histone methylation in certain subclasses of peripheral WBCs may be associated with the pathogenesis of BD. It is suggested that histone methylation could be a new candidate-biomarker for BD.

P1-210

Third party evaluation of clinical guidelines for vasculo-Behcet's disease in Japan

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Conflict of interest: None

【Objects】To evaluate the draft of clinial guidelines for vasculo-Behcet's disease (BD) externally. 【Methods】In the draft by the Behcet Disease Research Committee, MHWL, Japan in 2014, 26 statements were assessed using scoring from 1 to 9 on questionaries for rheumatologists and vascular surgeons in university hospitals. 【Results】The questionaries were collected from 20 rheumatologists and 6 vascular surgeons. Score of overall assessment was 7.4±1.1. The lowest score was noted in the statement concerning anticoagulation (6.9±1.3), because it was unclear whether the therapy was recommended or discouraged. Other comments addressed the priority of imaging studies, separate description of therapeutic recommendations for each lesion, and detail regimens of immunosuppressive therapies. Accordingly, the clinical questions are reset in revision. 【Conclusions】Based on collective opinions from rheumatologists and vascular surgeons who involved in management of BD patients, the guideline would be more useful in revision.

P1-211

Issues on diagnosis of Intestinal Behcet's disease: a retrospective analysis of 590 patients

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Conflict of interest: None

[Object] To examine discrepancies in the diagnosis among the Japanese Diagnostic Criteria for Behçet's Disease (BD), the International Study Group for BD (ISG criteria, 1990) and the International Team for the Revision of the International Criteria for BD (ITR-ICBD, 2014). **[Methods]** The study enrolled 590 patients who had been followed by our facilities as BD. We examined whether the patients met the Japanese Diagnostic Criteria for Behçet's Disease, ISG criteria (consist of mucocutaneous and ocular symptoms), and the ITR-ICBD (consist of vascular and neurological symptoms in addition). **[Results]** While 87.5% of the all patients met the ISG criteria, the criteria were not satisfied in 74 patients including 26 of 74 patients with intestinal lesions, 10 of 48 with vascular lesions, and 12 of 62 with neurological lesions. On the other hand, ITR-ICBD were satisfied in 97.1 % of patients except 13 patients

having intestinal lesions. **[Conclusions]** Diagnostic discrepancies occur more often in patients with intestinal involvement than those with other phenotypes. This subtype is characterized by high incidence in Japan, female predominance and lower frequency of HLA-B51. Diagnosis of atypical cases should be done with care in intestinal BD patients.

P1-212

Efficacy of infliximab and methotrexate in a Neuro-Behcet's disease patient with emerging pattern of acute on chronic

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Conflict of interest: None

Neuro-Behcet's disease is one of the serious complications of Behcet's disease, consisting of acute type and chronic progressive type. A 32-year-old Japanese female had recurrent oral aphthous ulceration and genital ulceration. She had a bulimic episode starting three months ago. She was referred to a local hospital because of tender cutaneous lesion, gait disorder and dysarthria. Fluid attenuated inversion recovery images on MRI scans revealed high density lesions in bilateral cerebral crus and right internal capsules. She was referred and admission to our hospital. Cerebrospinal fluid (CSF) examination showed elevated cell count and marginally increased IL-6 level (202.0 pg/ml). CSF IL-6 briefly impaired to 2.2 pg/ml with mPSL pulse, however it has increased again to 644 pg/ml with reduction of corticosteroids. She was given oral methotrexate (MTX) (12mg/week), CSF IL-6 impaired to 83.2 pg/ml. Following the adoption of MTX, she was given intravenous infusion of infliximab (300mg/body). CSF IL-6 was dramatically decreased to 7.0 pg/ml and improved neuropsychiatric manifestations. Of note, she was a patient with episodes of acute phase manifestations and chronic progressive neuro-behcet at the same time. In addition, MTX and infliximab have been demonstrated to be effective.

P1-213

A successful case of tocilizumab in HLA-A26 positive Behçet Disease resistant to anti-TNF therapy

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Conflict of interest: None

HLA-A26 is a second susceptibility gene for Behçet disease (BD), contributing independently of HLA-B51 to onset of the disease. Herein, we report an HLA-A26 positive case of BD resistant to TNF inhibitors (TNFi), successfully treated with tocilizumab (TCZ). A 9-year-old boy referred to our hospital due to uveitis was diagnosed with BD. His HLA type was positive for A26 and B27 and was negative for B51. Uveitis, which was transiently improved by infliximab, was progressively exacerbated in resistance to TNFi including adalimumab, resulting in vitreous hemorrhage with appearance of sacroiliitis. Switching of biologic agent to TCZ led to clearance of uveitis attack with clinical remission of sacroiliitis. TNFi, which has brought a therapeutic paradigm shift in ocular BD, is still ineffective in certain patients, presumably whose pathogenesis might be independent of TNF signaling. HLA-A26 positive BD is known to be susceptible to posterior uveitis with TNFi resistance. Our successful experience in "typical HLA-A26 positive BD" indicates TCZ might be a therapeutic option for refractory BD with TNFi resistance. It also suggests IL-6 might be closely involved in HLA-A26 positive BD via Th17 commitment recently discussed in immunogenetic aspects.

P1-214

Behçet's disease with repeatedly pulmonary hemorrhage

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Conflict of interest: None

43years old, male. He was diagnosed as incomplete type of Behçet's disease (BD) 15 years ago. He was admitted to our hospital because of hemoptysis. A Computed tomography and bronchoscopy study disclosed pulmonary hemorrhage from B4/5, however, the correct bleeding point was not identified. We performed bronchial artery embolization and the patient remained well without signs of active bleeding. After a discharge, he was affected with a little hemoptysis again, and he was hospitalized for the purpose of scanning a cause of repeatedly pulmonary hemorrhage. After admission, an analysis of the BALF revealed extreme lymphocytosis and CT-scan showed no aneurysm but diffuse Ground Glass Opacity (GGO) and thickening of the respiratory tract wall. Right lower lobectomy under complete video-assisted thoracoscopic surgery was performed to investigate a cause of pulmonary hemorrhage. Histological diagnosis was organized pneumonitis with septal fibrosis.Pulmonary involvement in BD is unusual and commonly manifests as pulmonary artery aneurysms. In this case, no aneurysm or uasculitis but interstitial pneumonia were revealed, although interstitial leasions with BD are uncommon. It is necessary to consider interstitial pneumonia as a cause of the hemoptysis of BD.

P1-215

A case with Behcet's disease who underwent brain biopsy to differentiate the cause of acute encephalopathy

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Conflict of interest: None

55 year-old man who had been diagnosed as having Behcet's disease commenced infliximab therapy in April 2015 for recurrent uveitis. After initiation of infliximab therapy, he complained of headache. Brain MRI on May 7th revealed multiple brain lesions with ringed enhancement in the basal ganglia and the cerebral white matter. On admission (May 11th), his body temperature was normal and neck stiffness was absent; however, mononuclear leukocytes count in the cerebrospinal fluid were increased. Since the brain lesions were not improved on the brain MRI on May 14th, diagnostic brain biopsy was performed. While lymphocyte infiltration around the blood vessels was observed, there was no evidence of infection or malignancy. On June 4th, the brain lesions on MRI were obviously improved and mononuclear leukocytes count in the cerebrospinal fluid was decreased. Given the result of brain histopathology and the clinical course, we prioritized the possibility of neuro-Behcet's disease over that of infliximab-induced demyelinating disease and continued infliximab therapy. Thereafter, the brain lesions are gradually improving. Here, we report a case of neuro-Behcet's disease with unique MRI findings and discuss the features of MR imaging of neuro-Behcet's disease with literature review.

P1-216

2 cases of Behcet's disease, complicated by TB and HIV-1 infection

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Conflict of interest: None

【Objectives】Presenting 2 cases of Behcet's disease (BD), complicated by TB and HIV-1. Case 1: a 21-year-old man presented a 3-month history of eye congestion, fever, oral ulcers, and a 10-day history of genital ulcers. He'd had ulcers since his teens. CXR revealed a right hilar shadow enhancement, which turned out to be not pulmonary artery aneurysm but lymphadenopathy by a contrasted *CT sca*n. A biopsy was performed: the cultures and PCR revealed TB. Anti-TB drugs cured all symptoms. Case 2: a 41-year-old man presented a 3 months history of oral ulcers. He had bilateral knee pain and experienced recurrent episodes of ulcers for 20 years. HBsAb and HBcAb were positive, a concurrent infection of

HIV was suspected. HIV Ab test was positive, and HIV-1 RNA PCR was 1.1×10^4copy/ml. We determined that he had BD concurrent with HIV-1 infection.【Conclusions】In the case of BD mimics presenting oral and genital ulcers, we should consider STDs. It's rare that oral ulcers occur due to TB, they can appear on back of the tongue and TB skin lesions present in various different ways. If ulcers and nodules are seen, we need to pay attention to the TB infection. Some reports of a HIV-1 infection concurrent with BD suggest an HIV-1 infection may be a trigger of increased autoimmunity.

P1-217

The effective concomitant use of anti-TNFα blocker in intractable intestinal Behcet's disease : two case reports

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Conflict of interest: None

We describe intractable cases of intestinal Behcet's disease (IBD) which achieved clinical remission by co-administration of anti-TNF-α blocker. Case 1: 62-years-old male, who had kept remission by prednisolone (PSL) and salazopyrin during his 9-year history of IBD, indicated the recurrence of intestinal ulcer with intractable abscess. A fenestration surgery for the abscess was performed, however, entero-cutaneous fistula appeared. In addition to the increase of PSL and the surgical managements, infliximab was administered. After all, he achieved clinical remission. Case 2: 36-years-old male was diagnosed as BD because of stomatitis, folliculitis and genital ulcer. Even though PSL was started, intestinal bleeding due to intestinal ulcer occurred. Initial high dose of adalimumab (ADA) was effective for repressing disease activity, however, the recurrence of intestinal bleeding with CRP elevation was shown after keeping ADA with the maintenance dose. Therefore, ADA was restarted by initial high dose, and azathioprine (AZA) was additionally given. He ultimately achieved clinical remission. In conclusion, anti-TNFα blocker is a successful treatment in IBD for preventing lethal situation. Furthermore, concomitant use of AZA is effective combination in intractable IBD.

P1-218

A case of vasculo-Behcet's disease for which infliximab was effective

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Conflict of interest: None

Case: A 68-year-old woman. She had a history of uveitis and erythema nodosum found at the hospital, respectively in 2011. In March 2015, she complained about discomfort in her chest and was diagnosed with congestive heart failure and aortic insufficiency. In April 2015, difference in temperature between both hands and difference in blood pressure between both upper extremities were found on preoperative close examination for aortic insufficiency. Left brachial artery stenosis was found on contrast-enhanced CT and based on the previous history, she was introduced to our department for suspected vasculo-Behcet's disease in July 2015. As accumulation was confirmed in the brachiocephalic artery on PET-CT, she was diagnosed with vasculo-Behcet's disease. Infliximab and cyclosporine were initiated at 5 mg/kg (250 mg/time) and 50 mg/day, respectively. She was discharged from the hospital as she tested negative for CRP and D-dimer. Brain (B-type) natriuretic peptide (BNP) was decreased from 517 pg/mL to 181 pg/mL and respiratory distress on exertion while ascending and descending the stairs was also improved. Conclusion: Improvement in respiratory distress on exertion and decrease in BNP suggested the improvement effect of infliximab on circulatory dynamics.

P1-219

A Case of Behcet's disease (BD) and SAPHO syndrome successfully treated with tonsillectomy

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Conflict of interest: None

A-51year-old man. A lot of painful vesicles appear in his intraoral pharynx and the gingival part subsequently common cold symptoms in April, 2015.Careful watching is advised by oral surgeon. Two months later, he admitted to our hospital under the diagnosis of BD of incomplete type. That's because, he got painful pubic ulcer and a lot of vesicles in palm and sole with positive needle reaction. We started colchicine treatment without any improvement of those symptoms. Newly complains was chest pain and pimples in palm and sole. Skin biopsy was performed with diagnosis pustulosis palmaris et plantaris. In additional gallium scintigraphy study, collection in stenoclavicular joint was shown and SAPHO syndrome became a definite diagnosis. Tonsillectomy was performed under many successful reports of tonsillectomy to BD or SAPHO syndrome. Chest pain diminished and also pimples in oral cavity palm and sole disappeared. We report a rare case of SAPHO syndrome with Bechet disease with some literature review.

P1-220

A case of chronic progressive neuro-Behçet's disease treated with Methotrexate and Infliximab

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Conflict of interest: None

A 64 year-old-man was admitted to our hospital for headache, fever, dysarthria. Brain magnetic resonance imaging (MRI)showed T2 high intensity ares both medulla oblongata ventral, midbrain tegmentum, and basal ganglia. CSF cell count and protein were elevated, and CSF IL-6 level was high. He has repeated erythema nodosum,painful oral ulcers about 30years old. We diagnosed acute neuro-Behçet's disease (ANB) and started methylprednisolone pulse therapy. CSF IL-6 fell to the normal range.Six months later, taking prednisolone (PSL), he had headache,fever and showed high inflammatory findings in blood test. MRI showed brain stem and cerebellum atrophy.We diagnosed chronic progressive neuro-Behçet's disease (CPNB) and added on MTX.Because of liver dysfunction, we couldn't increase MTX more than 12mg/weeks. Three months later, he had headache and high CRP levels, we further added infliximab (IFX). We report a case of CPNB treated with MTX and IFX.

P1-221

Deep vein thrombosis with Vascular Behcet disease : two cases report

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Conflict of interest: None

Case 1: A 42-year-old man had a history of oral aphthous ulcers, genital ulcers and deep vein thrombosis (DVT) in October 2009. The genotype testing was positive for HLA-B51, and he was diagnosed as vascular Bechet's disease (BD). Although the treatment with PSL 50mg/day gradually relieved the symptoms, his left thigh got swollen again after a dose of PSL was tapered to 9 mg/day. The CT imaging revealed multiple deep

vein thrombi in the left thigh. Infliximab and MTX initiated to recurrent DVT improved the vascular inflammation in the refractory BD. Case 2: A 31-year-old man who suffered a painful swelling in the left lower thigh developed DVT in April 2011. Although an anticoagulant agent was administered, DVT often recurred for three years. When erythema nodosum and polyarthritis occurred, he was diagnosed as a vascular BD. Combined therapy with PSL 60 mg/day and MTX reduced systemic inflammation including vasculitis. All sizes of the arterial and venous vessels can be involved in vascular BD. It was reported that phlebitis caused by vascular endotherial dysfunction might result in DVT, leading to the severe condition of the pulmonary embolism with patients of BD. Taken together, we should pay attention to DVTs in cases of leg swelling complicated with BD.

P1-222

Two cases of paraneoplastic syndrome (PNS) that presented with adult-onset still disease (AOSD)-like symptoms

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Conflict of interest: None

[Case 1] A-50-year-old man was referred to our hospital because of fever, sore throat, arthralgia, and inspiratory chest pain. The diagnosis of AOSD was made on the basis of his symptoms and laboratory dates. Corticosteroid therapy was initiated; however, a gastrointestinal fiberscopy revealed advanced esophageal cancer. He underwent radical operation followed by chemotherapy, and then the corticosteroid therapy was tapered and stopped. Subsequently, there has been no recurrence of his symptoms for 4 years. [Case 2] Polymyalgia rheumatica was diagnosed in a 50-year-old woman with a pain in shoulders. Corticosteroid therapy was initiated; however, we changed the diagnosis to AOSD on the basis of her symptoms and laboratory dates. Steroid pulse therapy didn't make her symptoms to be improved, and thus we added tocilizumab. FDG-PET/CT revealed an abnormal uptake of FDG at systemic lymph nodes. Examination of the biopsy specimen of the lymph node led to the diagnosis of diffuse large B-cell lymphoma. [Discussion] To make a diagnosis of AOSD, it is crucial to exclude malignancy with sufficient scrutiny. It should also be considered that there is a possibility that patients with AOSD may develop malignancy later.

P1-223

Study of clinical features of patients with adult onset Still disease in eight cases

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Conflict of interest: None

[Object and Methods] Adult onset Still disease (AOSD) is a well-recognized disease for hard to diagnose and treat. We studied the characteristics of 8 AOSD patients who admitted to our hospital in 4 years from our department founded. [Results] It showed various forms of rash in various locations and various fever types in all patients. We divided patients into two groups, in the younger group (< 50 years old, n =5), the WBC count showed the most positive correlation with the severity (r=0.956), and in the elderly group (≥50 years old, n=3), the HGB level was the most negative correlate factor with the severity (r=-0.999). The numbers of steroid pulse therapies were significantly higher in the elderly group compared with the younger group (p=0.037). The Neut count and HGB level were the most correlated factors with the prednisolone doses (r=0.895, r=-0.948 respectively) in the younger group. On the contrary, ferritin level and LDH level in the elderly group (r=0.988, r=0.834). [Conclusions] In this study, it is suggested that we should not use rash forms and fever types for diagnosing AOSD, and we should focus on neutrophil count and hemoglobin level for judging the severity. We want to take advantages for the early diagnosis and the choices of treatments with these results.

P1-224

Treatment of refractory adult onset Still's disease by tacrolimus

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Conflict of interest: None

Objective: To evaluate tacrolimus (TAC) treatment in patients with refractory adult onset Still's disease (AOSD). Method: TAC was administered to 9 patients with refractory AOSD. Symptoms and laboratory findings were analyzed retrospectively. Result: TAC was administered to eight patients with refractory to MTX, and a patient with refractory to biological agents (infliximab, etanercept). Improvement of clinical activity, CRP, ESR, ferritin was observed in six cases. Glucocorticoid was reduced in all 6 cases, and discontinued in four cases. In three cases, TAC was not effective. AOSD patient refractory to biological agents became remission in addition of tocilizumab. Two patients suffered from pneumocystis carinii pneumonia (PCP). Conclusion: TAC is useful for controlling AOSD patients refractory to conventional treatment. However, serious adverse events (PCP) were occurred. It is important that TAC treatment for refractory AOSD is considered by therapeutic efficacy and adverse event.

P1-225

An sudden onset of Adult Still's disease under the remission of Systemic lupus erythematosus

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Conflict of interest: None

A 38-year-old woman was diagnosed with Systemic lupus erythematosus (SLE) at 26 years old and has been in a remission state by oral prednisolone (5mg/day) therapy. Spike fever, joint pain, pharyngalgia,and rash was suddenly occurred at 37 years old and continued for 2weeks. On admission, she was administered antibiotics because the activity of SLE was stable. However, her clinical symptoms were not improved, and liver dysfunction appeared and was getting worse. Then, she was diagnosed the onset of Adult Still's disease (ASD), based on a diagnostic criteria following of the persistent spike fever, joint pains, pharyngalgia, splenomegaly, and liver dysfunction. She was administered steroid pulse therapy following oral prednisolone (60mg/day) and cyclosporine (100mg/day), resulting the improvement of clinical symptoms. On tapering oral PSL dose, she had a relapse of ASD. She was re-administered steroid pulse therapy, following tocilizumab therapy (8mg/kg) once a month in addition to oral prednisolone (40mg/day) and cyclosporine (100mg/day). Her symptoms were rapidly improved, and the relapse has been not detected in the course of tapering oral PSL dose. This is the interesting case of a sudden onset of ASD despite of the remission of SLE treated by a modicum of PSL.

P1-226

A case of adult onset Still's disease(AOSD)-related macrophage activation syndrome successfully treated with steroid and tocilizumab(TCZ) combination, and had achieved rapid tapering of steroid dose and discontinuation of TCZ

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Conflict of interest: None

A-71-year-old woman was admitted to our hospital with fever, rash, and arthropathy. The laboratory data of granulocytosis, elevated serum C-reactive protein and interleukin-18 level led to the diagnosis of AOSD. The pathological findings of skin biopsy revealed perivascular neutrophil-dominant infiltration, which was compatible with that of AOSD. Despite administration of prednisolone (PSL)50mg/day and methotrexate, high fever persisted and pancytopenia appeared. From the findings of hemophagocytosis in bone marrow aspiration and high serum ferritin level, MAS was suspected and started dexamethasone pulse therapy followed

by PSL (120mg/day). Because of progressive pancytopenia we added TCZ, and abnormal laboratory data had improved. She leaved our hospital with additional medication of cyclosporine A, and the dose of PSL could be tapered from 120 to 10mg/day in a month after TCZ initiation. Clinical remission has been maintained from the discontinuation of TCZ, which was injected six times in total. Our case demonstrated the improvement of AOSD-rerated MAS by combination of steroid and TCZ therapy, thereafter rapid steroid dose tapering and discontinuation of TCZ have been achieved. Combination therapy of steroid and TCZ for AOSD-related MAS is considered to be a possible choice.

P1-227

A Case of Refractory Adult-onset Still's Disease Treated with Tocilizumab in Systemic Lupus Erythematosus Patient

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Conflict of interest: None

【Case】A 39-year-old woman【Clinical Course】Thirteen years ago, she was diagnosed systemic lupus erythematosus (SLE). In the last year, she was admitted to our hospital with a high fever and skin rash. She additionally suffered from a sore throat and arthralgia. The laboratory test showed leukocytosis, liver dysfunction and elevated serum ferritin level (3643 ng/mL). According to these findings, the patient met the Yamaguchi criteria for adult-onset Still's disease (AOSD). The administration of prednisolone (PSL) (60 mg/day) was effective. However, accompanied by PSL dose reduction (12.5 mg/day), disease activity was flared. In the present year, she was admitted to our hospital for the recurrence of AOSD. PSL (60 mg/day) was initiated, however, this failed to control symptoms. She was treated with a high dose of PSL (120 mg/day). Nevertheless these therapies, the disease activity was not suppressed sufficiently. For the reason, we administered tocilizumab (TCZ) (8 mg/kg/week). Subsequently,therapeutic values were recognized.【Discussion】This case is the first report of AOSD with SLE patient. Clinical course suggests that the therapeutic strategies of AOSD differ from SLE. We report the case of refractory AOSD with the previous references.

P1-228

A case of adult onset still's disease(AOSD) accompanied with chondritis

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Conflict of interest: None

[Case] A 45-year-old woman has a chief complement of sore throat and high fever on Aug. 23 20XX. She prescribed a course of antibiotics and NSAID, but nothing has worked. Ga-scintigraphy did not show any abnormalities. She was admitted into our hospital on Sept. 14. CT-scan did not show any findings suggestive of infection, malignancy and lymphoma. Laboratory data revealed remarkable leukocytosis (21800/ml). The results of ESR (116 mm/h), AST (45 IU/l), ALT (78 IU/l), CRP (20.93 mg/dl) and ferritin (635ng/ml) were elevated. We diagnosed her as AOSD and started of treatment with PSL (30mg). After that, fever improved gradually although sore throat was continued. MRI showed inflammation at the arytenoid cartilage. Then, PSL was increased to 50 mg and combined with MTX. She recovered from symptoms and abnormal laboratory value. [Discussion] The pathogenic mechanisms of AOSD and chondritis are not fully understood. IL-18 producing by macrophages supposed to play a crucial role in pathogenesis of AOSD. Cathepsins, which have been contributed to cartilage degradation including condritis was shown to be secreted by chondrocytes. Macrophages produced cytokines which stimulate chondrocytes in chondritis. We will discuss the relationship between AOSD and chondrites.

P1-229

Clinical characteristics in arthritis-type of patients with adult-onset Still's disease

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Conflict of interest: None

[Objectives] Adult-onset Still's disease (AOSD) is an acute inflammatory disorder of unknown origin. It is well known that a number of patients with AOSD have RA-like clinical courses. In the present study, we examined the clinical characteristics in patients with AOSD treated with biologics. [Methods] Ninety four patiets with AOSD who were treated in Institute of Rheumatology, Tokyo Women's Medical University enrolled in this study. The patients group consisted of 31 men and 63 women. We classified the patients with AOSD into 2 groups; RA-subtype (n = 21) who met the revised criteria of American College of Rheumatology clinical diagnostic criteria for RA and nonRA-subtype (n = 73) who didn't met it. [Results] The patients with RA-subtype AOSD were classified into two groups, those developing ankylosis or not and then the differences in the patient characteristics between the two groups was investigated. Six patients developed to ankylosis with RA-subtype. Cervical spine, wrist, knee and Lisfranc's joint developed to ankylosis.

P1-230

A case of adult onset Still disease complicated with hemophagocytic syndrome treated successfully with dexamethasone palmitate

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Conflict of interest: None

【Case report】A 26-year-old woman was admitted because of fever, erythema of hand and thigh, and joint pain. The results of laboratory tests were WBC 16600, ferritin 54800. CT of the chest and abdomen, Echocardiography, Ga scintigraphy and blood culture were normal. We excluded infections and malignancy as a cause of her illness. We diagnosed her as adult-onset Still's disease in various exams. She was treated with prednisolone and cyclosporine after steroid pulse therapy, but she didn't got better. She developed hemophagocytic syndrome two months after administration. Once hemophagocytic syndrome was showed get cured, after 3 weeks it was relapsed. We treated her with tocilizumab after plasma exchange and dexamethasone palmitate and it was successful.【Discussion】She developed too refractory adult-onset Still's disease but we treat it with dexamethasone palmitate successfully.【Clinical significance】Dexamethasone palmitate is useful to use tocilizumab for patients have too refractory adult-onset Still's disease.

P1-231

Evaluation of disease activity of Adult Still's disease by neutrophil CD64 during tocilizumab treatment: A case report

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Conflict of interest: None

[Objectives]Neutrophil CD64 (nCD64), known as a marker of infection, is reported to be upregulated in the active phase of Adult still's disease (ASD). Although it is difficult to evaluate inflammatory response in the patients treated with Tocilizumab (TCZ), we present a case of active phase ASD treated with TCZ successfully evaluated by nCD64.[Case] A

thirty-eight-year-old man with ASD was initially treated with prednisolone (PSL). But due to being resistant to PSL monotherapy, additional immunosuppressants were administered in combination with PSL. His disease activity remained unstable and TCZ was introduced. Although serum level of CRP became negative soon after initiating TCZ, his articular pain worsened and he developed leukopenia. Drug-induced leukopenia was suspected and TCZ was discontinued; however, at that time nCD64 expression was increased to 7829 molecules/cell. Bone marrow aspiration revealed hemophagocytic syndrome (HPS), and he was treated with high dose corticosteroids. After the treatment, nCD64 expression decreased to 2104 molecules/cell.[Discussion] This is a case of active phase ASD complicated with HPS. During TCZ treatment only nCD64 correlated with disease activity, indicating the efficacy of nCD64 for the evaluation of disease activity of ASD.

P1-232

A case of steroid-resistant adult onset Still's disease successfully treated with tocilizumab

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Conflict of interest: None

[Case] About 40 years old, female. She entered our hospital due to spike fever, arthritis of right knee, and palpable erythema. We diagnosed as adult onset Still's disease (AOSD) after close serological and survey, and prescribed prednisolone (PSL) 70 mg/day. The arthritis and fever were disappeared after administrating PSL, but the rash was not disappeared. After adding cyclosporine A, PSL was started to taper 3 weeks after starting to dose PSL. The rash and arthritis were appeared again when PSL was reduced to 45 mg/day. Tocilizumab (TCZ) was initiated once a month a week after the rash flared, and steroid semi-pulse therapy was done. After adding TCZ, the rash and arthritis were disappeared. No recurrence was observed after that. [Conclusions] The effectiveness of TCZ to steroid-resistant AOSD is reported in some case reports. We experienced a case of AOSD that flared with reducing prednisolone (PSL), and successfully controlled the disease activity by TCZ.

P1-233

A refractory case of Adult onset Still's disease with dermatomyositis-like skin lesions, complicated with recurrent macrophage activation syndrome, which was successfully treated with tocilizumab

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Conflict of interest: None

【Case】A 53-year-old woman suffered from fever, pharyngalgia, polyarthralgia, and rash. On admission, she had systemic pruritic rash, which resembled dermatomyositis including Gottron-like erythematous lesions and V-neck sign. Skin biopsy showed perivascular lymphocyte infiltration and mucin deposision in the dermis. On the 6th hospitalized day, she became hypotensive with thrombocytopenia and abnormal liver function test. Leukocytosis (398,000/μL), hyperferritinemia (4,600ng/mL), and elevation of serum IL-18 level (45,000pg/mL) were consistent with Adult onset Still' disease. She was complicated with Macrophage activation syndrome twice during the course of the treatment even under high-dose corticosteroid (CS) and cyclosporine. However, after the introduction of tocilizumab, her symptoms improved and the dose of CS could be rapidly reduced. We report a case of refractory Adult-onset Still's disease complicated with recurrent macrophage activation syndrome, whose cutaneous manifestation resembled dermatomyositis.

P1-234

RS3PE presenting in an unilateral pattern differentiated from rheumatoid arthritis

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Conflict of interest: None

<Introduction>RS3PE is characterized by elderly acute onset seronegative symmetrical polyarthritis with pitting-edema of distal extremities,without no definite diagnostic criteria.We hereby report a case of seropositive polyarthritis patient who developed unilateral pitting-edema.<Case Report>A 76-year-old male farmer with bilateral gonarthrosis,rapidly revealed arthritis of bil knees & bil ankles with edema of bil lower legs & bil dorsum pedis in mid-Sep of 2015,followed by arthritis of right fingers & wrist with edema of right dorsum manus.Early in Oct,he entered hospital and showed high CRP,without fever or obvious infectious symptoms. CRP19.5,ESR1H123,RF19(H),ACPA0.7,ANAx40,MMP-3 714.6.X-ray of hands was without bony erosions.We investigated infection and malignancy with negative evaluation. We reasoned that relatively lacking in active synovitis findings by joint echo contrary to high CRP could not support rheumatoid arthritis (RA).Within a week of PSL 15mg,the symptoms promptly remitted, concurrently with CRP decreasing.<Discussion>Asymmetrical RS3PE is hard to differentiate from RA,so we should consider of complication or transition.This case may possiby present more apparent pathology of RA, needed to carefully follow up clinical course.

P1-235

The efficacy of MTX to reduction of glucocorticoid in patients with polymyalgia rheumatica

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Depratment of systemic immunological diseases

Conflict of interest: None

Objective. The purpose of this study is to investigate the efficacy of methotrexate (MTX) to dose of glucocorticoid (GC) in patients with polymyalgia rheumatica (PMR). Methods. We performed a retrospective study of 48 PMR patients (female n=36 and male n=12, mean age 72.1±8.9 years) who were diagnosed from October 2010 to September 2015. We collected the data of the dose of GC and MTX at final visit of patients with PMR within observation period. Patients were divided two groups. One group is who could discontinue GC at final visit and the other is who continue GC. We compared patients who relapsed and not too. Results. Eight (17%) patients could discontinue GC and 3 patients used MTX. Thirty-eight patients continued GC and 4 patients used MTX. Final daily dose of prednisolone (PSL) in patients who did not use MTX was 5.0±2.8mg and who used MTX was 3.8±2.5mg. Twelve (26%) patients relapsed and 7 patients used MTX. Three relapsed patients combined with MTX could finally discontinue GC. Final daily dose of PSL in other 9 patients was 4.4±1.7mg. Five patients could discontinue GC in 34 non relapsed patients and final daily dose of PSL in other 29 patients was 5.1±3.0mg. Conclusion. Relapsed PMR patients could discontinue PSL in combination use of MTX.

P1-236

Initial dose of prednisolone for Japanese patients with polymyalgia rheumatica

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Conflict of interest: None

[Object] The recent UK guidelines stated the adequate initial dose of prednisolone (PSL) for polymyalgia rheumatica (PMR) was 15 - 20 mg daily. The majority of Japanese PMR patients are smaller and of lower weight than western patients. To explore the requisite doses of PSL, we examined the initial doses of PSL and the clinical course for Japanese patients. [Methods] We conducted a retrospective study of 24 PMR patients

who achieved remission in 3 hospitals in Japan. All patients met EULAR/ACR classification criteria. [Results] 16 (67%) were women. The mean ± SD age at the diagnosis was 76 ± 8.5. The mean ± SD body weight was 53 ± 9.9 kg. The median initial PSL dose was 15 mg daily. The median duration of PSL treatment until remission was 23 months. The patients were divided into two groups according to the initial doses of PSL. Group L consisted of the patients treated with PSL less than 0.25mg/kg/day. Group H consisted of the patients treated with 0.25mg/kg/day or more. There were no significant differences in sex, age, symptoms at diagnosis, and the duration of PSL treatment between the two groups. [Conclusions] The smaller PSL dosage might be effective for the treatment of PMR especially for elderly low-body weight Japanese females.

P1-237

Relapsing polychondritis with refractory scleritis treated with tocilizumab

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Conflict of interest: None

A 54-year-old woman was admitted because of bilateral scleritis and auricular chondritis for about 2 weeks. She felt ocular pain, photophobia, and auricular pain. She also had left costochondral and tracheal cartilage pain. The tracheal narrowing and abnormality of pulmonary function test were not observed. On day 3, we performed biopsy of the left auricular cartilage and diagnosed her with relapsing polychondritis. We treated her with prednisolone (PSL) 45 mg/day, but with little effect. We performed intravenous pulsed methylprednisolone therapy on day 10 and 17, however her scleritis and auricular chondritis persisted. On day 25, we added methotrexate 8 mg/week and infliximab (IFX) 3 mg/kg, which made her symptoms better. We tried to reduce the dose of PSL, however her scleritis was flared and C-reactive protein (CRP) increased. We repeated intravenous pulsed methylprednisolone therapy and switched the biologics from IFX to tocilizumab (TCZ) 8 mg/kg/month. Her scleritis disappeared and CRP was normalized, and the dose of PSL could be reduced without flare. The case of relapsing polychondritis with refractory scleritis treated with TCZ has not been reported. This case suggests that TCZ is effective for relapsing polychondritis with refractory scleritis.

P1-238

A case of SAPHO syndrome successfully treated with infliximab

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Conflict of interest: None

Back ground: SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome is characterized by typical skin lesions and sternocostoclavicular hyperostosis. The treatment for SAPHO syndrome is not established. Recently, bisphosphonate and TNF-inhibitors have been reported as effective therapies. Case: A 72-year-old woman was admitted to our department due to left chest pain. Two years before admission, pustulosis appeared in the sole of the left foot. Joint pain in the left shoulder and sternocostoclavicular joints developed and she was hospitalized in the next year. She showed the synovitis and hyperostosis in these joints by CT, MRI, and bone scintigraphy. Skin lesion was diagnosed as pustulosis palmoplantaris. Therefore, we diagnosed her as SAPHO syndrome, and intravenous bisphosphonate administration was started. Although salazosulfapyridine was started additionally, her joint pain was not improved. She was hospitalized again and infliximab was started. After 3 courses of infliximab (5 mg/kg), her joint pain was improved. Discussion: Whether infliximab could control not only the synovial inflammation, but also the hyperostosis, and could achieve the remission is unclear. It is necessary to observe the long-term efficacy of infliximab.

P1-239

A case of SAPHO syndrome showing the efficacy of tonsillectomy and stopping smoking

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Conflict of interest: None

SAPHO syndrome is one of similar conditions to seronegative spondyloarthritis. Established therapies have yet to be described. The case is 50 years female. She had a history of smoking and had palmoplantar pustulosis (PPP) and low back pain at age 32. Those symptoms spontaneously relieved. But at 46, anterior chest pain started and her backache and PPP worsened and continued. The effect of oral loxoprophen was limited and oral ciclosporin was not effective. Oral biotin was also ineffective, so she visited our hospital at 49. Her pain was so severe that she couldn't move her body in the morning. She had PPP and X-ray showed hyperostosis of lumber spine (LS). Adding the positive findings of bone scintigraphy and MRI, she was diagnosed with SAPHO. We prescribed oral MTX and SSZ, but her pain was not improved. At 50 the tonsillectomy was performed and she stopped smoking. After that, her p-VAS was decreased from 2 to 7 to below 2. BASDAI improved from 5 to 1.7, and PPP was cured. She became able to perform gardening and hiking. Some of SAPHO patients have continuous severe pain which lead to impaired ADL. For such patients, new effective therapy is needed. We experienced a case of refractory SAPHO showing the efficacy of tonsillectomy and stopping smoking.

P1-240

2 cases of SAPHO syndrome treated with anti-TNF-α blocker

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Conflict of interest: None

<Introduction> SAPHO syndrome is defined as a clinicoradiological entity complicated with synovitis, acne, pustulosis, hyperosteosis and osteitis. But treatment strategy of this disease is not firmly established. We report 2 cases of SAPHO syndrome treated with TNF-α blocker. Case1: A 48-year-old woman presented with left sternoclaviculor and shoulder pain. She was initiated with PSL and MTX. But these treatments were unsuccessful. She was started with GLM50mg/4w with favorite response. GLM and MTX were stopped after 3 months of the therapy. But arthritis and palmoplantar pustulosis were appeared. She was diagnosed as SAPHO syndrome. She was restarted with GLM50mg/4w, and these manifestations were improved. After 9 months, pustulosis recurred. Case2: A 75-years-old woman was suffered from palmoplantar pustulosis for 11 years. She was given a diagnosis of SAPHO syndrome because of arthralgia and sternoclavicular pain. She was started with MTX, but this treatment resulted in failure. Pustulosis and arthralgia were greatly improved, after MTX was switched to ADA 40mg/2w. Pustulosis was recurred after 6 months of the treatment with ADA. <Discussion> Anti-TNF-α blocker can be effective against synovitis of SAPHO syndrome, but cause exacerbation of skin lesion.

P1-241

A case of successful treatment with infliximab for palmoplantar pustulosis with osteoarthritis in the right hip

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Conflict of interest: None

A 71-year-old female developed nuchal pain and numbed in right upper extremity in January 2012. She received symptomatic treatment, but the efficacy was unclear. As MRI showed inflammation around the cervical vertebra and she was suspected infectious spondylitis. Antibiotics

were sufficiently used, but ineffective. The symptoms got better and worse for two years. Because she had the nuchal pain and right hip joint pain strongly and high inflammatory response (CRP: 8mg/dl) in August 2014. Antibiotics were administered again, but the symptoms were not improved. Culture of joint fluid was negative. In the past, she suffered from palmoplantar pustulosis. Inflammation and deformity of the vertebrae and right hip joint on MRI expanded, but inflammation of sternoclavicular was mild. Taken together, she was diagnosed as palmoplantar pustulosis with cervical spondylitis and hip arthritis. She was treated with methotrexate and infliximab (5mg/kg). Her symptoms were getting better. Afterwards, no relapse was observed for 6 months. Palmoplantar pustulosis causes various type of osteoarthritis, but there are only a few cases with hip arthritis. Therefore, we report it with a review of the literature.

P1-242

Psoriatic arthritis with trismus treated with adalimumab

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Conflict of interest: None

Case presentation: A 27-year-old Japanese man was admitted to our hospital complaining of trismus. Seven years earlier prior to his admission, he was diagnosed with psoriasis. Three years earlier, he started to experience cervical pain and cervical disturbance of excursion. One year earlier, he was diagnosed with psoriatic arthritis (PsA) because of existence of spondyloarthropathy and negative rheumatoid factor based on CASPAR criteria. Methotrexate was started, but not effective. Three months earlier, he experienced trismus. On admission, MRI showed arthritis of temporomandibular joints. He have no enthesitis, dactylitis and peripheral arthritis. We used adalimumab to his PsA. Although CRP and BASDAI were improved, improvements of cervical disturbance of excursion and trismus were slight. Discussion: Our patient's PsA was not typical because there was no peripheral arthritis and rapid progression of trismus during three month was seen. There are some case reports of patients with PsA with trismus. It is important to include PsA as a differential diagnosis of trismus. Clinical importance: Once bony ankyloses of temporomandibular joints occurs, it is difficult to improve and a quality of life is impaired. To keep needs to treat earlier by biologics in mind may be important.

P1-243

A Case of Type 2 Peripheral Enteropathic Arthritis due to Ulcerative Colitis

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Conflict of interest: None

Clinical importance: It is suggested that the treatment with methotrexate (MTX) was effective for a case of type 2 peripheral arthritis of enteropathic arthritis (EA) due to ulcerative colitis (UC). **Case**: A 30-year-old male visited our clinic with non distractive polyarthritis. He had a history of UC remitted with PSL, cyclosporine and mesalazine. These drugs were tapered and he became a drug free. However, he suffered from polyarthritis. His levels of RF, ACPA, and ANA were negative. He did not show digestive symptoms. MTX was effective. **Discussion**: EA is one of spondyloarthritis due to inflammatory bowel disease (IBD) such as UC, with axial and peripheral arthritis. Moreover, the peripheral EA is classified into type 1 (pauciarticular) and type 2 (polyarticular). Type 2 has lesions of 5 or more joints and symptoms usually persist for months to years, runs a course independent of IBD, and associated with uveitis but not with other extraintestinal manifestations. Sulfasalazine (SSZ) is the first drug to treat type 2, and the biologics is selected for resistant cases to SSZ. In the present case, MTX was effective for type 2 peripheral EA after remission of UC.

P1-244

Clinical analysis of cases with possible axial spondyloarthritis

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Conflict of interest: None

This study was conducted to evaluate the issue of clinical diagnosis of axial spondyloarthritis (SpA) including ankylosing spondylitis and non-radiographic axial SpA in Japanese patients and to examine possible reasons for diagnostic difficulties. Clinical, laboratory and imaging parameters in patients with possible axial SpA were assessed. Recognition of inflammatory back pain and extra spinal manifestation is important to diagnose axial spondyloarthritis. If sacroiliitis on imaging is negative, diagnosis based on ASAS axial SpA criteria can not be made under the condition where HLA -B27 laboratory results are not available in real clinical practice in Japan.

P1-245

A case of ankylosing spondylitis complicated with RS3PE syndrome

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Conflict of interest: None

A 70 years old man was suffering from morning back pain from 20 years old, and performed lumber osteotomy at 25 years old. He was diagnosed as ankylosing spondylitis at 40 years old. In February, he fell down and broke his left distal radius fracture. After removing the cast, his left hand became swelling and pain, and was diagnosed as CRPS. In June, he recognized swelling and pain in his right hand. Treatment with SASP, NSAIDs and PSL had been started, but his symptoms were not improved. Bamboo spine was observed on the X-ray, and he have both swollen hands and pain, stiffness and weakness at the level of the shoulders and pelvic girdle. MRI imaging shows the bone marrow edema and synovial thickening in the ring finger proximal phalanx bone head, ulnar distal end and carpal bone. These findings indicated that ankylosing spondylitis complicated with RS3PE syndrome. Treatment with PSL 15mg/day had been started. Although the rapidly improvement for pain and swollen of hands had been observed, stiffness of the whole body and inflammatory was still continued. BASDAI and BASMI showed high disease activity of ankylosing spondylitis. Finally, biological agents (IFX) had been started, and promptly improved the stiffness and joints pain, and inflammation.

P1-246

A case of Yersinia triggered reactive arthritis

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Conflict of interest: None

A-23-year-old man was visited our hospital on August 6, 2015, because of polyarthralgia. He participated in a barbecue, two week before visit to our hospital and noticed polyarthralgia, a week before. At the time of the first medical examination, his C-reactive protein (CRP) was remarkably high. Rheumatoid factor, anti-CCP antibody and anti-nucleolar antibody were negative and HLA B27 was positive. US and MRI revealed active synovitis of elbow, hip, knee and ankle joints. Although he did not complain about abdominal symptom, CT revealed lymphadenopathy at ileocecal area. On the colonoscopy, the mucosa of ileocecal area was edematous and erosive. Histological examination showed bacterial bodies, and no granuloma. On serum, antibody to Yersinia enterocolitica was elevated. So, a diagnosis of the Yersinia triggered reactive arthritis. Antibiotic and NSAIDs were ineffective. His symptom was resistant to

steroid. MTX was added, poly arthritis gradually improved. We reported a rare case, in Japan, of yersinia triggered rafractory arthritis.

P1-247

A case of ankylosing spondylitis successfully treated with methotrexate

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Conflict of interest: None

The patient is a 38-years-old man. He was aware of the low back pain since he was a high school student. He took NSAIDs when he felt strong pain. However, NSAIDs didn't work well. There was a possibility of Ankylosing Spondylitis (AS), so he was introduced to our hospital. He had buttocks pain, extension disturbance of the lumber vertebra, and tenderness of sacroiliac joints. The pain became to be strong by having a break, to be weak by moving. It is a symptom specific to the AS. X-ray showed typical 'bamboo spine' and osteosclerosis of sacroiliac joints. Therefore, we diagnosed AS based on Modified *New York* Criteria in *1984*. Now, the fundamental treatment for AS is not established. We usually treat the patients by drug therapy and physiotherapy. The drug therapy includes painkiller, DMARDs (for example Salazosulfapyridine;SASP and Methotrexate;MTX), *or TNF-α inhibitors* (for example *infliximab and* adalimumab). The evidence of DMARDs for AS has not been established, but a few studies report the effect of DMARDs. So we dosed him with MTX 6mg/week. The treatment eased him of his pain gradually, and decreased CRP. We report the experience that MTX relieved the sacroiliac arthritis of chronic AS.

P1-248

The interim analysis of post-marketing all-patient surveillance of canakinumab in Japanese patients with cryopyrin-associated periodic syndrome

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Conflict of interest: None

[Objectives] A post-marketing all-patient surveillance of canakinumab, a human Anti-interleukin-1β monoclonal antibody is under way to assess its safety and efficacy in Japanese patients with cryopyrin-associated periodic syndrome. This is an interim report of 3 years post-launch in daily medical practice. [Methods] A total of 55 patients were registered at 36 clinics or hospitals with 48 included in a database lock in December 2014. 47 patients were included in the safety population, excluding one for off-label use. [Results] The mean age of the patients at treatment initiation was 20.8 years. Adverse drug reactions (ADRs) were reported in 34.0%. Nasopharyngitis (8.5%) and upper respiratory tract infection (6.4%) were most frequent. 46 patients were included in the efficacy population. At 24 to 104 weeks, 80-90% of the patients remained flare free after achieving remission. [Conclusions] The interim analysis showed no new safety concerns of canakinumab and remission was maintained in many of the patients. The assessment of the safety and efficacy of canakinumab should be continued through this surveillance. This surveillance is sponsored by Novartis Pharma K.K. and professional medical writing assistance was provided by Novartis medical writers.

P1-249

Mevalonate kinase deficiency in Japan

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Conflict of interest: None

Mevalonate kinase deficiency (MKD) is a autosomal recrssive disease caused by mutations in the gene encoding mevalonase kinase (*MVK*). Patients experience recurrent fever of unknown origin accompanied with rash, and there have been no reports of nationwide study in Japan. Recent reports describe liver damage or hemophagocytic syndrome in MKD patients, but the incidence of these complications is unclear. We therefore performed nationwide study and identified 10 patients of MKD. They show typical symptoms such as persistent or recurrent fever since infants accompanied with rash or abdominal symptoms. We identified increased levels of urine mevalonate acid and MVK mutations in all the patients. In case of novel mutations, we measured the mevalonate kinase activity of peripheral blood, and found potent decrease in all the cases. Notably, 4 of the 10 cases showed liver damage, and 3 of them fulfilled the diagnostic criterion of HLH-2004. While patients with recurrent fever achieved the remission of the inflammation with NSAIDs alone, those with persistent fever experienced severe side effects such as low stature or obesity due to continuous steroid treatment. These patients achieved reduction of steroids and catch-up growth after the introduction of anti-IL1 biological treatment.

P1-250

Functional analysis of inflammasomes in human peripheral blood mononuclear cells expressing *PYCARD/ASC* variant

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Conflict of interest: None

[Objectives] We previously found the *PYCARD/ASC* variant mRNA lacking exon2 portion in Japanese patients with palindromic rheumatism (PR). Although PYCARD/ASC is essential factor of inflammasomes, the biochemical function and the pathogenesis for PR of this variant are still unclear. Here we compared IL-1β production of PBMC expressing variant or wild type form of *PYCARD/ASC*. [Methods] The subjects were three healthy donors expressing heterozygous *PYCARD/ASC* variant, and two healthy donors expressing homozygous *PYCARD/ASC* wild type. PBMCs obtained from these donors were primed by using PMA (0.5 μM), then stimulated with 100 μg/mL monosodium urate (MSU). IL-1β concentrations in culture supernatant were measured by ELISA. [Results] IL-1β concentrations without stimulation in case with heterozygous group and wild type homozygous group were 31.11 ± 10.65 and 13.43 ± 6.98 (pg/mL), respectively. The activation rate of NLRP3 inflammasomes which was calculated from increasing ratio of IL-1β concentrations by MSU stimulation in case with heterozygous group and wild type homozygous group were 132 ± 8 and 158 ± 21 (%), respectively. [Conclusion] Our results suggest that the variant PYCARD/ASC interfere the activities of NLRP3 inflammasomes.

P1-251

Prevalence of MEFV gene for Autoinflammatory diseases

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Conflict of interest: None

【Object】The MEFV gene was identified that was characteristic of familial Mediterranean fever (FMF), and has begun to be paid attention even in this country. We examined about participation of MEFV gene variation by the FMF and the autoinflammatory disease, which was fever of unknown origin and in which we can't find any autoantibody.【Results】We analyzed genetic date for 95 patients during a period from 2008 through 2015. Eight of 12 typical FMF were with positive M694I variation, 11 were with E148Q. Three of 8 atypical FMF were with E148Q, three with R202Q, one with R408Q and P369S.Five of 11 Seronegative Rheumatoid Arthritis (RA) were with positive E148Q, three with L110P.

Two of 11 AOSD were with positive E148Q, one with R202Q.Four of 10 Gout were with E148Q, two with R202Q.Thee of 8 Behcet's disease were with E148Q, two with R202Q, one with positive G304R. All Three cases of Psoriatic Arthritis were with E148Q.【Conclusions】Not only MEFV exon 10 variants (M694I) but also exon 2 (E148Q) is positive frequently.M694I is negative in all cases of FMF variants Seronegative RA, AOSD, Gout, Behcet's Disease, Psoriatic Arthritis, E148Q is positive frequently in these cases. Relations of Exon2 such as E148Q and Exon3 is suggested in such autoinflammatory diseases except for FMF.

P1-252

A suspected case of PAPA syndrome responding to Adalimumab

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Conflict of interest: None

PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne) is categorized in autoinflammatory syndrome, and it is rarely reported in Japan. We report a 19-years-old Japanese case of clinically suspected PAPA syndrome without known genomic mutation. His mother was diagnosed as having osteoarthropathy, and his older brother have camptodactyly of bilateral thumb and fifth finger. His grandmother and her son were treated as having rheumatoid arthritis. The patient presented pyoderma gangrenosum at the age of five. After 3 years, he developed polyarthritis, and received synovectomy of hand and knee joint. The pathological findings showed the infiltration of neutrophil, and the synovial fluid contained numerous neutrophil. He started Infliximab at age 11 years and showed dramatic improvement of arthritis and pyoderma gangrenosum. However, he discontinued infliximab due to lichenoid eruption at age 17 years. After four months, arthritis was worsening. He started tocilizumab, and he achieved remission of arthritis. After one month, pyoderma gangrenosum was relapsed. He started Adalimumab, led to remission of both skin and joint involvement. He have no mutation of *PSTPIP1*, but have heterozygous mutation of E148Q in *MEFV* gene, and it might cause neutrophilic inflammation.

P1-253

A case of the severe gouty polyarthritis, and took the subacute progress

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Conflict of interest: None

A 68-years-old man was admitted to the Rheumatology because of polyarthritis and fever. Laboratory tests revealed leukocytosis, high CRP level, and hyperferritinemia. We ruled out infection, rheumatoid arthrits, polymyalgia rhueumatica, paraneoplastic syndrome. He had gout and recurrent polyarthritis before admission. Ultrasonography (US) showed the power doppler (PD) enhancement of the synovium, double contour, and cristal deposition. Thus we diagnosed gouty arthritis. We gradually reduced PSL since the arthritis was reduced. We carried out only a colchicine cover. In addition, the PD enhancement of the synovium was disapeared. So he was discharged. However, serious polyarthritis recurred. In spite of the treatment of PSL30mg/ day for seven days, the polyarthritis recurred again two weeks later. Therefore We maintained PSL at 10 mg/ day. We prescribed it for two months and finished it since the inflammatory findings disappeared. Recently US spread in rheumatologist, and was useful for the diagnosis of the gouty arthritis in this case. Whearas, the gout is classified in the autoinflammatory syndrome, but the mechanism are not clear. We experienced a case of the severe gouty polyarthritis which took the subacute progress and add some consideration from literatures and report it.

P1-254

One case of high riding vertebral artery associated with vertical subluxation of upper cervical spine

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Conflict of interest: None

The affect of rheumatoid arthritis (RA) on the anatomy of the cervical spine was still unknown. Previous our study described for the RA patients there was a significant correlation between isthmus height and vertical subluxation as well as between internal height and vertical subluxation. We present a case of isthmus height "so called high riding vertebral artery" associated with vertical subluxation of upper cervical spine for short term period. A 58-year-old female was diagnosed as having rheumatoid arthritis at age of 49. Radiographic findings revealed atlantoaxial subluxation without vertical subluxation at upper cervical spine. At aged 59 radiographic findings revealed vertical subluxation at upper cervical spine. We diagnosed high riding vertebral artery at the same time. At aged 67 her subluxation did not develop and not have neurological deficit.

P1-255

A comparison of anterior approach and posterior approach rheumatoid arthritis patients in hip arthroplasty

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Conflict of interest: None

[Object]Whether there is a difference in the perioperative period by the Anterior or posterior approach in total hip replacement (THA) patients with rheumatoid arthritis (RA). [Target] Direct anterior approach (DAA) of the THA, which was carried out in our department was 9 hips and the crotch that was carried out in, since 2012 posterior approach (Posterior Approach, PA) target 31 crotch that was carried out in. [METHODS] compared DAA and PA cases about surgery time, amount of bleeding, drainage amount of drain, perioperative complications, dislocation rate, progression of postoperative ADL, change of postoperative pain scale. [RESULTS] The proficiency level of problem or surgery time, amount of bleeding tended covered with DAA. Complications was less. Improvement of postoperative ADL is seen early trend, the strength of the pain was reduced. Dislocation it was not seen. [Conclusion] When the procedure is familiar DAA I considered advantage of early recovery is large in the low activity RA patients.

P1-256

Medial Soft Tissue Releases Reduce External Rotation Angle of the Femoral Component during PS-TKA with Modified Gap Technique

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Conflict of interest: Yes

Introduction: The effect of medial soft tissue releases on the external rotation angle of the femoral component was assessed during PS-TKA with a modified gap control technique, Methods: 840 consecutive knees were assessed. All knees were divided into 5 groups according to the degree of soft tissue release. Only deep MCL release was necessary in 464 knees (Group I). Only the superficial MCL was released in 49 knees (Group II). Only POL was released in 129 knees (Group III). Both the superficial MCL and POL were released in 169 knees (Group IV). Additional pes anserinus was released in 29 knees (Group V). Seven parameters were compared among the five groups. Results: The average external rotation angle of the femoral component was 4.8°, 5.3°, 4.6°, 4.3°, 4.1°, respectively. The external rotation angle in Group IV and V was significantly smaller compared to those in Group I ($p<0.001$). Discussion: The more knees that were varus before TKA, the more medial soft tissue release were necessary during TKA. The external rotation angle of the femoral component varied among the cases, and medial soft tissue release reduced the external rotation angle.

P1-257

Treatment of rheumatoid arthritis, which took differentiate from infectious knee arthritis

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Conflict of interest: None

It is necessary to rule out infection, pseudogout to diagnose rheumatoid arthritis (RA). We report three cases that was difficult to diagnose rheumatoid arthritis and infectious knee arthritis. Case1:80-years-old female. She was consulting from nearby orthopedic clinic to treatment infectious knee arthritis. We took arthroscopy to this patient because bacteria culture was negative. Pathological result was RA. Blood sampling results were RF, ACPA positive. Though we started MTX for treatment, effect was insufficient, and we took total knee arthroplasty (TKA). Finally examination, RA control was well because DAS-CRP was 2.38. Case2:73-yeasr-old female. We performed TKA to diagnose osteoarthritis from X-ray, CRP was negative. After 6-months she complained knee swelling. We erformed synovectomy and exchanging polyethylene liner. Pathological result was not RA. After 6-months synovectomy, loosening was not occurred at all. We started PSL+SASP diagnosing RA because bilateral shoulder arthritis were complicated. Blood sampling results were RF, ACPA negative. Finally examination, RA control was well because DAS-CRP was 2.52

P2-001

Profiles and clinical parameters of elderly rheumatoid arthritis(RA) patients

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Conflict of interest: None

In eldery RA patients, appropriate assessment and treatments are important. But we often experience that there is a great difference with evaluator's global assessment (EGA) and patient's global assessment (PGA). We investigate that profiles and clinical parameters of elderly RA patients. As of September 2015, we analyze 56 RA patients (9 men, 47 women, average age 72.0 years old, average duration 106 months, average DAS28-CRP 2.00) who treated with our hospital. And the results for the two groups, group A (≧65 y.o.) and group B (≧75 y.o.) were analyzed separately. We define 20mm and more between EGA and PGA as a significant divergence. In all RA patients, both EGA and PGA are significantly correlated with disease activity. PGA is also correlated with bone fractures and HAQ. Group A denote the same tendency, and there is positive correlation between EGA and Stage, PGA and Class. In group B, EGA only correlated with SJC, and PGA correlated with TJC and HAQ. The divergence between EGA and PGA is affected by disease activity, HAQ and PGA regardless of age. In elderly RA patients, evaluator make much account of subjective assessment. While patients make much account of objective assessment. We should fill the divergence to achieve effective treatment for elderly RA patients.

P2-002

Patients aged over 80 years with rheumatoid arthritis in AORA registry

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Conflict of interest: None

[Objectives] We investigated the data of elderly patients with RA in Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry. [Methods] Of 2021 RA patients (mean age, 66 years) in the AORA registry, we examined 324 patients (59 men and 265 women) aged ≥80 years (mean age, 84 years; range, 80-99 years). [Results] The mean disease period was 14 years (range, 2 months-66 years). The Steinbrocker classification of the patients was as follows: stage I, 82 patients; stage II, 69 patients; stage III, 80 patients; stage IV, 87 patients; class 1, 77 patients; class 2, 128 patients; class 3, 89 patients; and class 4, 22 patients. MTX was administered to 101 patients (mean, 5.5 mg/week), and PSL to 170 patients (mean, 3.8 mg/day; range). The csDMARD use was as follows: BUC, 95 patients; SASP, 84 patients; TAC, 21 patients; and others, 26 patients. Biologics were administered to 31 patients (ETN, 12; ABT, 6; ADA, 4; TCZ, 4; and others, 5). According to DAS28ESR, remission and low disease activity were found in 134 patients. [Conclusion] The study showed the low using ratio of MTX and high using ratio of PSL, similar to previous reports. DAS28ESR of the elderly RA patients were higher than those in the entire AORA registry.

P2-003

The causes of death in deceased patients with RA by NinJa 2014 cohort

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Conflict of interest: None

[Objectives]The purpose of the present study is to evaluate the age at death and the cause of death in patients with rheumatoid arthritis (RA) in 2014 [Methods]100 Japanese deceased patients with RA, who were registered in the large cohort database (NinJa: National Database of Rheumatic Diseases by iR-net in Japan). We investigated the age at death, the causes of death of all patients. [Results]The mean age at death was 75.5years old. The major cause of death in deceased patients was infection in 28patients involving in pneumonia in 23patients. Next was malignancy in 24 patients, respiratory dysfunction involving intestinal pneumonia in 17 patients, cardiovascular disease in 12 patients. [Conclusion] The life expectancy of Japanese patients with RA was getting better. But the average of RA onset is recently older, the duration from RA onset to death is shorter. The major causes of death were still infection involving in bacterial or viral or pneumonia, opportunistic infection.

P2-004

The locomotive syndrome in Japanese patients with RA by NinJa2014

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Conflict of interest: None

[Objectives]The purpose of the current study is to evaluate the locomotive syndrome in patients with RA in Japan[Methods] The materials are 2255 Japanese patients with RA, who were registered in the large cohort database (NinJa: National Database of Rheumatic Diseases by iR-net in Japan). We used the 25-question risk assessment (locomo25) and investigated the number of locomotive syndrome in those patients.[Results] The 1221 patients with RA are diagnosed the locomotive syndrome in these group. The rate is 59.6%.[Discussion] The Japanese Orthopaedic Association (JOA) proposed the concept of locomotive syndrome in 2007. This syndrome, or "locomo" in short, refers to those elderly who have come to need nursing care services because of problems of the locomotive organs, or have risk conditions which may require them to have such services in the future. The current study is showed the high rate of the locomotive syndrome in Japanese patients with RA.

P2-005

The clinical features of elderly-onset rheumatoid arthritis

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Conflict of interest: None

Background: It could be difficult to diagnose elderly-onset rheumatoid arthritis (EORA), because patients with EORA frequently present with different clinical manifestations from younger-onset rheumatoid arthritis (YORA). We conducted this study to investigate the difference in clinical presentations between EORA and YORA. **Patients and Method:** Eighty patients of newly diagnosed RA were enrolled. The patients divided into 2 groups by age: patients aged ≤ 70 (EORA) and < 70 (YORA). We compared the clinical features between the EORA group and the YORA. **Results:** Twenty-two patients were categorized as EORA. There were no significant differences between two groups with respect to gender, involved joint numbers, visual analogue scale, and seronegative rate of rheumatoid factor and anti-citrullinated protein antibody. On the other hand, the frequency of major joints onset was significantly higher in the EORA than in the YORA (86.3% vs 39.7%, p = 0.0003). Furthermore, significantly lower hemoglobin level and higher C-reactive protein and ferritin levels were found in the EORA than in the YORA. **Conclusion:** The patients with EORA present with higher frequency of major joints onset and more severe serological inflammatory reaction compared with YORA.

P2-006

The clinical features of anti-centromere antibody-positive arthritis patients

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Conflict of interest: None

[Object] Anti-centromere antibody is known related with Sjögren's syndrome and primary biliary cirrhosis in addition to the CREST syndrome. Rheumatoid arthritis-like polyarthritis can be seen in the part of the antibody-positive cases. [Methods] We investigated with respect to clinical characteristics in arthritis patients with anti-centromere antibody-positive. [Results] Anti-centromere antibody was measured 523 cases in our department from January 2005 to September 2015. Positive case was 168 cases, and existed polyarthritis was 20 cases (11.9%). Clinical diagnosis, including overlap cases, was rheumatoid arthritis 19 cases (94.7%), Sjögren syndrome 9 cases (45%), localized type systemic scleroderma two cases (10%), diffuse type systemic scleroderma one cases (5%). Anti-CCP antibody-positive case was 6/16 cases (37.5%), rheumatoid factor positive case was 10/17 cases (58.8%). Corticosteroid alone or anti-rheumatic drug combination as a treatment for arthritis was 11 cases (55%). anti-rheumatic drugs was 15 cases (75%), biologics was only 1 case (5%). In most cases, joint destruction of the X-ray was mild. [Conclusions] Most of anti centromere antibody-positive arthritis were diagnosed as rheumatoid arthritis and treated with anti-rheumatic drugs.

P2-007

Prevalence and clinical features and risk factors associated with non-tuberculous mycobacteriosis in patients with rheumatoid arthritis -Analysis of NinJa 2012-2014 database-

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Conflict of interest: None

Objectives: In RA patients (pts) the epidemiologic data about non-tuberculous mycobacteriosis (NTM) are scarce. We aimed to analyze the prevalence, clinical features and risk factors associated with NTM in RA pts. **Methods:** We investigated NTM prevalence rate in RA pts registered in NinJa in 2012 to 2014. We surveyed the complication of NTM, the reasons of diagnosis of NTM, associated other diseases, detecting bacterial species, chest radiographic findings. **Results:** By the reason of hospitalization prevalence of the pts associated with NTM (RA-NTM) by NinJa 2014 was 12/15,023 (79.9 cases/100,000 persons). Prevalence of NTM surveyed by questionnaire was 751.2 in 2012 and 971.1 in 2013, both of which were remarkably high. Incidence rates of RA pts enrolled in NinJa 2012 in the fiscal year of 2013 was 58.5 cases/100,000 persons year and is considered to be remarkably high. By analyzing NinJa 2012, RA-NTM showed a higher age, a higher disease activity and a higher class of functional impairment than in non-NTM pts. Considering with treatment, RA-NTM were less frequently used with MTX and TNF inhibitors, and more glucocorticoids compared with non-NTM pts. **Conclusion:** It is suggested that NTM prevalence rate in RA pts was remarkably high compared to that in the general population.

P2-008

IL-1β and IL-17A regulate CXCL2 through AU-rich element in 3'UTR of its mRNA

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Conflict of interest: Yes

[Object] CXCL2 is a chemokine that is secreted from various cells to attract chemotaxis of polymorphonuclear leukocytes. CXCL2 has unique sequence in its 3' untranslated region (3'UTR) named AU-rich element (ARE), which is characterized by repeats of AUUUA motif. It is known that some RNA binding proteins including TIA1, TIAR, TTP and HuR associate with ARE of mRNA and regulate their post-transcriptional metabolism. We examined the effects of cytokines on metabolism of *CXCL2* mRNA. [Methods] The 3'UTR of *CXCL2* mRNA was cloned into firefly luciferase gene in the pmirGLO Dual-Luciferase miRNA Target Expression Vector. TIA1, TIAR, TTP or HuR were co-transfected with the reporter. The expressions of *CXCL2* mRNA were examined by real-time PCR in fibroblast-like synoviocytes. [Results] IL-1β and IL-17A increased the luciferase activities of the reporters harboring the 3'UTRs of CXCL2. The effects depended on the dose of these cytokines. Co-transfection of TTP with the reporter plasmid suppressed the luciferase activities. IL-1β and IL-17A up-regulated the *CXCL2* mRNA expressions in fibroblast-like synoviocytes. [Conclusions] IL-1β and IL-17A increase the expression of *CXCL2* mRNA. It is suggested that the metabolism of *CXCL2* mRNA is accelerated by TTP through ARE.

P2-009

The involvement of ADAM family and inflammatory cytokines in the inflammatory myopathy

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Conflict of interest: None

[Object] To examine the involvement of a disintegrin and metalloprotease (ADAM) family and inflammatory cytokines in inflammatory myopathy such as polymyositis (PM), dermatomyositis (DM), clinically amyopathic dermatomyositis (CADM). [Methods] Serum levels of ADAM15, ADAM17, CX3CL1, CXCL16, and TNFα of patients with inflammatory myopathy were measured by the ELISA method. The association with clinical manifestations and clinical data were examined. [Results] Serum ADAM15 and ADAM17, CX3CL1, CXCL16 levels of patients with inflammatory myopathy were significantly high level in comparison with the control group, and were showed a significant correlation between ADAM family and inflammatory cytokines. Also, serum ADAM15 level was correlated with serum ferritin level. In the comparison between three groups of PM, DM, CADM, serum ADAM15 and ADAM17 levels were higher in DM group, and were lower in CADM group. Serum CX3CL1 level was higher in DM. [Conclusions] ADAM family was involved in the expression of inflammatory cytokines such as CX3CL1 and CXCL16 in the pathogenesis of the inflammatory myopathy.

P2-010

The relationship between Ets transcription factors, Ets-1 and Fli-1, and interferon signature genes in peripheral blood mononuclear cells from patients of systemic lupus erythematosus

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Conflict of interest: None

Objective Previous studies using lupus model mice have shown that *Ets-1* knockout mice had more and *Fli-1* hetero-knockout mice had less severe lupus pathogenesis than wild-type mice. We speculated that a relationship exists between Ets transcription factors and interferon (IFN) signature genes in patients with systemic lupus erythematosus (SLE). **Methods** We collected peripheral blood mononuclear cells (PBMC) from 53 SLE patients, 41 rheumatoid arthritis (RA) patients and 30 healthy donors (HD). Total RNA was extracted from the PBMC of each patient and reverse transcribed into cDNA. Expression levels of *Ets-1*, *Fli-1* and several IFN signature genes were measured by real-time PCR and analyzed for relationships between them. **Results** *Ets-1* expression was low in SLE and RA, and higher in untreated than treated SLE patients. *Fli-1* expression was lower in SLE than in RA and HD. *Ets-1* and *Fli-1* were positively correlated, and expression levels of both were low in SLE patients treated with high-dose prednisolone. Expression levels of *IFIT1* and *PKR* were higher in SLE than in RA and HD, and were each positively correlated with both *Ets-1* and *Fli-1*. **Discussion** Expression of *Ets-1* and *Fli-1* might affect the expression of type I IFN in the PBMC of SLE patients.

P2-011

A genetic prediction model for methotrexate efficacy based on the predictive model for methotrexate hepatotoxicity

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Conflict of interest: None

[Objectives] 1) To evaluate the performance of our genetic predictive model for MTX hepatotoxicity (Model A, 13 SNPs) in terms of prediction of the efficacy of MTX in another cohort. 2) To construct a new prediction model for efficacy by adding MTX metabolism-related SNPs to Model A. [Methods] 1) According to the EULAR response criteria, 49 RA patients were classified into 22 responders and 27 non-responders, and discriminative ability of Model A for MTX efficacy was examined. 2) A new predictive genetic model for efficacy of MTX (Model B, 9 SNPs) was created by a stepwise selection procedure after addition of 8 SNPs in MTX metabolism-related genes to the 13 SNPs. [Results] 1) Model A (hepatotoxicity model) could discriminate 22 responders from 27 non-responders with a sensitivity of 73% and a specificity of 81%. 2) Model B (9 SNPs) consisting of including 5 SNPs related to MTX metabolism and 4 SNPs from Model A showed a sensitivity and a specificity were of 100% and 85%, respectively. [Conclusion] Our 13-SNP prediction model for MTX hepatotoxicity was shown to discriminate MTX responders from the non-responders. Moreover, a new predictive genetic model including MTX metabolism-related genes could discriminate predict the therapeutic efficacy of MTX more accurately.

P2-012

Lymphomas in rheumatoid arthritis patients treated with methotrexate

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Conflict of interest: None

Background:RA patients treated with methotrexate (MTX) can develop lymphoproliferative disorders that share characteristics with the lymphomas occurring in immunosuppressed patients. Patients and Methods: We analyzed 1905 RA patients admitted to our clinic including 119 RA patients received MTX. Results: A total of 27 cases of lymphadenopathy were found. 5 cases showed improving of lymphadenopathy after stop to use MTX, although 4 cases of lymphoma were recorded. Among the 2 patients who were treated by MTX withdrawal alone, This study indicated that the risk of NHL was not significantly increased in dose of MTX and duration of RA compared to non-malignant lymphoma patient. Conclusion: We have to aware of lymphoproliferative disorders using immunosuppressant.

P2-013

The risk factors of adverse effects with methotrexate in treatment of rheumatoid arthritis

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Conflict of interest: None

Methotrexate (MTX) is an important to the conventional care of patients with rheumatoid arthritis (RA). The aim of this study was to assess the risk factors for the discontinuation of MTX by adverse effects. The patients with RA completed at least 5 years of follow-up were registered and examined the risk factors for discontinuation of MTX by its adverse effects. In total, 128 patients had completed at least 5 years of follow-up. During the period of follow-up, 17 cases discontinued within 8 weeks due to adverse events (vomiting, eruption, liver dysfunction or oral ulcer). 11 cases discontinued after 12 weeks (interstitial pneumonia 3, pancytopenia 3, malignant lymphoma 3).40 cases (31.2%) needed dose change of MTX, increased dose in 24 cases, and decreased dose in 16 cases. Within 8 weeks no risk factor was detected for discontinuation of MTX. Although, the hazard ratio for discontinuation after 12 weeks with high disease activity versus moderate or low disease activity was 3.350 (95%CI 1.06-10.6 P=0.0396). RA patients show high persistence rates with MTX compaired with othe DMARDs, however high disease activity was the risk factor for adverse effect of MTX after 12 weeks. Attention is necessary for serious adverse effects when teat a patients with high disease activity by MTX.

P2-014

Multi-disciplinary approach for the prevention of methotrexate-associated adverse events

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Conflict of interest: None

[Purpose] Methotrexate (MTX) is golden standard for the treatment of rheumatoid arthritis (RA). MTX-associated severe adverse events and death are continuously reported particularly in elderly people. In order to prevent these events, we have established clinical team including the in-house pharmacists, RA care nurses and a rheumatologist since October 2013. This study reports the improved results of our multi-disciplinary approach for the prevention of MTX-associated incidence. [Methods] Medical charts of RA patients to whom MTX was prescribed from July 2012 to March 2015 were retrospectively reviewed. [Results] MTX were prescribed in 94 patients, total 137 potential events were reported in 58 (62%) cases. They included 11 adverse adherence to MTX in 9 cases, and 126 events associated with sick days in 54 cases. Among them potential adverse events were reported in 18 cases. Incident events decreased and MTX-related adverse events were not observed during the research periods. [Conclusion] Our multi-disciplinary patient's care seems to decrease MTX-associated incidence resulting in the prevention of MTX-related adverse events.

P2-015

Efficay and tolerability of iguratimod in patients with rheumatoid arthritis.

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Conflict of interest: None

Iguratimod (IGU) is a novel csDMARD that exerts effects by inhibiting the production of immunoglobulins and cytokines such as interleukin-1,-6,-8 and TNF. (Objective) To investigate the efficacy and safety of IGU in Japanese patients with active rheumatoid arthritis (RA). (Methods) We evaluated forty eight patients with rheumatoid arthritis who received IGU (mean age: 71.7, male/female ratio:5/11, mean disease duration: 146.7 months, stage I:7,II:18,III:12,IV:11,Class1:5,2:36,3:5,4:2). All patients fulfilled the ACR /EULAR criteria for RA and the efficacy was assessed by DAS (CRP), HAQ and MMP-3. (Results) Of the forty eight patients evaluated, twenty six patients stayed on the drug, and their DAS (CRP) improved from 3.79 to 2.44. Liver dysfunction and drug inefficacy were the main causes of discontinuation. Patients with non-tuberculous mycoplasma pulmonary infections who were unable to receive biological treatments and those who suffered MTX associated lymphoproliferative diseases also tolerated treatment with IGU. (Conclusion) Our data indicate that IGU alone or in combination with other csDMARDs may effectively treat active RA.

P2-016

Efficacy and safety of iguratimod in patients with rheumatoid arthritis: focus on the continuation rate

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Conflict of interest: None

[Object] To investigate the efficacy and safety of iguratimod in patients with rheumatoid arthritis (RA) with a focus on the continuation rate of iguratimod. [Methods] This study included the RA patients who had been Iguratimod at our hospital until May 2014. The continuation rate was evaluated at month 6, 12 and 18. [Results] One hundred one patients were included in this study. Of these patients, nineteen patients received concomitant biologics, and fifty-eight of other 82 patients received comcomitant methotrexate (MTX). The continuation rate of iguratimod at month 6, 12, and 18 were 83%, 75 %, and 70 %, respectively. At month 18, the continuation rate of iguratimod with concomitant biologics was 100%(19/19), those with concomitant MTX was 76% and those without concomitant MTX was 33%. The rate of withdrawal because of adverse reaction was 14%(n=14, MTX (+)=5, MTX (-)=9). Ten cases were withdrawn within 3 months after the first administration, and 5 cases were within one month. [Conclusions] The combination therapy of iguratimod with biologics or MTX seem to be effective and safety.

P2-017

Use of US in outpatient clinic can contribute to the selection of favored site for corticosteroid injections

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Conflict of interest: None

[Object] To explore the conditions which are suitable for intra-/peri-articular corticosteroid injection therapy by clinical assessment and musculoskeletal ultrasound (US) in outpatient clinic. [Methods] We analyzed consecutive records of intra-/peri-articular corticosteroid injection during 2 years before and 1 year after a portable US device became in operation. Doses of triamcinolone acetonide were classified into 3 grades (low, 2~4mg; moderate, 6~15mg; high, 16~40mg). Efficacy of injection was classified into 3 grades by the duration of good condition (effective, >3 Ms; partial, 1~3 Ms; ineffective <1 M). US evaluation of synovitis before and after injections was done in some patients. [Results] After the US became in operation, frequency of injections increased, doses per injection decreased, frequency of injection to fingers and toes increased, frequency of injection to tendon sheath and bursa increased, and frequency of effective injection increased. Effective injections were associated with injections to fingers and toes and injections to tendon sheath and bursa. US follow-up revealed that tenosynovitis responded better than joint synovitis did. [Conclusions] Use of US in outpatient clinic can contribute to the selection of favored site for corticosteroid injections.

P2-018

Medication adherence of MTX in Japanese RA patients

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Conflict of interest: None

【Introduction】Although MTX is important drug for RA treatment, There have been no studies of MTX adherence in Japan. The purpose of this study was to estimate the medication adherence of MTX in Japan. 【Methods】Study design was Cross sectional study. Participants were RA patients in Showa University Hospital, Showa University Northern Yokohama Hospital, Showa University Fujigaoka Hospital and Kanto Rosai Hospital. We assessed RA activity (DAS28ESR), Age/Gender, ADL (mHAQ), MTX dose/usage, Depression (CESD), Reliability for medication (BMQ), pain (BPI), Social desirability (SDS), QOL (SF8). Primary outcome was distribution of MTX adherence by MMAS-8. Seconday outcome were the association between MMAS8 and pre-described variables.【Results】165 RA patients were enrolled. The mean age was 62.0 years and 86.0% were female. MMAS-8 were low adherence (sore <6) 20/165, medium adherence (6<= sore < 8) 99/165, high adherence (score=8) 46/165. There were significant difference between groups of MMAS8 in age (p=0.014), mHAQ (p=0.015), SDS (p=0.001), SF-8 PCS (p=0.036).【Conclusion】The majority of MTX adherence in Japan was medium adherence. There may be associations between adherence and age, QOL, social desirability.

P2-019

Recent trend for pain management by pharmacotherapy in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Though clinical remission and absence of inflammation and immunologic activity have become realistic goals in rheumatoid arthritis (RA), pain remains a common experience for RA patients. [Methods] 151 RA patients at Nagoya University Hospital who could follow up for 3 years, and tender joint count, swollen joint count, and CRP were all under 1, were enrolled in this study. Disease activity was assessed using DAS28-CRP, and PGA 0-100 visual analog scale. [Results] Patients were primarily women (80.1%). Mean age was 58.7 years, disease duration 11.5 years, HAQ-DI 0.46, and DAS28-CRP 1.71. In 2012, 52 cases had a pharmacotherapy. Mean pain VAS of cases that had a pharmacotherapy was 31.7, and 18.1 that had no pharmacotherapy. In 2012, used drugs were; NSAIDS 50 cases, tramadol/acetaminophen 3, and others 4. In 2015, NSAIDS 38 cases, pregabalin 7, tramadol/acetaminophen 4, others 4. Of the case of NSAIDs, percentage of celecoxib increased in this 3 years. [Conclusion] Usage of NSAIDs decreased, on the other hand, usage of pregabalin and tramadol/acetaminophen increased.

P2-020

Denosumab versus bisphosphonates for the treatment of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is characterized by overexpression of receptor activator of nuclear factor kappa-B ligand (RANKL) in the synovial membrane, which promotes osteoclast differentiation and thus increases bone resorption. Denosumab, an antibody against RANKL, prevents RANKL/RANK interaction and inhibits osteoclast-mediated bone resorption. This study investigated whether denosumab could prevent inflammation caused by excessive bone resorption in RA patients compared with bisphosphonates, which directly prevent osteoclast-mediated bone resorption. [Methods] RA patients included 58 and 44 newly denosumab- and bisphosphonate-treated patients, respectively. Steinbrocker classification (pre-treatment) and use of glucocorticoid, methotrexate and biological agents, simplified disease activity index, erythrocyte sedimentation rate, and matrix metalloproteinase 3, were measured pre-treatment, 6- and 12-months post-treatment. [Results] Steinbrocker class and stage, and use of biological agents, were significantly higher in the denosumab group compared with the bisphosphonate group (p=0.0002, p<0.0001, and p=0.0021-0.0075, respectively). [Conclusions] Denosumab and bisphosphonates did not suppress RA activity, and there was no significant difference between groups.

P2-021

The positioning of the Iguratimod administration in RA treatment, efficacy for contraindications and refractoriness cases of methotrexate

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Conflict of interest: None

(Objective) To evaluate the administration of Iguratimod (IGU), we examined the clinical efficacy of IGU for patients who were contraindication of methotrexate (MTX), stopped MTX due to adverse effects or non-responder. (Methods) A total of 106 cases were included and divided into 3 groups of M-(contraindication such as chronic renal failure, intersticial pneumonia or stopped MTX due to adverse effect such as pancytepenia, MTX pneumonitis), B+(additional administration to inadequate biological therapy) and M+(additional administration to inadequate MTX therapy). (Results) DAS28-ESR improved from 5.0 to 3.92 at 3 month, 3.6 at 6 months and 3.4 at 12 months after administration. The RF significantly decreased after treatment together with CRP and MMP3.The degree of the improvement was remarkable in order of M-, B+ and M+. There was no relation with ACPA, it was obvious the improvement of the RF high-price example. (Conclusion) IGU is a useful drug not only for patient who quitted MTX but for additional treatment who take MTX or BIO therapy.

P2-022

Experiences of Iguratimod (IGU) therapy in RA patients in a single institute (Part 2)

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Conflict of interest: None

[Objectives] To assess the efficacy and safety of Igratimod (IGU) in Rheumatoid Arthritis (RA). [Patients and Methods] One hundred and one RA patients who had been treated with IGU were evaluated. Patients background data were as follows; mean age:67.0 years old, female rate:82.2%, mean duration of RA:12.3 years, Past biologics use:16 (ETN:6, ADA:3, GLM:3, TCZ:2, CZP:2,TOF:1), %MTX combination:71.3 (%). Clinical efficacy and safety profiles (at week 0,week 12 and week 24) were assessed for patients enrolled in our institute. DAS28-ESR, SDAI and HAQ-DI was assessed and all safety data were collected. [Results] Mean DAS28-ESR (at week 0, week 12 and week 24) was 4.1/3.2 (p<0.001)/3.0 (p<0.001), and mean SDAI was 14.2/8.0 (p<0.001)/6.9 (p<0.001), both were significantly decreased. HAQ-DI was 0.4/0.4/0.4. Remission rate of at week 24 were as follows; DAS28-ESR:43.8%, SDAI:32.5%. The continuation rate of IGU at week 24 was 79.2%, and most common reasons for discontinuing is rash in 7 cases. Adverse events were observed in 28 cases (gastrointestinal dysfunction:

15, rash: 7, liver function disorder:3, fatigue: 2, feeling discomfort: 1).[Conclusion] Both DAS28-ESR and SDAI were significantly improved at 24 weeks, and HAQ-DI was maintain remission status.

P2-023

Effects of oral glucocorticoid and conventional synthetic disease-modifying antirheumatic drugs in patients with idiopathic multiple flexor tenosynovitis: Part 2

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Conflict of interest: None

[Objective] Flexor tenosynovitis may appear as an initial symptom of rheumatoid arthritis (RA), and is assumed to share the same pathogenesis with arthrosynovitis. Beneficial effects of glucocorticoid (GC) and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in patients with idiopathic multiple flexor tenosynovitis (IMFTS) were reported in the 58th meeting of this society. This study is the 2nd report in which I examined 10 additional patients. [Methods] Among 10 outpatients who had IMFTS in both hands at their initial visit and did not fulfill the 2010 Rheumatoid Arthritis Classification Criteria, 2 patients were treated with low-dose GC (methylprednisolone 6mg/day) and salazosulfapyridine (SASP), and 8 with iguratimodo and/or SASP and/or bucillamine. [Results] All patients showed obvious improvement in their symptoms of IMFTS and 2 patients given GC could withdraw from it. [Conclusion] It is important that csDMARDs are effective against IMFTS. These results indicate that the patients with MFTS may be in a status of Pre-RA and early treatment with csDMARDs may prevent those patients from progression to RA.

P2-024

Rheumatoid arthritis diagnosed 4 years after the onset with multiple flexor tenosynovitis: a case report and literature review

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Conflict of interest: None

[Introdaction] Tenosynovitis (TS) in rheumatoid arthritis (RA) is assumed to share the same pathogenesis with arthrosynovitis (AS). Although TS may precede AS, it is difficult to determine the precise onset of RA because the diagnosis of RA is not made until the onset of obvious AS. We report here a case in which the patient was diagnosed with RA 4 years after the onset with multiple flexor tenosynovitis (MFTS). **[Case report]** The patient was a 52-year-old Japanese woman. Around April 2010, she presented at a local clinic and received treatment with tendon sheath injection. When she attended our clinic in October 2011, she was diagnosed with MFTS based on palpation; no joint swelling was observed and laboratory tests showed no abnormalities. Tendon sheath incisions were performed on three fingers between 2012 and 2014. The patient subsequently re-attended our clinic in August 2014. At this time, she was found to be RF-positive and had increased C-reactive protein levels and eythrocyte sedimentation rate. Magnetic resonance imaging revealed AS on radioulnar joint. The patient fulfilled the 2010 Rheumatoid Arthritis Classification Criteria. **[Conclusion]** As MFTS can be an initial sign of RA in some cases, early treatment should be considered in order to prevent its progression to AS.

P2-025

Efficacy of adding iguratimod therapy(IGU) in rheumatoid arthritis patients who had inadequate response to biologic DMARDs

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Conflict of interest: None

Objective IGU was approved in June 2012 and recommended by guideline 2014 in the treatment of RA. Although there have been efficacy of monotherapy and concomitant MTX in clinical trials, however, there have been no reports of Bio.Therefore, we investigated efficacy of concomitant IGU therapy in RA who had inadequate response to Bio at the author's institution. ***Methods*** IGU were prescribed to 62 RA patients from August 2012 to October 2015, subjects were 36 patients adding IGU who had inadequate response to Bio. In previous treatment Bio, ADA of 34 patients, other ABT and GLM of 1 patients. And concomitant MTX (mean 12.9 mg/week) of 34 patients (94%). Baseline characteristics were Mean age 52 years, mean duration of illness 8 years, corticosteroid use 16.7%(mean 2.8mg/day). The course of DAS28, SDAI, CDAI and remission rates were analyzed. ***Results*** Mean DAS28-ESR, DAS28-CRP, SDAI, CDAI were significantly decreased from the initiation of IGU treatment at 24 weeks (3.1→2.3, 2.6→1.7, 6.8→2.4, 6.1→2.2). Remission rates of DAS28-ESR, DAS28-CRP, SDAI, CDAI were 64%, 81%, 67%, 69% at 24 weeks. There were no side-effect after adding IGU. ***Conclusion*** IGU might be a new RA treatment option for aiming remission in patients who had inadequate response to Bio.

P2-026

Safety and efficacy of methotrexate administered once a day to RA patients

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Conflict of interest: None

Purpose: In order to demonstrate the everyday utility of methotrexate (MTX), we examined its safety and efficacy when administered once a day for a few consecutive days to rheumatoid arthritis (RA) patients. **Patients and Methods**: This trial was a prospective, single arm study. We switched from the standard MTX schedule, in which MTX is administered three times a week, to everyday medication, in which the dose and number of doses per week were the same as the standard MTX schedule for each patient, but with an addition dose (1 mg or 2 mg) at bedtime. **Results and Conclusion:** After informed consent was obtained, 2 patients were excluded. Four men and 14 women with a mean age of 68.8 years completed the 4-month study period. Doses per week were 4 mg (n = 5), 6 mg (n = 8), and 8 mg (n = 5). Severe adverse effects were not observed in any patient. There were 4 moderate responders (22.2%) based on EULAR response criteria, and 5 in whom DAS28 increased by more than 1 point (27.8%). However, a sub-analysis identified 3 moderate responders (60%) at 4 mg, 1 (12.5%) at 6 mg, and 0 (0%) at 8 mg. Our results demonstrated that disease activity improved in RA patients and safety was maintained when MTX (4 mg/week) was given once a day at bedtime.

P2-027

Iguratimod is effective to the RA patients who have high titer Rheumatoid Factor (RF)

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Conflict of interest: None

[Object]To identify the factor predicting the efficacy of iguratimod on patients with rheumatoid arthritis. [Methods]EULAR good response rate of 98 patients who had administered iguratimod in our hospital were assessed by multivariate logistic regression using variables, age, sex, disease duration,CRP, SDAI, RF titer, ACPA titer, MTX dose, oral prednisolone dose, previous biological DMARDs use. And similar analysis was done for 97 patients in Centre for Rheumatic Disease of Mima Hospital. [Results]This analysis revealed that RF titer had significant association with the EULAR good response rate ($p=0.015$). We divided them into the higher RF group ($RF \geq 93$, n=53) and lower RF group ($RF < 93$, n=45) by the ROC curve analysis. The odds ratio for the achievement of EULAR good response in the higher RF group estimated by multivariate regression analysis was 10.0 (95%CI: 1.5-16, $p<0.0001$) in our hospital and 4.5 (95%CI: 1.5-16, p-0.008) in Mima Hospital, respectively. [Conclusions]

Iguratimod is strictly effective to RA patients who have higher RF titer.

P2-028

The effectiveness of every other week methotrexate administration in patients with rheumatoid arthritis

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Conflict of interest: None

[Background]It is the most important to lead patients with rheumatoid arthritis (RA) to the induction of remission.Although Guidelines and Recommendation reveal how to treat aiming at remission, it is not clear how to keep the sustained remission with safety.We converted MTX treatment from weekly to every other week for the purpose of maintaining remission with safety without changing MTX dosage. [Object and Method] 11 patients (one male, ten female) who were treated with MTX and achieved remission in DAS28CRP4 recruited in this study. We evaluated that the change in DAS28CRP4 and dosage of MTX. [Results] The mean age was 61.8 years old. The mean disease duration was 7.8 years at the reduction of MTX. At the beginning of MTX, the mean dosage of MTX was 5.5 mg/week, and the mean value of DAS28CRP4 was 4.85. Before reducing MTX, the mean dosage of MTX increased to 8.7 mg/week. The mean value of DAS28CRP4 was improved to 1.62.Three cases flared disease activity 6, 8, 12 weeks later and were returned to MTX weekly.Eight cases maintained remission. The mean value of DAS28CRP4 was 1.63.An adverse event did not occur during this study. [Conclusion] In RA patients who were categorized to remission, every other week MTX administration might be useful and safe in maintaining efficacy.

P2-029

Effectiveness of generic tacrolimus – Doubtful effectiveness of generic tacrolimus –

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Conflict of interest: None

[Objective] To explore the effectiveness of generic tacrolimus. [Methods] This study examined 16 patients with decreased response after switching from original tacrolimus (Pro) to generic tacrolimus (Tac) for certain reasons, among those who were started on Pro at our institution by April 2015 (n=183), continued Pro over 6 months (n=124), and switched to Tac (n=26). The effectiveness measures were patient-rated visual analog scale (VAS), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), trough tacrolimus level, matrix metalloproteinase-3 (MMP-3), and rheumatoid factor (RF) from 2 months before to 2 months after switching. [Results] All six effectiveness measures were likely worse at 2 months post-switching than at 2 months pre-switching, with significant differences for patient-rated VAS, trough tacrolimus level, and MMP-3. [Conclusions]Our results indicate that switching from Pro to Tac to treat rheumatoid arthritis requires caution, although recommendation of generic drugs is encouraged to reduce growing healthcare costs.

P2-030

Efficacy of low-dose tacrolimus therapy in patients with rheumatoid arthritis. ~SERA study Group~

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Conflict of interest: None

[Objectives] To assess efficacy of low-dose tacrolimus (TAC) in patients with rheumatoid arthritis (RA). [Methods] Thirty-one patients (M: 10, F: 21), who were treated of low-dose TAC (0.5-1mg/day), were analyzed prospectively. [Results] All patients treated by MTX and mean dose was 8.7mg/week. Nineteen were treated by prednisolone and mean dose was 5.5mg/day. Five patients were used biologics. [Result] DAS28 (CRP) score was significantly decreased 3.98±0.79 to 3.23±1.10 and 12 patients having Low disease activity. But thirteen patients were not attained more than moderate response. Mean dose of steroid was decreased statistically 4.1±2.9mg/day to 3.4±2.8 mg/day and dose of MTX was not significantly increased. No serious adverse events were observed during 24 weeks. [Conclusion] Low-dose TAC therapy was considered statistical effective for RA patients and safety, but 42% of patients were not attained good or moderate response.

P2-031

Accidental overdose of methotrexate in patients with rheumatoid arthritis

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Conflict of interest: None

[Object] Accidental overdose of MTX is life-threatening, but professionals and patients in many countries still make mistakes. We investigated clinical characteristics of patient who took MTX daily by mistake. [Methods] We retrieved the patients who used calcium folinate (leucovorin) from April 2003 to June 2015 in Tokyo Metropolitan Tama Medical Center. Calcium folinate was administrated in 26 patients. Seven of 26 patients took MTX daily by mistake. We investigated clinical characteristics of 7 patients.[Results] Average age of 7 patients was 74.4±9.8 years old. All patients were female. Duration of rheumatoid arthritis was 13 years (range 1-39). Dosage of MTX was 6.0±2.3mg/week and duration of MTX use was 9.5 months (range 0-156). Duration of taking MTX daily was 7 days (3-28). As reasons of overdose, 6 cases had patient-related factor and 1 case had iatrogenic factor. In 5 patients taking MTX daily by mistake, the score of Hasegawa dementia scale-revised (HDS-R) were 24, 24, 27, 22 and 25 respectively.[Conclusion] Accidental overdose of MTX must be avoided. When we prescribe oral MTX to elderly patients, it is necessary to give enough explanations for patients including their family.

P2-032

Efficacy and safety of low dose tofacitinib in Japanese patients with active rheumatoid arthritis

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Conflict of interest: None

We investigated the efficacy of eight RA patients who were treated with low dose TOF (starting dose: 5mg/day (once daily)) for 24weeks. Three were male and five were female. Results: Mean age of the patients was 70.9±18.9, duration of RA was 16.8±13.7. Three patients were treated with MTX, four patients were treated with oral prednisolone (PSL) at baseline, and three patients were previously treated with biologics. The mean of disease activity of the patients, DAS28 (CRP), decreased from 3.78 (baseline) to 2.79 (at 24 week) by TOF treatment. The proportion of patients achieving DAS28-defined remission at 24 week was 50%, and that of low disease activity was 75%. All patients who achieved DAS28-defined remission were those who were treated with TOF 5mg/day throughout the observation period. The persistency rate of TOF at 24 week was 75%. Three patients were treated with TOF by dose-escalation manner (from 5mg to10mg/day) at certain time point, and five could be treated with TOF 5mg/day throughout the period. According to the treatment with TOF, the mean dose of PSL was decreased from 4.25mg/day at baseline to 2mg at 24 week. Conclusion: Half of the patients achieved DAS28-defined remission at 24week who were treated with low dose initiation (5mg/day) of TOF.

P2-033

Iguratimod, a DMARD, shows the anti-allodynic effect in a rat model of neuropathic pain

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Conflict of interest: None

[Objective] Patients with rheumatoid arthritis have been assumed to be afflicted with not only inflammatory pain but also neuropathic pain. We investigated the effect of iguratimod (IGU), a disease-modifying anti-rheumatic drug, on neuropathic pain in rats. [Method] Chronic constriction injury (CCI) was made in male 7-week-old SD rats by 4 loose ligations on the left sciatic nerve. Two weeks after surgery, the rats with mechanical allodynia symptoms were selected, and drug treatments were started (day 0). The drugs were orally administered once daily from day 0 to day 14, and withdrawn on day 15. The threshold for mechanical pain response in hind paw was evaluated by von Frey filament test on days 0, 6, 14, 15 (the first day of the drug withdrawal) and 21 in a blind manner. [Results] IGU showed the anti-allodynic effect in CCI rats on days 6 and 14, but not 90 min after the first administration on day 0. Unlike pregabalin, IGU maintained the rise of pain threshold even after the withdrawal (days 15 and 21). [Conclusion] IGU showed the anti-allodynic effect in a rat model of neuropathic pain, and the effect was sustained in a washout period. It was therefore suggested that IGU relieved a neuropathic pain through a different mechanism from those of current therapeutic agents.

P2-034

The Possible Utility of Salazosulfapyridine in the Prophylaxis of Pneumocystis Pneumonia in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Object]Trimethoprim-Sulfamethoxazole is the standard regimen of treatment for pneumocystis pneumonia (PCP), and salazosulfapyridine (SASP) is one of the anti-rheumatic drugs. Both agents contain sulfonamide. In this study, we therefore examined the effectiveness of SASP for preventing PCP in patients with rheumatoid arthritis (RA). [Methods] We retrospectively investigated the clinical features of 13 cases (12 patients) with RA developing PCP between January 1, 2006 and November 13, 2015 in Kitasato university hospital. A diagnosis of PCP was presumptive if a patient met the following two criteria; a) progressive dyspnea, associated with diffuse bilateral ground glass opacity on chest computed tomography, b) detection of *Pneumocystis jirovecii* DNA by PCR in respiratory specimens or elevated plasma β-D-glucan level. [Results] At the onset of PCP, 5 of 13cases were treated with TNF inhibitors, 11 with methotrexate, 3 with tacrolimus, 1 with mizoribine, 9 with prednisolone, and none with SASP. Administration of SASP to one patient was started for RA flares after first PCP. Of note, after the withdrawal of SASP due to refractory arthritis, she developed second PCP. [Conclusion] These results suggest that SASP might be useful in the prophylaxis of PCP in RA patients.

P2-035

Treatment of rheumatoid arthritis with low-dose tacrolimus using the T2T strategy

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Conflict of interest: None

OBJECTIVES: The aim of this study was to evaluate the effect of treatment of Rheumatoid Arthritis with low-dose tacrolimus (TAC) with a 24-week follow-up under a Treat to Target strategy. **METHODS:** 123 Patients who had started tacrolimus from Jan 2012 to April 2015 were enrolled. The safety data collection and evaluation for 123 patients and effectiveness data collection and evaluation for 72 patients were reported. Effectiveness was evaluated using the Disease Activity Score 28-ESR (DAS28-ESR). **RESULTS:** Data from 123 patients (mean age 65.5years) were evaluated in the safety analysis. Of the safety population, 76%were female. 72 patients (59%) showed effectiveness at week24.The dose of average tacrolimus was 1.26mg/day.The most common concomitant disease modifying antirheumatic drug (DMARD) was methotrexate, used in 62% of the patients. The mean DAS28-ESR decreased from 3.23 at baseline to 2.02 at week 24. We focus the efficacy showed at week 8.Adverse drug reactions occurred in only 3 patients. No severe adverse reaction were occurred. **CONCLUSIONS:** Low dose tacrolimus is well tolerated and effective in RA patients under a Treat to Target strategy.

P2-036

Clinical experience of iguratimod add-on concomitant therapy on RA patients with secondary failure to biological preparations

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Conflict of interest: None

【Objective】: Iguratimod (IGU) is a DMARD that was approved in September 2012 in Japan. The efficacy and safety of IGU addon concomitant therapy was investigated in RA patients with secondary failure to BIOs. 【Methods】: The subjects were 33 RA patients with secondary failure to BIOs (1 male and 32 females, mean age 65.8 years). As addon concomitant therapy, IGU 25 mg/day was administered and efficacy assessed at 24 weeks after the initiation of treatment. 【Results】: Adverse events occurred in 2 (6.1%) patients, however, there was no case of discontinuation due to adverse events. Twenty four (72.7%) patients continued IGU treatment for 24 weeks, showing a high rate of continuation. In particular, the rate of continuation of the add-on concomitant treatment was high with tocilizumab (88.9%) and golimumab (77.8%). 【Conclusions】: IGU add-on concomitant therapy for RA patients with secondary failure to BIOs produced no case of discontinuation due to adverse events and high safety was demonstrated. Rate of treatment continuation after 24 weeks was also high, suggesting it as a useful treatment for cases of secondary failure to BIOs. In particular, high efficacy for patients with secondary failure to tocilizumab was demonstrated.

P2-037

Analysis of iguratimod addition at the time of attenuation of biologics efficacy in treatment of rheumatoid arthritis

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Conflict of interest: Yes

Purpose: When we use biologics in treatment of rheumatoid arthritis (RA) patients, sometimes decrease of the efficacy occur. In these cases, we increase the dose of biologics, shorten the period of the administration of biologics, switch the biologics, add the disease modifying anti-rheumatic drugs (DMARDs), and so on. Adding of the DMARDs is easy to do in clinical practice. In this study, we analyzed the efficacy of iguratimod (IGU), one of the DMARDs, addition at the time of attenuation of biologics effects. Methods: There were 22 RA patients whose biologics efficacy decreased during the treatment. IGU was added and the IGU efficacy was observed. Results: In 18 cases, IGU showed the good response after 4 weeks of administration. Most of all cases had a good response to IGU, except one patient who stopped taking drugs because of diarrhea. It is suggested that addition of IGU therapy at attenuation of biologics efficacy may be one of the useful way to maintain the biologics therapy.

P2-038

High-dose Methotrexate Increases remission and cessation rate in Rheumatoid arthritis Patients

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Conflict of interest: None

OBJECTIVE: To evaluate the remission and adverse event rate of high-dose methotrexate (MTX) in rheumatoid arthritis (RA) patients. METHOD:324 RA patients received MTX in our institutions. 207 patients were evaluated based on: high-dose group (more than 10mg of MTX, 57 patients), low-dose group (less than 8mg, 145 patients). The remission and adverse event rate were examined.RESULTS: The average dose of MTX was 10.5mg and 6.84mg for high-dose group and low-dose group. 7 and 6 patients received biologicals. The remission and cessation rate was 6/57 (10.5%) and 6/145 (4.1%). The adverse event rate was 5/57 (8.7%) and 18/145 (12.4%). 11 patients in high-dose group reduced MTX to less than 8mg and 8 patients in low-dose group increased dose up to 10mg in the next year. The 3 year-adherence rate was 80.7% and 80.6% for each group.DISCUSSION: MTX is a highly effective drug with good adherence. In this research, 10.8 % of high-dose group receive remission and stop MTX medication. The incidence of adverse event was increased in low-dose group.CONCLUSION: High-dose MTX increases cessation rate and decreases the incidence rate of adverse event.

P2-039

Experience of iguratimod (IGU) for rheumatoid arthritis (RA) patients with our hospital

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Conflict of interest: None

【Objects】 We consider the efficacy in RA patients treated with IGU in our hospital. 【Methods】 19 cases (women 14 cases, five cases of men) followed up 24-week from April 2014 in our hospital were intended for. We had investigated about patients background, disease activity and drug retention rate. 【Results】Patients background were mean age 71.7 years old, with a mean disease duration 7.3 years. Reasons for use were that, Three cases had been added for the MTX effect insufficient, 16 cases were MTX use difficult. Among these, there was a bio use in four cases. MTX use difficult example:12 cases were lung existing disease, two cases were renal dysfunction, one case was pancytopenia and patient hope was one case. DAS28-CRP at 0w is 3.81, the DAS28-CRP at week 24 was 3.17. The retention rate of at 24 week was 79%. Discontinuation reason, one case was gastrointestinal bleeding, two cases were pancytopenia and one case was palpitation. Among the discontinuation, three cases were low-weight's less than 40kg and it were accounted for 75 percent of the total. 【Conclusions】 DAS28-CRP at the time 24 weeks by using the IGU had been improved. However, it deemed necessary by carefully administered in low body weight cases.

P2-040

Benefits of Using Iguratimod (IGU)

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Conflict of interest: None

Objective: This study aimed to compare the benefits of using iguratimod (IGU) among those receiving IGU alone (group A), poor responders to methotrexate (MTX) receiving IGU concomitantly (group B), and poor responders to biologics (Bio) receiving IGU concomitantly (group C). Subjects and Methods: There were 40 patients (6 men, 34 women) in group A, 26 (4 men, 22 women) in group B (MTX, 8.23 mg/W [mean]), and 13 (only women) in group C (6 receiving abatacept, 4 etanercept, and 1 each adalimumab, tocilizumab, or certolizumab pegol). CRP levels (mg/dL) and DAS28-ESR were compared among the 3 groups. Results: CRP levels/DAS28-ESR at 0, 12, 24, and 52 weeks of treatment were, respectively, 1.49/4.35, 0.91/3.66, 0.91/3.79, and 0.37/3.23 in group A; 1.65/4.08, 0.31/3.46, 0.32/3.45, and 0.30/3.00 in group B; and 0.75/4.01, 0.51/3.30, 0.22/3.28, and 0.04/2.7 in group C. At week 52, along with low disease activity, 35 and 69% of patients, respectively, in groups B and C showed remission. Discussion: We previously reported that some patients receiving IGU alone present with low disease activity. Concurrent IGU can be used in poor responders to MTX or Bio to achieve low disease activity, and as an alternative treatment in patients receiving Bio or before switching to Bio.

P2-041

Examination of iguratimod for patients with rheumatoid arthritis

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Conflict of interest: None

Objectives: In rheumatoid arthritis treated with iguratimod (IGU) in our hospital, we experienced pain improvement effects not to be associated with blood test results and X-rays findings. Therefore, we examined the patients introduced IGU. Methods: In 41 cases treated with IGU in our hospital by October, 2015, we examined the tender joint count (TJC), swollen joint count (SJC), patient's global assessment (VAS), various blood test results of a continuous administration after induction with IGU for 24 weeks and 52 weeks. Results: As for the patients background, the age was 69.7±11.0 years old (mean ± S.D.) and disease duration was 5.8±7.9 year. Other drugs were methotrexate at 7.3±2.5 mg/week in 19, prednisolone at 4.9±2.1 mg/day in 16, and the biological preparation was treated in 7 cases. IGU induction 24 weeks later was 28 cases and 52 weeks later was 16 cases. The significant difference was not found in TJC, SJC, CRP, RF and MMP-3 after induction for 24 weeks. We recognized a significant difference in VAS 24 weeks (p=0.0194) and 52 weeks (p=0.0365) later, and MMP-3 52 weeks later (p=0.0309). Conclusion: The possibility that IGU improved VAS regardless of joint symptom such as TJC or SJC and various blood test results was suggested.

P2-042

Biological DMARDs-free remission in patients with rheumatoid arthritis from our rheumatology clinic

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Conflict of interest: None

To investigate whether bDMARDs might be discontinued after achievement of remission and evaluate the duration of bDMARDs free remission in patients with RA from our rheumatology clinic. (Method) We evaluated 526 patients with RA who had received infliximab (IFX):127,etanercept (ETN): 204, adalimumab (ADA):57, toclizumab (TCZ):89, and abatacept (ABT):49. All subjects were full-filled with the 1987 ACR criteria or the 2010 ACR/EULAR classification for RA and evaluated by DAS 28 (ESR), SDAI, HAQ, and MMP-3. (Result) 1. Of the 127 patients treated with IFX, 21 patients achieved bDMARDs free remission, whereas other drugs showed very low frequency of these remission (ENT:3/204, ADA: 5/57, TCZ: 0/89, ABT3/49). 2. Of bDMARDs free remission in IFX there was the shorter disease duration (34 months vs 60.2) and the lower stage in Steinbrocker classification than no IFX stopping group. 3. The duration of remission after discontinuation of IFX showed 34.0±26.5 months. (Conclusion)Our data indicate that the remission after discontinuation of IFX was achieved more frequently than other biologics, then IFX was useful for bDMARDs-free remission.

P2-043

Study on 27 patients with rheumatoid arthritis reaching biological agents free

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Conflict of interest: None

(Object) Rheumatoid arthritis (RA) is influenced by two major different types of cytokines such as TNF a and IL- 6. However, these cytokines are gradually overlapped in established RA. Therefore it is very difficult to choose the first biological agents. In our clinic, we investigated how to use the biological agents to bio-free (BF). (Methods) They included 129 RA patients (male 24) treated with biologic agents (BA) for over 6 months. WBC (over 9000) or thrombocyte (over $30x10^4$) are higher than normal range. Amount of TCZ and ETN were reduced in the activity of RA, following regular use. Where a half dose is administered by two

years in completed remission, TCZ and ETN use were terminated as BF. (Results) Eleven of 42 (26%) treated with TCZ and 12 of 51 (23.5%) with ETN reached to BF and half of them continued being completed remission for mean two years after BF. Four of 11 including 7 with baseline of WBC or thrombocyte high normal, treated with TCZ and 2 of 12 including only 4 with baseline of WBC or thrombocyte high normal, with ETN were flared up within 6 months. Regarding other TNFa blocker, 4 of 36 (11.1%) reached to BF and 1 with IFX was flared up. (Conclusion) WBC and thrombocyte count might be good biomarkers to choose BA, especially in the early stage of RA.

P2-044

The necessary condition obtained from the cohort study by Michinoku Tocilizumab Study Group (MTSG) for long-term structural remission and the improvement of therapeutic strategy for it

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Conflict of interest: None

[Objectives] Determination of the necessary condition for long-term structural remission in RA patients and improvement of therapeutic strategy to achieve it. [Methods] Joint damage was assessed by calculating mTSS in 50 patients who had received tocilizumab (TCZ) for 3 years in MTSG. The six parameters (CRP ≤1mg/dl, ESR ≤15mm/h, tender joint count (TJC) ≤1, swollen joint count (SJC) ≤1, Boolean remission, and DAS28ESR <2.6) were assessed at 3, 6, 9, and 12 months. The *p*-values for mTSS < 1.5 during the 3-year study were determined by Fisher's exact tests. In Spellman hospital, 101 patients received TCZ 8 mg/4w, while 17 patients received dexamethasone palmitate (DMP) 4 mg/4w 1 ~ 5 (mean 1.5) times in combination with TCZ. [Results] The *p*-value of SJC ≤ 1 and Boolean remission was consistently less than 0.05 from 3 and 6 months onward, respectively. Other parameters did not show significant difference. Mean SJC in the TCZ group was 4.0 at baseline and 0.57 at 3 months, while mean SJC in the TCZ+DMP group was 4.4 at baseline and 0.64 at 2 months. No additional adverse event was observed in the TCZ+DMP group. [Conclusion] Achievement of SJC ≤ 1 within 3 months predicted long-term structural remission. TCZ in combination with DMP may produce a more rapid decrease of SJC.

P2-045

Study for 5years' Treatment Adherence of RA with Tocilizumab Compared between Launch Within One year and After One year by means of Registry approach

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Conflict of interest: None

[Objectives] The object is study for treatment adherence of RA with Tocilizumab (TCZ) for 5 years compared between Launch Within 1year and After 1year. [Methods] 26 cases treated TCZ within 1year from TCZ Launch (5/2008- 6/2009) are registrated, and named Within 1year group. 34 cases after 1year from TCZ Launch (7/2009 - 10/2010) are registrated, and named After 1 year group. All Cases treated at one of Nagoya University Hospital, Toyohashi Municipal Hospital, Chutoen General Medical Center, or Tokyo Shinjuku Medical Center. Continuation rate of treatment RA with TCZ for 5 years is figured out 2 groups. [Results] 5year continuation rate is altogether 43%(continuation 26 / 60), from Within 1 year group is 23%(6/26), and from After 1year group is 59%(20 / 34). After 1year group's rate is close to the various houses reported 60%, for TCZ 5years continuation. 13cases are changed doctor, we cannot follow. Except for 13cases, 5year continuation rate is altogether 55%(26 / 47), from Within 1year group is 40%(6/15), and from After 1year group is 62%(20 / 32). We show reason for discontinuation. [Conclusions] RA patients treated with TCZ, except change doctor cases, 5years continuation rate is 40% within 1year after launch, is 62% from more than 1year within 2years after launch.

P2-046

Effect of CZP in 58 patients with RA in our hospital

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Conflict of interest: None

[Objective] To evaluate the efficacy of certolizuamb pegol (CZP) monotherapy and combination therapy in 58 patients with RA. [Methods] Efficacy of CZP monotherapy (n=16) and combination therapy with MTX (n=26), IGU (n=7), or TAC (n=5) in RA patients was evaluated using DAS28 and ultrasonography. [Results] Patients with relatively old age, long disease duration, and disease stage of II or III were included in this report. Combination therapy groups showed trend of older age, longer disease duration, and advanced disease stage compared with CZP monotherapy group. Significant improvement in DAS28 was observed in patients with CZP monotherapy and combination therapy with MTX or IGU, but not with TAC. MMP3 level was significantly decreased only when combined with MTX, and RF level was decreased only when combined with IGU. Although ultrasonography assessment showed trend of improvement in all groups, only combination therapy with MTX showed significant difference at week 24. [Conclusion] The efficacy of CZP differed by concomitant medication. MTX was considered to be the first choice for combination therapy with CZP. For patients who cannot use or increase the dose of MTX, IGU was suggested as a substitute.

P2-047

Evaluate the safety and efficacy of golimumab through over 24months in adults with active RA

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Conflict of interest: None

OBJECTIVE: Evaluate the safety and efficacy of golimumab through over 24months in adults with active RA METHODS: Assessments included ACR20/50/70 response, DAS28-CRP scores. Efficacy was analyzed using an intent-to-treat analysis. Pharmacokinetics and immunogenicity were evaluated at selected visits. RESULTS: Rheumatoid arthritis treated with GLM since September 2011 (RA) 17 patients (man 3, women 14 cases, 62.5 years old average age, duration 152.1 months) 13 cases that have elapsed 6 months did. GLM dosage 50mg: 11cases, 100mg: 2 cases. MTX combined rate of 82.4%(average 7.9mg). Bio naive cases 9 cases, switch example was 8 cases. Clinical results we were evaluated by DAS28CRP high disease activity 6 disease activity prior to administration (46.2%), moderate six cases (46.2%), had a remission one cases (7.7%). high disease activity 2 when 24 weeks (15.4%), moderate 5 cases (38.5%), remission six cases (46.2%), the retention rate was 100%. Two cases of the switch from other biologics, one cases of remission, were one cases of high disease activity. 3 cases of bio- naive led to all patients' remission. Infections were the most common type of AE CONCLUSIONS: Clinical efficacy with golimumab treatment was maintained through week24months RA patients. No unexpected AEs occurred.

P2-048

Golimumab adoption cases in our hospital study

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Conflict of interest: None

[purpose]This time, in patients with rheumatoid arthritis and introduced the GLM report evaluated the clinical results. Materials and methods: GLM implementation in 17 cases, 2 males, 15 females, average age is 59.7 (30-80 years old), was. Naive patients is 12, switch cases 5 cases. Continue in 10 patients, ranged from scratching the other agent Bio

switch example 6 example (TCZ 2 CZP 3, ETN 1 example) and cancel example 1 example. 10 cases of continuous duration is 14 years and 7 months (4 months-52 years) and was in a long period of time. Also here continue MTX combined rate is 10 in 8 patients (80%) and the high rate. [Results and discussion] Bio-free example is achieved in 3 and 4 patients in remission. Which one achieved MTX-free and Drug-free. In addition, patients in the continuation of other LDA can be achieved in 4 cases the remission, LDA was in 8 patients (80%). In the 100 mg dose in individual cases and HDA Establish RA but with MTX in naive patients, the effect is obtained even after 24 weeks. In naïve patients with Early RA, MTX combined with the 50 mg dosage, accepts the remission at week 24.

P2-049

Analysis of the clinical efficacy and safety during the first year after initiation of adalimumab administration

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Kyoto Yamashiro General Medical Center

Conflict of interest: None

【Objective】To evaluate the efficacy and safety of adalimumab in rheumatoid arthritis (RA) patients in our hospital. 【Methods】Included in the present study were 85 patients followed up for at least 54 weeks of treatment with adalimumab from December 2009 in this unit, including 81 women (mean age: 62.4 years). Each clinical composite measure (DAS28-CRP, CDAI, SDAI) was assessed at 12, 24 36 52 weeks change from baseline. Safety was also assessed. 【Results】61 patients were biologics naïve (naïve group) and 24 patients had already been treated with another biologics (switched group). PSL was used by 32 patients at 4.0mg/day. MTX (4-16 mg/week) was concurrently used by 59 patients. Adalimumab was highly effective for patients of naïve group, and can be expected to be at least as effective in patients not receiving concomitant MTX as in those receiving concomitant MTX. While improvements in activety were observed in both group. ADA appears useful in RA treatment.

P2-050

Long-term clinical effects of etanercept and treatment continuation rate in our hospital

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Conflict of interest: None

[Objectives] We compared the clinical effects and continuation rate of etanercept (ETN) with those of other biologics (adalimumab (ADA), abatacept (ABT), and tocilizumab (TCZ)) based on our experience. [Methods] The subjects consisted of 120 patients for whom ETN was introduced between September 2005 and October 2015, 32 for whom ADA was introduced, 50 for whom ABT was introduced, and 40 for whom TCZ was introduced. We evaluated DAS28-CRP on the introduction of each preparation and in October 2015, and compared the results before and after treatment and among these drugs. Furthermore, the treatment continuation rate was compared. [Results] ABT was used for elderly patients, but there were no differences in the duration of disease.The mean doses of MTX in the ETN-, ADA-, ABT-, and TCZ-treated patients were 8.2, 7.6, 8.1, and 8.0 mg, respectively, showing no differences. The mean DAS28-CRP at the time of introduction/evaluation were 5.25/3.23, 5.21/3.11, 5.23/3.36, and 5.27/2.63, respectively, showing decreases in all groups. The DAS28-CRP remission rates were 31.2, 36.0, 29.0, and 40.0%, respectively, showing no differences. The 2-, 5-, and 10-year continuation rates of ETN were 61.7, 43.6, and 39.2%, respectively. The 2- and 5-year continuation rates of ADA were 44.1 and 44.1%,

P2-051

Withdrawing after achieving sustained remission in rheumatoid patients in the biologics registry of our institute

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Conflict of interest: None

[Background] Data on withdraw of biologics (BIO) medication after sustained remission are limited. [Objectives] To retrospectively analyze the re-flare of disease in RA patients in sustained remission after withdrawing of BIO. [Methods] Biologics registry of our institute which is open-labelled biologics cohort study in our area has registered 315 RA patients. RA Patients were enrolled into this study if they maintained in DAS remission (DAS28-ESR < 2.6) more than one year after starting BIO and were observed more than one year after their remission. [Results] Six RA patients (five female) using BIO (etanercept 2, adalimumab 2, infliximab 1, golimumab 1) was fulfilled in the criteria of this study. Mean age was 44.5 year-old, mean RA affiliation 3.6 years before BIO. In the observation, five of all have observed flare over DAS28-ESR 2.6 including BIO restart in three patients. [Conclusions] Withdrawing of BIO may be difficult to maintain the remission for RA.

P2-052

The evasuation of Akita Orthopedic Group on Rheumatoid Arthritis registry patients who received adalimumab

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Conflict of interest: None

[Objectives] To investigate the clinical evaluation of the patients who received adalimumab (ADA) in Akita Orthopedic Group on Rheumatoid Arthritis (AORA) 2015 registry. [Methods] We evaluated 61 patients in AORA registry (mean age, 58.3 years old). [Results] The mean disease period was 10.5 years. The cases had Steinbrocker classication stages I/II/III/IV (14/9/18/20 patients), classes 1/2/3/4 (23/29/8/1patients). Fifty-eight patients (95%) received methotrexate (MTX; mean dosage, 7.81 mg/week); and 38 (62.2%), prednisolone (3.5 mg/day). The mean DAS28CRP (4) was 3.45 in the first administration. The mean follow-up period was 165 weeks. The cumulative continuation rates were 88%(1 year), 78%(2 years), and 69%(3 years) in the Kaplan-Meier analysis. Sixteen patients (26%) had failure of ADA administration. The cessation was caused by primary failure in 7 patients and secondary failure in 4. The mean disease activity score was 1.55, and 44 patients (72.1%) of cases had good response according to the criteria of the European League against Rheumatism. [Conclusion] The evaluation of ADA remedy suggested that a relatively appropriately with naïve patients, and a high rate of MTX use may contribute the high continuation rate, and an excellent

outcome.

P2-053

Tofacitinib administration by switching from tacrolimus (TAC) in TAC+/-MTX-IR patients with active RA

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Conflict of interest: None

[Objectives] To investigate the efficacy and safety of tofacitinib (TOF) administered by switching from tacrolimus (TAC) in TAC+/-MTX-IR patients with active RA. [Methods] We analyzed 10 RA patients who received TOF more than 6 months after switching from TAC. [Results] The background of 10 switch cases was as follows; age: 58.3 yo, disease duration: 8.05 years, Stage (I/II/III): 2/5/3, Class (1/2/3): 8/2/0, ACPA/RF positive 6/6: DAS28-ESR (before switch): 5.2, MTX: 8 cases, MTX dose: 10mg/week, Biologics naïve: 9 cases, TAC dose: 1.5mg/day. Initial TOF dose was 5mg/day in all cases, and dose was increased to 10 mg/day in 6 cases. TOF administration period: 10.2 months, persistence rate was 90%. EULAR response at 24 weeks was as follows; good 6, moderate 3, no 1. TOF was effective in 9 cases (90%) at 24 weeks. Low dose (5mg/day) of TOF was also effective in 4 remission cases. Several adverse events were observed: upper respiratory tract infection, nausea, and 1 case with appendicitis. Herpes Zoster and malignancy were not observed. [Conclusion] Switch from TAC to TOF in TAC+/-MTX-IR patients with active RA seemed to be useful even at low dose.

P2-054

Effect of Intraarticular Triamcinolone Acetonide injection for Wrist, Ankle, Shoulder and Elbow Pain in Rheumatoid Arthritis Patients

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Conflict of interest: None

【Object】 A significant number of patients on long-term treatment and users of biologics complains of wrist pain. For these patients triamcinolone acetonide was injected into the joints, then evaluated the clinical benefit and safety of the wrist joint. 【Methods】 We injected triamcinolone acetonide into the wrist, ankle, shoulder and elbow joints. We evaluated the clinical benefit and safety by analyzing data on (1) the number of injections, (2) visual analog scale, (3) changes in joints in X-ray imaging, and (4) the adverse reactions on the subcutaneous tissue and extensor tendons. 【Results】 1. The number of injections per patient over 5 years 2 months was an average of 1 to 4 injections for all joints. 2. The overall mean VAS improved remarkably. 3. In the grade III and IV group, the carpal height ratio showed a significant decrease. Other joints showed no remarkable changes. 4. Neither subcutaneous atrophy nor extensor tendon rupture was reported. 【Conclusions】 More than 90% of patients of all disease grades responded to an average of 1 to 4 injections during 5 years 2 months.

P2-055

Nursing intervention for Leukocytapheresis (LCAP) in RA patients ~ Sweet Cohort~

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Conflict of interest: None

Objectives: LCAP is effective treatment for RA patients who are refractory to DMARDs and biologics, and who are not able to continue medication due to side effect or complications. However, it also comes with uneasy pain by paracentesis on blood vessels for several hours and uncertainty for efficacy. Here, nursing intervention during LCAP treatment is assessed. Methods: 21 RA patients who are treated with LCAP between Aug 2012 and Sep 2015 are assessed for questionnaires at baseline, post-treatments (at 1month and 3 months) Results: At first dose of LCAP, questionnaires report that uneasiness and a wish to improving symptom are 88% and 88% respectively. During LCAP, rate of patient reported adverse events occurred was 33% but actual rate was higher at 65%. 89% of patients are more comfortable and felt necessary to accompany with nurse during LCAP treatment. Conclusion: Nursing intervention gain trust through communication to specialty nurse and clinical engineer during LCAP and reduce pain and uneasiness. As a result, all of the 21 patients were able to perform one cycle of LCAP safely and smoothly. We will continue further assessment for improvement by nursing intervention.

P2-056

Studies on the efficacy of supplemental treatment of rheumatoid arthritis with milk antibody by a multi-center double-blind clinical study

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Conflict of interest: None

(Purpose) To confirm the efficacy and safety of supplemental treatment of RA with milk antibody by a double-blind clinical study (Clinical trial number: UMIN000009492). (Subject and Method) Ninety patients inadequately responded to DMARDs were divided into 3 groups, and treated with skim milk (20g), low and high dose of Asama whey protein®(milk antibody content: 300mg and 600mg, respectively) for 12 weeks. (Results) By EULAR response criteria, moderate and good responses were observed in 37%, 50 % and 43% of patients in low dose group at 4, 8, 12 weeks, 27%, 23% and 27% of patients in high dose group, and 20%, 23% and 40% of patients in control group, indicating that consumption of skim milk may influence arthritis as well as milk antibody. Nausea was observed in only 1/90 patients. (Conclusion and discussion) A low dose of milk antibody was effective at early period (8 weeks) compared to skim milk ($P<0.05$). We will further analyze the potential linkage of intestinal environment and RA based on serum antibodies and fecal bacteria in these patients.

P2-057

Effect of neutral "carbonated spring" bathing tablet on Raynaud's symptoms in patients with connective tissue diseases

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Conflict of interest: None

«Objectives» To examine the efficacy of neutral "carbonated spring" bathing tablet on Raynaud's symptoms in patients with connective tissue diseases. «Methods» Patients took bath as usual for the first 4 weeks. They took bath using the bathing tablet (Sparkling HotTab (HOT ALBUM Tansansen Tablet, Inc., Tokyo, Japan)) for the second 4 weeks. Patients recorded the Raynaud diary, which contained visual analog scale about influence of Raynaud's phenomena on the day and forms for length of each Raynaud's phenomenon episode and how to take bath. Eight cases who reliably recorded diary in 8-week period with the mean air temperature of the second 4 weeks similar to that of the first 4 weeks were analysed. «Results» Medians of average Raynaud condition score (0-10

VAS) were 3.3 before using tablets and 1.9 with tablets (Wilcoxon's signed rank test, p = 0.012). Medians of average total time with Raynaud's phenomenon were 14.3 min before using tablets and 11.3 min with tablets (Wilcoxon's signed rank test, p=0.012). «Conclusion» The neutral "carbonated spring" bathing tablet may reduce the strength of the suffer of Raynaud's symptoms and shorten the total length of Raynaud's symptoms.

P2-058

Effective removal of circulating microRNA from serum of systemic lupus erythematosus patients by Apheresis method

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Conflict of interest: None

[Object] MicroRNAs are important factors in coordination with mRNA expression. In peripheral blood, circulating microRNAs exist in a relatively stable form and are found in the exosomes and complexed proteins. We focus on the possibility that the clinical condition may be improved by directly removing microRNA from the blood and have investigated the removal of circulating microRNA by apheresis. [Methods] The study was approved by the ethics committee of the School of Medicine of our university, conducted on 5 systemic lupus erythematosus patients who had received apheresis. After blood sampling before and after the use of the therapeutic membrane (Plasma Flo®(Asahi-Kasei medical, Japan)) for each apheresis and to separate the plasma, microRNA will be separated using a kit. Global expression analysis will be subsequently performed to observe changes in the profile of circulating microRNAs. For microRNA array chip, the miRNA Oligo Chip 3D-Gene®(Toray Industries, Japan) is used for analysis. [Results] Circulating microRNA was observed in separated plasma in all of patients. [Conclusions] This is the first report that prove circulating microRNAs of systemic lupus erythematosus patients can be isolated from blood by therapeutic apheresis using membrane plasma separator.

P2-059

Individual case report of the 4 patients of ankylosing spondylitis that tried adalimumab treatment

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Conflict of interest: None

[Object] It is a long time, adalimumab becomes the adaptation for ankylosing spondylitis. I want to report what kind of patient is effective for by true clinical practice. [Methods]1) Age 2) Sex 3) Weight 4) CRP level 5) Bamboo Spine 6) Symptoms out of joints reports 4 different cases as follows. Case1:1) 57 years old 2) man 3) 86.5 kg 4) 0.10 5)yes6)no, Case 2:1) 43 years old 2) man 3) 60.5 kg 4) 7.65 5)no 6)no, Case 3: 1) 50 years old 2) woman 3) 50 kg 4) 2.66 5)no 6) uveitis, Case 4: 1) 29 years old 2) woman 3) 83 kg 4) 18.81 5)no 6) no [Rusults] CRP level of Case 2and Case3 became negative, but case 4 and case 1 that originally CRP was normal level did not have a change. The uveitis of case 3 disappeared. [Conclusions]The anti-inflammatory action seems one speciality to be shown by many reseaches. I think that I have an effect on the patient who is high in a CRP level in the meaning called antiinflammation. But I was made to think that the dose per weight had to examine it.

P2-060

Successful treatment of leukocytapheresis in a patient with refractory rheumatoid arthritis

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Conflict of interest: None

Case report: A 70 year-old man with rheumatoid arthritis (RA) was admitted for acute arthralgia. He had about 4-year history of RA, total prostatectomy for prostatic cancer at 66, bucillamine-induced proteinuria at 69, and MTX-induced lymphoma 3 months before admission. He was given salazosulfapyridine 1.0 g/day and predonisolone 5 mg/day on admission. Because he was associated with infectious organizing pneumonia, it was difficult to be treated with the biologics. Leucocytaheresis (LCAP) was started with satisfactory improvement of joint symptoms. **Summary:** LCAP should be considered as the second line therapy for the immunocompromised RA patients who were refractory to conventional DMARDs.

P2-061

A case report of the efficacy of plasmapheresis for systemic lupus erythematosus complicated with hypercytokinemia and thrombotic thrombocytopenic purpura

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Conflict of interest: None

33-years-old man who was diagnosed as systemic lupus erythematosus (SLE)in2001 :fever, erythema,arthralgia,leukopenia,hypocomplemen temia,antinuclear antibody positive, antiDNA antibody positive, antiSm antibody positive.He was treated with prednisolone 30mg/day for leukopenia. The steroid,changed from prednisolone to rinderon because of headache and palpitation,was tapered. Rinderon was taperd 0.6 mg/day in February, 2011, but an increase of DNA antibody, face edema, proteinuria developed. It became the hospitalization by a diagnosis of the SLE exacerbation. We were going to start therapy after kidney biopsy was performed,but treated with methylprednisolone pulse because leukocyte decreased 800/μL, serum ferritin levels increased to 39450ng/ml,IL-6 inreased 289pg/ml in CSF.Unfortunately,he he had a high fever again after methylprednisolone pulse and wad diagnosed as thrombocytopenic purpura (TTP) by high fever,renal disorder,unconsciousness with seizure,crushed erythrocyte in peripheral blood.He was treated with plasmapheresis and intravenous cyclophosphamide (IV-CYC),and recovered from TTP and hypercytokinemia.It was suggested that plasmapheresis was effective for those condition.

P2-062

Surgery for the patients with rheumatoid arthritis

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Conflict of interest: None

Aim To clarify the number and region of surgeries for rheumatoid arthritis (RA) in our hospital. **Methods** We extracted the patients with RA from our surgery data bank, who were operated in our hospital from 2003 to 2014. According to Momohara et al. (J Rheum, 2010), various surgeries were divided into total joint arthroplasty (TJA), arthroplasty (without replacement), arthrodesis, synovectomy, and soft tissue operation (tendon surgery, carpal tunnel release et al.). In the same periods, total patients with RA of outpatients and inpatients were counted each year. **Results** Annual variation of total patients with RA peaked in the year 2011. Patients with RA treated with biologics were rated 3 % of total patients with RA in 2004, then steadily increased in ratio (18 % in 2014). Surgeries for patients with RA occupied approximately 100 in 1000 patients with RA each year and the rate did not change. Half of the surgeries

were TJA. The number of total knee arthroplasty was the largest, however, it was replaced by finger and toe arthroplasties in recent years. Knee and hip replacement surgeries were continuously decreased. **Discussion** Methotrexate and biologics may change the number and region of total joint arthroplasties.

P2-063

Effects of total hip/knee arthroplasty on disease activity and drug therapy in patients with rheumatoid arthritis treated with TNF inhibitor

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Conflict of interest: None

[Objectives] Total joint arthroplasty (TJA) improve the quality of life in patients with rheumatoid arthritis (RA). The aim of this study is investigate the effects of TJA in patients with RA treated with TNF inhibitor (TNFi). [Methods] Participants comprised 71 patients with RA who were treated with TNFi and were scheduled to undergo THA or TKA excluded postoperative infection. The Disease Activity Score 28 (DAS28) and hematologic test were examined just before TJA and at one year after surgery. We investigated the number of patients who used methotrexate (MTX), predonisolone (PSL) and biological agent. Also, we investigated the difference the dose of MTX and PSL between pre-TJA and post-TJA at one year. [Results] Disease activity significantly improved from 3.7 to 2.9 in DAS28, 2.0 to 1.5 in CRP, 251.4 to 171.7 in MMP-3 and 295.5 to 243.0 on RF respectively. All patients used biological agents postoperative at one year. The number of patients who used PSL was decreased significantly from preoperative to postoperative at one year. The mean dose of MTX decreased from 6.8 to 4.8 mg/week. That of PSL decreased significantly from 5.6 to 4.0 mg/day at one year postoperatively. [Conclusion] TJA not only improved RA activity but also reduced dose of MTX and PSL in RA patients with TNFi.

P2-064

The results of total hip arthroplasty by direct anterior approach for rheumatoid arthritis

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Conflict of interest: None

【Introduction】We have performed total hip arthroplasty (THA) by direct anterior approach (DAA) for osteoarthritis (OA) since 2009. Non-rheumatoid arthritis (RA) patients recieved THA by DAA started to walk with T-cane and returned earlier than those treated with the posterior approach. We performed primary THA by DAA for RA patients and reported the result. 【Materials and Methods】THA by DAA were performed 9 hips of 8 patients. We assessed JOA score, DAS28-ESR, complications, radiographic analysis before and after surgery. 【Results】The mean age was 57.8 y-o, the mean period from on set of RA was 20.2 years, the mean follow-up period was 30 months. JOA score was improved from 45 points preoperatively to 80 points postoperatively. DAS28-ESR showed no significant change. Intraoperative fracture, femoral nerve palsy, infection, displacement and periprosthetic fractures have not been observed. The radiographic analysis revealed the mean lateral inclination of 39 degrees, all patients were in Lewinnek's safe zone. The mean anteversion was 22 degrees. All stems were not placed varus, but were placed in flexion of 4.2 degrees. 【Discussion】DAA proceed in internervous plane with minimum muscle damage. We could place acetabular component almost in satisfactory position in THA by DAA.

P2-065

Stress analysis of the acetabular reinforcement ring: Effects of the graft location and the hook

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Conflict of interest: None

[Objectives] An acetabular support ring can be applied in total hip arthroplasty, depending on the mass and location of bone grafting in rheumatoid arthritis. We used the finite element method and analyzed the biomechanical effects of the hook of the Ganz ring for various types of bone grafts. [Methods] Geometric data were obtained by CT scanning. The bone graft model of the acetabulum and the acetabular reinforcement ring (Ganz ring) was modelled. We created three bone grafting models, superomedial type, superolateral type, and central massive type that simulate surgical treatment of acetabular defects. Fixed restraints were applied to the sacroiliac joint and the pubic symphysis, and the load was applied at the center of the femoral head. [Results] The stress of the Ganz ring with a hook showed higher values of von Mises stress around the screw and the hook; in particular, bone graft models showed higher stress than the intact model. In the without hook model, the stress of the contact area between the hook and the bone was low and the stress of the screw was higher than that of the model with the hook. These data suggest that the stress is dispersed biomechanically by the Ganz ring, and that the hook can effectively disperse the stress.

P2-066

Clinical result of Harris Galante II cementless THA for rheumatoid arthritis

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Conflict of interest: None

[Object] To evaluate the clinical result of Harris Galante II cementless THA for rheumatoid arthritis. [Methots] Study participants consisted of patients who received a primary THA between May 1985 and March 1996. 17 patients (20 hips) were included in this study, 16 cases (19 hips) were female. The average age at time of surgery was 54-year-old (range 33-73). The average follow up period was 14-years. In the operation, Harris Galante II prosthesis was used for the acetabular component in all cases. Evaluation methods included the X-ray film for checking the polyethylene wearing and JOA score for the objective outcome. Also Kaplan-Meier survival rate of the acetabular component was evaluated. [Results] In the X-ray, polyethylene wear late was 0.13mm/year. In the average JOA score was 70 at 14 years after the operation. 50% of Kaplan-Meier survival rate was 19.8-year. [Conclusions] Clinical result of Harris Glante II cementless THA was good in comparison.

P2-067

Long-term outcomes of intramedullary nail with fin for rheumatoid ankle

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Conflict of interest: None

[Object] To investigate the long-term outcomes of intramedullary nail with fin for rheumatoid ankle. [Methods] Study participants consisted of patients who received an ankle arthrodesis between May 2002 and June 2005. 4 patients (4 ankles) were included in this study. All cases were female. The average age at time of surgery was 70-year-old (range

64-75). The average duration of time from RA onset to the surgery was 29 years (range 24-34). The average follow up period was 12-years (range 10-13). In the operation, intramedullary nail with fin was used in all cases. Evaluation methods included walking pain of affected joint, walking ability, presence of bony fusion in affected joint in X-ray film. [Results] when the latest follow-up, 3 cases have no ankle pain in walking, their walking ability gained from pre-operation, and their ankle and subtalar joint have been fused in X-ray film. Another case who caught Parkinson's disease has been not able to walk, had no pain in affected joint and her ankle joint had already fuse but subtalar joint was not fused in X-ray film. [Conclusions] Our long-term outcomes of intramedullary nail with fin for rheumatoid ankle was good in comparison.

P2-068

Cementless Total Hip Arthroplasty in Patients with Rheumatoid Arthritis

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Conflict of interest: None

In this study, we evaluate mid-term results of uncemented total hip arthroplasty (THA) in patients with rheumatoid arthritis (RA). In our institute, 93 uncemented THAs in 73 patients with RA were carried out from April 1999 to September 2010. Of these 93 THAs, 32 THAs (25 patients) were lost to follow up, and the remaining 61 THAs (48 patients) were included in this study. The mean age at surgery was 61.0 years; the mean follow-up period after surgery was 9.7 years (minimum 5 years). We evaluated the clinical results (in terms of JOA score) and radiographic findings. The average JOA score was significantly improved at 83.2 points from 40.6 points preoperatively. Regarding postoperative complications, dislocation occurred in 6 hip joints. Re-replacement surgery was performed on one hip of frequent dislocation. As for the stability of the cup, bone ingrowth fixation or stable fibrous fixation were obtained except one hip joint. As for the stability of the stem, bone ingrowth fixation was obtained in all hip joints. In this study, we demonstrated satisfactory mid-term (minimum 5 years) results of uncemented THA for patients with RA. We consider that uncemented THA is a promising candidate for such a patient population.

P2-069

Changes in the background characteristics of rheumatoid arthritis patients who underwent total hip arthroplasty

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Conflict of interest: None

[Objectives] We investigated the background characteristics of RA patients who had undergone total hip arthroplasty (THA) in our hospital. **[Methods]** Subjects were 82 RA patients (108 hips) with a mean age of 61.3 years who underwent primary THA from 2000-2015. Changes in the number of surgeries, patient background characteristics and preoperative X-ray images were investigated. **[Results]** The number of surgeries in the second 8-year period was decreased compared with that in the first 8-year period. The mean age in the second period was significantly higher than that in the first period. There was no significant difference in disease duration between the two periods. The incidence of other arthropathies was significantly decreased from 70.3% to 56.8%. There was no significant difference in the proportion of patients who were on corticosteroids, while those on methotrexate and biological agents were increased from 14.1% to 31.8% and from 0% to 6.8%, respectively. There was no significant difference in the number of cases with severe joint destruction. **[Conclusion]** Medication for RA has changed, and a decrease in the number of surgeries. The age of patients who required THA has risen. Such trends will continue and decreases in the number of THA cases are expected in the future.

P2-070

Inter-observer and intra-observer reliabilities of preoperative 3D planning using Zedhip for total hip arthroplasty

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Conflict of interest: None

【Objects】Conventionally, preoperative planning of total hip arthroplasty (THA), was performed using simple X-ray radiographs. Recently, three-dimensional (3D) planning based on computed tomography (CT) has been used in many institutions. We also use 3D planning for THA. Several papers have reported the usefulness of the 3D planning. But, reports of Inter-observer and intra-observer reliabilities of preoperative 3D planning for THA were few. In this study, we investigated Inter-observer and intra-observer reliabilities of preoperative 3D planning for total hip arthroplasty. 【Methods】 15 patients, 20 hips that were underwent total hip arthroplasty in our institution were included. 12 hips had osteoarthritis and 8 hips had osteonecrosis of femoral head.Three surgeon planned with a dedicated planning software (Zed hip®),We performed planning twice and spaced two weeks or more intervals. All implant for planning was same. 【Results】 We investigated the match rate of implant size, and radiographic aliment. Tend match rate is high in intra-observer, it was a low trend in inter-observer. 【Discussion】 3D planning in the past reports is often reported that useful. But, we thought that it required further consideration.

P2-071

Total hip arthroplasty in cases of rheumatoid arthritis: Does medication work?

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Conflict of interest: None

Background: Some recent reports indicate that the number of total hip arthroplasty (THA) for RA patients has been decreasing in recent years. Bone destruction inhibition by use of biological drugs has been suggested as a possible reason. **Objectives:** The purpose of this study was to examine whether the number of RA cases requiring THA has shown a decreasing trend, and to identify any reason for a change. **Methods:** We investigated the records of all patients with RA who underwent a THA at our hospital from 2005 through 2014. We noted the number of THA cases each year, age at surgery, duration of RA, medications and pre-operative X-ray findings. **Results**: In the ten year period there were 615 primary THA cases in our hospital, of which 35 (5.7%) were RA cases. The number of THA showed a decreasing tendency. The rate of steroid use decreased, whereas the rate of biological drug use increased. **Conclusions:** The number of THA for RA was decreased and the patient medications administered were also changed. We consider that bone destruction of hip joint can be inhibited by use of biological drugs.

P2-072

A survey on attitudes toward wound care after joint arthroplasty

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Conflict of interest: None

Objectives: The purpose of this study was to document a survey on attitudes toward wound care after joint arthroplasty. Methods: From May 15 to July 8 in 2014, we conducted a survey of 54 orthopedic nurses with response rate of 73%. Operative method was as follows; intravenous tranexamic acid of 1g, no drain, compressive bandage, subcuticular suture without stitches, and early bathing. Results: As for drain, 57% were

no idea, 35% no drain, and 8% drain. Advantages of no drain were early ambulation, low risk of accidental removal and retrograde infection, although disadvantages were hematoma and lack of blood count. Wound care should be on demand 92% and everyday 8%. Bathing should be as soon as possible 79%, after pain free 14%, and after wound healing 7%. Subcuticular suture without stitches were favorable 51%, no idea 47%, and unfavorable 2%. Conclusion: Traditional way with drain and daily disinfection has been changing due to development of new would coating material and opinion.

P2-073

Factors influencing the intraoperative blood loss in total knee arthroplasty in rheumatoid arthritis patients

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Conflict of interest: None

Objective: To assess the factors influencing the intraoperative blood loss in patients who had undergone total knee arthroplasty (TKA). **Methods:** The study involved 71 patients (86 knees) who had undergone TKA at our hospital between January 2014 and October 2015. We examined the relationships between Body Mass Index (BMI), preoperative CRP, preoperative number of blood platelets, Larsen grade, operative time and the intraoperative blood loss calculated using the formula of Nadler et al. **Results:** There was a negatively-correlation between preoperative number of blood platelets and the intraoperative blood loss (r=-0.303, p=0.005). But there was no significant difference in the intraoperative blood loss between other factors. **Conclusions:** The preoperative number of blood platelets was a factor influencing the intraoperative blood loss.

P2-074

Long-term results of the cementless, cruciate-retaining total knee arthropla sty in patients with rheumatoid arthritis

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Conflict of interest: None

The purpose of this study was to report the long-term results of the cementless, cruciate-retaining (CR) total knee arthroplasty (TKA) in patients with rheumatoid arthritis (RA). We performed 203 primary TKAs in 146 patients with RA using cementless CR TKA between 1984 and 2005. Forty-six patients (64 knees) were available for more than 10 years' follow-up analysis (mean 16.2; 10 to 27), 100 patients (139 knees) were lost to follow-up. There were 3 men (6 knees) and 43 women (58 knees). The mean age at the time of surgery was 60.2 years (38 to 77). The posterior cruciate ligament (PCL) was preserved, and the patella was not resurfaced. Cancellous bone chips were used to fill any bony defects. The tibial component was fixed with 4 screws. Complications occurred in 4 knees; supracondylar femoral fractures in 3 knees, and patellar fracture in 1 knee. There were no cases of deep infection or pulmonary embolism. Three knees have required revision surgery at a mean of 18.7 years (11 to 26) after primary surgery; 2 knees had aseptic loosening, 1 had instability. At a mean of 16.2 years' follow-up, the revision rate was 4.7%. Good results can be obtained using cementless CR TKA in patients with RA.

P2-075

Total knee arthroplasty without patellar resurfacing in patients with rheumatoid arthritis ―A comparison between total knee arthroplasty with and without patellar resurfacing―

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Conflict of interest: None

【Objective】We performed TKA with and without patellar resurfacing in the present study,which was designed to evaluate the short, mid and long-term results of TKA in patients with RA and to determine whether patellar resurfacing is necessary in all TKA patients with RA.【Methods】Our subjects were 37 patients (43 affected knees; 7 males, 36 females) who had undergone TKA at least 36 months prior to the initiation of the study. In clinical evaluation, we examined the JOA score for RA of the knees, ROM, whether or not patellofemoral joint pain (pf-pain) remained, and whether or not revision surgery for the patella had been performed.【Results】The average JOA score improved significantly from 47.8±11.3 before surgery to 73.8±12.6 after surgery (P<0.05). The average ROM (ext/flex) was improved from -7.2±9.2˚/115.8±14.0˚ before surgery to -4.0±4.7˚/118.7±10.0˚ after surgery. Pf-pain was observed in 4 patients. There were no significant differences in postoperative JOA score in long-term cases between with and without patellar resurfacing.【Conclusion】The present clinical evaluation of TKA without patellar resurfacing in patients with RA was favorable overall.Our results suggest that TKA without patellar resurfacing should be considered in TKA patients with RA.

P2-076

Treatment of infected total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] We report our current investigation into the treatment of infection after total knee arthroplasty (TKA) in rheumatoid arthritis (RA) patients. [Subjects and Methods] The subjects were 10 patients with RA who received treatment for infected total knee arthroplasty during the past decade. The average age at the onset of infection was 69.3 years and infection was detected an average of 5 years and 2 months after TKA. We investigated whether the primary implant was salvaged or whether revision TKA was required, as well as the other results of treatment. [Results] The implant was salvaged in 5 joints and revision TKA was needed in the other 5. In 4 joints, antimicrobial cement was used when inserting the implant. In 2 joints with salvage of the primary implant, it was removed to allow adequate curettage of the infection and then the sterilized implant was refixed with antimicrobial cement. [Discussion] There is a risk of infection even 5 years after TKA, and particular attention should be paid to patients receiving bio treatment. Placing antimicrobial cement in joints with preservation of the implant or refixing the implant after sterilization might be worth trying in RA patients due to their low activity and compromised status.

P2-077

Inter-observer and intra-observer reliability of preoperative CT-based 3D planning for total knee arthroplasty

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Conflict of interest: None

【Object】 Preoperative planning is an important factor of total knee arthroplasty (TKA). Recent studies suggest the usability of preoperative CT-based 3D planning for TKA, but few studies show its inter-observer and intra-observer reliability. The aim of this study is to document the reliability of preoperative CT-based 3D planning for TKA.【Methods】Twenty knees who underwent TKA at our hospital were included. The indication was primary osteoarthritis in ten knees and rheumatoid arthritis in ten. All knees were planned with zed knee system (Lexi) by three orthopaedic surgeon independently twice at more than 2 weeks intervals. We studied about femoral and tibial component size, the degree of valgus and external rotation of femoral component.【Results】 We achieved 100% intra-observer and 70% inter-observer agreement within 1 size in femoral component size and 96.7% intra-observer and 55% inter-observer agreement in tibial component size. The inter-observer difference of the degree of valgus was 0.80 degree on average and that of external rotation

was 1.32 degree. 【Conclusions】 We studied about the reliability of preoperative CT-based 3D planning for TKA. Percent agreement was higher in femoral component size than in tibial component size.

P2-078

Short term clinical results for the total ankle replacement in the patient with rheumatoid arthritis

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Conflict of interest: None

【objective】 There are few reports of excellent clinical results of total ankle replacement (TAR). We compared clinical results of TAR in Osteoarthritis (OA) and rheumatoid arthritis (RA). 【method】 21 patients were underwent TAR from 2007 to 2014 in our hospital. All patients were used FINE total ankle system. There were RA group: eight patients, eight ankles, OA group: 13 patients, 14 ankles. 【result】 The ankle ROM did not have the difference between two groups in preoperative. The patient of the RA had decreased ROM of the ankle after surgery in comparison with OA group. Talus component subsidence was RA group: three ankles, OA group: one ankle. Radiolucent line with more over 2mm is RA group: two ankles, OA group: two ankles had it. There was many subsidence of the component of the talus side in the RA group than OA group. However, subsidence existed, but sharp pain was slight, and there was not the drop of the walking ability. Loosening of the tibia side was equally in both groups. 【Conclusion】 In both group, revision TAR did not need for the short term period. The clinical results of the TAR in the patient with RA is good. In RA group, there is a need for preoperative evaluation for the talus condition because of talus component subsidence.

P2-079

Posterior crucial ligament tear following total knee arthroplasty for a patient with RA

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Conflict of interest: None

【Case report】We present a 72-year-old female with RA whose PCL suddenly tore in her right knee replaced with CR-type total knee. She had received total knee arthroplasty (TKA) 20-years ago and had been doing well. From 7-years ago, she had been treated with a biologic agent and the disease activity well controlled. Since her right knee got swollen without any traumatic events, she admitted to our hospital. The joint fluid was bloody and its bacterial culture showed negative. The posterior drawer test was positive and the lateral view of the radiographs showed posterior shift of the tibia, suggesting PCL tear. MRI of her right knee demonstrated PCL tear on its tibial side. After walk training with a knee orthosis, she discharged and is followed at our outpatient clinic. 【Discussion】In this case, PCL tear occurred without any traumatic events at 20-years after TKA. The radiographs showed good alignment of the implants and polyethylene wear was not likely. She had been treated with glucocorticoids for a long period of time, therefore, long-standing joint inflammation and glucocorticoids may have caused fragility of the PCL, resulting in its tear. 【Clinical significance】PCL tear should be noticed as a significant complication related to TKA, especially for patients with RA.

P2-080

A case of periprosthetic fracture following THA and TKA in patient with RA

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Conflict of interest: None

Case:A 62- year-old woman who previously underwent left THA and left TKA fell and had broken her left femur bone. She developed RA at 39 years old. She underwent fixation of left periprosthetic fracture with a LCP distal femur. Three periprosthtic screws and one cable system were constructed at the part of the stem. Two locking screws were constructed between the tip of the stem and the fracture line. Six locking screws were constructed below the fracture line. She was allowed to move her left lower leg the day after surgery. She started to walk one month postoperatively. At the six months follow up, radiographs showed signs of bone healing. Discussion: It is difficult to stabilize periprosthetic fractures firmly around THA since intramedullary nail and bicortical screws can not be used. Locking plate has advantages that monocortical screws can be constructed and blood circulation of the periosteum is not so damaged. To insert screws above the fracture line strengthens resistance to rotation and shortening.To roll the cable prevents the plate from sliding. Severe osteoporosis exists around TKA. To use locking plate can move the knee soon after surgery. Clinical significance: Locking plate is the effective way to treat periprosthetic fractures after THA and TKA.

P2-081

perative planning for Joint-preserving Surgery of rheumatoid forefoot deformity using three-dimensional full-scale model;a case report

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Conflict of interest: None

【Introduction】We make a three-dimensional full-scale model (3d model)of affected forefoot bone for pre-operative planning of Joint-preserving Surgery for rheumatoid forefoot deformity.【Case】The case was a 76-year-old woman with 10-year history of rheumatoid arthritis (RA) She have sever forefoot deformity with painful hallux valgus,clawing toes with associated metatarsi-phalangeal joints (MTPs) subluxation and dislocation.The affected limb (from the ankle to the farefoot) was scanned using a computed tomography (CT).Digital data of the bone were segmented,and 3D surface models (STL file)were constructed using AZE virtual place.This was embodied as a salt model through rapid prototyping technology.The simulation was done by using this 3D model and actual surgical instrument.We were able to performed the surgery as planned.The hallux valgus angle improved from 65 degrees preoperatively to 15 degrees postoperatively. The 1-2 intermetatarsal angle improved from 15˚ to 5 ˚.The 1-5intermetatarsal angle improved from 35˚ to 3˚.The duration of non-weight-bearing was 4 weeks,after which the patient was allowed to do full weight-bearing with an insole.【conclusion:】It is very useful to perform 3-dimensional evaluation preoperatively and the surgical simulation.

P2-082

A case of early stage of adverse reaction to metal debris diagnosed by the leg edema

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Conflict of interest: None

Metal-on-metal total hip arthroplasty (THA) was performed for a 79-year-old woman who had osteoarthritis of left hip. Four years after the surgery, she started to suffer from edema in the left lower extremity. A deep venous thrombosis was not detected by CT scanning. MR image revealed a mass lesion with liquid component stretched from the hip joint to pelvic cavity. Because blood test detected no signs of infectious diseases, we diagnosed it as pseudo tumor of ARMD (Adverse Reaction to Metal Debris). We performed the curettage of the pseudo tumor and the exchange of metal liner to that of polyethylene. Debris-like tissue was found in and around hip joint. Pathological finding showed the necrotic granuloma containing phagocytosis of metal particles, which was compatible to its diagnosis of ARMD. There was little solid component inside the pseudo tumor, indicating that it was still in early stage. Leg edema improved immediately after the operation. It might be because the pseudo tumor had compressed femoral and external iliac veins.Since ARMD

could induce osteolysis and consequent loosening of implants, it is quite important to diagnose ARMD at earlier stage. We here report a rare case in which we happened to diagnose the early stage of ARMD with a clue of its severe leg edema.

P2-083

A case of simultaneous bilateral proximal closing-wedge osteotomy for hallux valgus deformity with destructions of MTP joints in a young patient with rheumatoid arthritis

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Conflict of interest: None

[Case report] A-30-year old woman who had been shifted from JIA on set at 13-year-old, Stage 3 Class 2. She was in the Boolean remission state by abatacept 500mg monthly. We underwent simultaneous bilateral proximal rotational closing-wedge osteotomy using locking plates, and arthroplasty of the left 2-4 MTP joints by proximal slanting metatarsal bone cutting and fixed by 2.0 mm screws. We permitted foot loading and using wheelchair with casts since the next day. After 4 weeks we removed K-wires and casts, permitted walking by a go-cart. After 6 weeks she left our hospital with full bearing. Bone union was completed after 3 months. After 16 months HVA was improved from 36˚ to 16˚ of the right side, from 38˚ to 16˚ of the left side, JSSF RA foot ankle scale was improved from 55 to 83 point of the right side, from 63 to 93 point of the left side. After 9 months osteophyte formations were admitted in both hallux MTP joints. About this case, we supposed that the patient would be dissatisfied with poor ADL by arthrodesis of MTP joints in both sides and the silicon implant would be damaged in the early period by joint replacement. She has been satisfied with the comfortable state, we think that the joint preserved operation is useful for a young RA patient even if MTP joint is damaged.

P2-084

Revision knee arthroplasty due to varus instability after total knee arthroplasty in rheumatoid arthritis: A case report

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Conflict of interest: None

[Introduction] Lateral instability after total knee arthroplasty (TKA) may lead to revision TKA. We report the case with rheumatoid arthritis (RA) for whom revision TKA was performed using semi-constrained prosthesis because of varus instability after primary TKA. [Case report] A 66-year-old woman was diagnosed with RA at the age of 48 years. She experienced knee pain since the age of 60 years. She underwent left TKA at the age of 63 years. Immediately after TKA, she experienced varus deformity, and the femorotibial angle (FTA) was 187˚ at 1 week after surgery. She did not complain of pain, however, varus deformity gradually worsened to FTA of 195˚. She felt instability while walking, therefore, revision TKA using a semi-constrained prosthesis was performed when she was 66 years old. Although radiographic varus remained, the feeling of instability improved. [Discussion] Lateral instability after TKA are caused by varus-valgus imbalance, flexion-extension imbalance, component malalignment and obesity. Ligament reconstruction and revision TKA have been reported as treatments. Since no ligament injury was observed in this case, we selected revision TKA. Although the patient's feeling of instability disappeared, further careful follow-up is required as varus deformity remain.

P2-085

Intractable wound healing after total knee arthroplasty accompanied by subcutaneous seroma in a patient with highly advanced rheumatoid arthritis

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Conflict of interest: None

A case report; 40 years old female with 22 years history of stageIII/class 4 rheumatoid arthritis (RA) presented with dysstasia due to severe left knee pain. MTX, tacrolimus, IFX and PSL of 10mg/day were medicated for RA control. Severe valgus deformity and insufficiency patellar fracture was also revealed in plain radiographs. Total knee arthroplasty (TKA) with constrained implant and wiring of the patella fracture were simultaneously performed. At 2 week postoperatively, skin necrosis of 10mm in diameter emerged in anterior aspect of the knee. Then, the necrotic skin was removed and sutured. Despite various treatments such as wire removal and re-suture or vacuum assisted closing therapy, the wound had never healed due to continuous serous distarge, unless gastrocnemius muscle-cutaneous flap transfer was performed at 5 month after TKA. Furthermore, harvested site of the cutaneous flap also dehisced with subcutaneous seroma formation, and also never healed conservatively. The wound was finally healed by debridement and 7days suction drainage with ankle immobilization at 11 month after TKA. **Conclusion:** Although subcutaneous seroma in RA patient has not been well documented, it would be an intractable complication of joint replacement surgery for RA patient.

P2-086

MEK5 suppresses osteoblastic differentiation

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Conflict of interest: None

Objectives Extracellular signal-regulated kinase 5 (ERK5) is a member of the mitogen-activated protein kinase (MAPK) family and is activated by its upstream kinase, MAPK kinase 5 (MEK5), which is a member of the MEK family. Although the role of MEK5 has been investigated in several fields, little is known about its role in osteoblastic differentiation (OD). **Methods** We investigated the role of MEK5 in OD in mouse preosteoblastic MC3T3-E1 cells and bone marrow stromal ST2 cells. **Results** We found that treatment with BIX02189, an inhibitor of MEK5, increased alkaline phosphatase (ALP) activity and osteoblastic gene expression, as well as it enhanced the calcification of the extracellular matrix. Moreover, cell proliferation decreased. In addition, knockdown of MEK5 using siRNA promoted OD. In contrast, overexpression of wild-type MEK5 suppressed OD, but promoted cell proliferation. Additionally, TNF α activated ERK5 pathway, and the negative effects of TNF α on OD are restored by inhibition of MEK5. **Conclusions** MEK5 suppressed OD, but promoted cell proliferation.Inhibition of MEK5 signaling in osteoblasts may be of potential use in the treatment of osteoporosis in patients with and without RA.

P2-087

Short-term bisphosphonate treatment reduced the 25(OH) vitaminD_3 level, and changed the values of parathyroid hormone , pentosidine, and bone metabolic markers by short-term bisphosphonate treatment

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Conflict of interest: None

[Object] This study aimed to clarify the effects of short-term bisphoshonate (BP) administration in Japanese osteoporotic patients. [Methods] The daily minodronate (MIN) (MIN group) or weekly risedronate (RIS) (RIS group) were primarily prescribed for each patient in a non-randomized fashion. We analyzed the laboratory data of female 35 cases (18 of

MIN and 17 of RIS) before the start of treatment and at 4 months afterwards. Specifically, changes in 25 $(OH)D_3$, whole PTH, serum pentosidine, and bone turnover markers were evaluated. [Results] 25 $(OH)D_3$ significantly decreased after 4 months of BP administration. PTH significantly increased at the study end point, as was pentosidine. Whereas 25 $(OH)D_3$ and pentosidine showed comparable changes in the MIN and RIS groups after 4 months of treatment, PTH significantly more increased in the MIN group. All bone turnover markers significantly decreased at 4 months in both groups. Compared with the RIS group, the MIN group had significantly larger value changes of urinary NTX, TRACP-5b, and BAP at the study end point. As 25 $(OH)D_3$ significantly decreased, and PTH and pentosidine significantly increased, at 4 months of BP treatment. [Conclusions] This study suggested that MIN more strongly inhibited bone turnover as compared with RIS.

P2-088

The effect of intravenous infusion of bisphosphonate for osteoporosis patients

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Conflict of interest: None

As problems of the oral bisphosphonate preparation, it is pointed out that taking medicine compliance and a taking medicine continuation rate are lower than other osteoporotic therapeutic drugs. The bisphosphonate intravenous infusion is the drug that an effect is expected as one of the dosage methods that can solve those problems. We report it this time because we investigated it about a bisphosphonate intravenous infusion use example. The object is 26 cases using the alendronate intravenous infusion in patients with osteoporosis. All patients are female, and the average age is 79.1 years old. The examination item is 1) continuation rate 12 months later, 2) use reason, 3) bone mineral density of lumbar vertebrae and proximal femur before dosage and after the dosage in 12 months, 4) TRACP-5b, BAP and Ca level before dosage and after the dosage in 12 months, 5) appearance of complications. A continuation rate of one year was 76.9%, and there was not the serious side effect, and the improvement of bone mineral density and the bone metabolism marker was recognized after beginning to use. The bisphosphonate intravenous infusion could expect a high continuation percentage, and it was thought that it was one of the useful osteoporotic therapeutic methods.

P2-089

Is the rheumatoid arthritis itself a cause of the osteoprosis?

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Conflict of interest: None

[Purpose] To clear the relation of rheumatoid arthritis (RA) and osteoprosis (OS). [Object] 287 patients with RA who did not recieve glucocorticoid. There were 44 males and 243 females whose average age was 61.2 year old (28-88 year old). [Method] RA patients were measured BMD by the DXA method using HOLDGIC QDR-BELPHI W. We examined the BMD in the lumbar vertebrae not the femur which RA activity would influence, and used %AM not YAM to exclude influence of gender or age. Furthermore, we checked the background of the cases that had a diagosed of OP. [Result] BMD was measured after RA onset of 6 years in average. Mean %AM was104.1%, and mean %YAM 86.4% did not decresed significantly. 52 patients given diagnosis of OP, and their mean %AM was 84.5%, and mean %YAM 63.3%. OP group except 39 year old one, all were older than 57 year old and were average age 69.4 year old. Activity of RA was high in the group with less than 5 years of desease period, and DAS28-ESR was high average of 5.47. [Conclusion] Lumbar vertebrae BMD did not have the clear depression in patients with RA who did not recieve glucocorticoid. Age, treatment with glucocorticoid and frailty due to the disease activity, not RA in itselfe, related to the vertebrae BMD of patients with RA.

P2-090

The present conditions and problems of the osteoporotic management of the rheumatoid arthritis patient

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Conflict of interest: None

[Purpose] I investigate a tendency of the osteoporotic treatment of the rheumatoid arthritis (RA) patient with osteoporosis and clarify the present conditions and problems. [Object and method] Intended for 80 cases treated for the RA patient that an outpatient visited our hospital as osteoporosis, and examined the contents and a result of the bone mineral quantity and the result of the bone metabolism marker. [Result] The medication contents were 44 bisphosphonate (BP preparation), 10 denosumab, 7 teriparatide. The most recent bone quantity, the bone metabolism marker had few cases inspected together, and there was not the constant tendency in the value either. [Discussion] Usability of BP preparation and denosumab is guidelines on osteoporosis, but is recognized in osteoporosis of RA. It was thought that even this investigation almost obeyed guidelines. But BP preparation was rambling, and it became clear to have been given without investigating bone quantity and a bone metabolism marker thoroughly though I did periodical consultation and drawing blood of RA in a large number of cases. It was thought that it was necessary to be careful about not only the condition of a patient of RA but also the situation of the osteoporosis in future.

P2-091

Characteristics of osteoporosis patients with rheumatoid arthritis and the importance of bone marrow density measurement

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Conflict of interest: None

[Objective] The characteristics of osteoporosis (OP) patients with rheumatoid arthritis (RA) were compared with those patients with osteoarthritis of the knee (OA). [Methods] Past 10 years of medical records were searched and 40s years or older patients with RA and OA were extracted, respectively. Mean age, BMI, complications, and steroid taking were compared between the groups by gender. The intervention rate for bone marrow density measurement (DXA of proximal femur), prevalence of OP (defined by <70% of YAM values), and therapeutic intervention rate were also evaluated. [Results] In total, 1452 and 4794 (519 and 1923) cases of women (men) with RA and OA were investigated, respectively. RA group had lower BMI for female and higher rate of steroid taking. Female (male) RA group had higher complication rate of CKD and COPD (DM and COPD). DXA revealed that OP rates increased more rapidly in female RA group since 60s years old. The therapeutic intervention rate increased more than twice in patients who underwent DXA compared with those who did not. [Conclusions] RA group have several risk factors and increased rate of OP, showing that RA need aggressive therapeutic intervention for OP. DXA which leads to increased therapeutic intervention is important.

P2-092

Evaluation of changes in mineral bone density and drug survival rate following 36 months of treatment with eldecalcitol in rheumatic diseases

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Conflict of interest: None

[Objectives] The aim of this study is to evaluate the changes in mineral bone density and drug survival rate following 36 months of treatment with eldecalcitol in rheumatic diseases. [Methods] Eldecalcitol was daily administrated to 43 rheumatic disease patients at a dose of 0.75 ug for 36 months. Lumber and total hip bone mineral density were measured at 0,

6, 12, 24 and 36 month. Serum Ca, P, TRACP-5b, bone-specific AP (BAP), P1NP, parathyroid hormone (PTH) and urinary type-I collagen cross-linked-N-telopeptide (uNTx) were measured. [Results] The percentage changes from baseline (0 month) in lumber and total hip bone mineral density were increased at 6, 12, 24 and 36 month. In addition, Serum Ca was significantly increased at 6 month and TRACP-5b, uNTx, P1NP and BAP were significantly decreased at 6 month as compared to each biomarker at baseline. In addition, The percentage of drug survival was 88%, 79%, 70% and 65% at 6, 12, 24 and 36 month, respectively. Drug survival rate of ELD was significantly lower in elderly person, low body weight and renal dysfunction. [Conclusions] Eldecalcitol was effective in osteoporotic treatment in rheumatic disease patients. Additionally, age, body weight and renal function predict time to discontinuation.

P2-093

Influence of oral prednisolone on effect of denosumab on osteoporosis in patients with Japanese rheumatoid arthritis ~a Multicenter Registry Study~

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Conflict of interest: None

[Objectives] We investigated the influence of oral prednisolone on the efficacy of DMB in OP patients with Japanese RA. [Methods] The final study cohort of 67 patients received continuous DMB therapy more than 12 months from Tsurumai Biologics Communication Registry (TBCR-BONE). We reviewed the results for 6 and 12 months about the increase and decrease of bone mineral density (BMD) of lumbar spine (LS) and total hip (TH) by DEXA and bone turnover markers, PINP and TRACP-5b. [Results] In the patients receiving oral prednisolone group (n=21, group P) and not receiving group (n=46, group NP), the mean age was 68.5 and 69.9 years old (p=0.657); disease duration was 16.3 and 16.0 years (p=0.532). The rate of decreased PINP and TRAC-5b from baseline to 6 and 12 months were each -29.4% vs -40.2%(p=0.289), -13.7% vs -41.5%(p=0.118) and -28.5% vs -35.1%(p=0.868), -21.4% vs -31.6%(p=0.401) in the group P vs NP group. The rate of increased LS-BMD and TH-BMD from baseline to 6 and 12 months were each 3.4% vs 4.5%(p=0.305), 4.7% vs 6.8%(p=0.175) and 3.0% vs 3.0%(p=0.816), 3.9% vs 3.9%(p=0.898) in the group P vs NP. [Conclusion] DMB was effective in OP of RA patients. Oral prednisolone use did not influence the efficacy of DMB in the short period of 12 months.

P2-094

Current status of femorak fractures in rheumatoid arthritis patients

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Conflict of interest: None

Objectives: To understand current status of in RA patients who had undergone surgery of femoral fractures. Methods: 73 RA patients (male:female 2:71, average 72.2 years old) who had operated by femoral fractures between 2006 and 2014 were enrolled. Results: As for the type of the fracture, there were neck:39, trochanter:30, shaft:5 and distal:10 cases. A contralateral fracture was five cases. Two sites 6 cases, three sites were 1 case in the same case. The steroid use example was 57 cases. The treatment of the osteoporosis was provided in 49 cases, and as for the breakdown, there were BP:35,VitD:7,VitK:11,PTH:6 and Ca agent:2 cases. The use was 57 cases after bone fracture treatment. In the discharge, there were home:61, institution:8 and changing hospital: 4 cases. The investigation death was six cases. An average of 1.1 declines were seen by the Fujibayashi classification. Conclusion: Though there was a diagnosis of the osteoporosis, only as for 67% of preoperation, medical treatment was seen, and only 78% were added after operation. It will seem that further aggressive treatment is necessary in future.

P2-095

Digital image of chest X-ray as a screening tool of fragile spine fracture

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Conflict of interest: None

Background The screening of osteoporosis in the management of rheumatoid arthritis is essential and the evaluation of fragile spine fracture is one of the recommended examinations. Digital chest X-ray is widely available, and spine can be evaluated focusing on its lateral view. Therefore, we assessed the efficacy of the screening of fragile spine fracture using a lateral view of chest X-ray. **Method** We studied retrospectively all patients who had newly met the 2010 ACR/EULAR rheumatoid arthritis criteria and also received osteoporosis screening including chest X-ray, spine X-ray, FRAX, and dual-energy X-ray absorptiometry (DXA). **Result** We identified 17 eligible patients and fragile spine fracture was detected in 4 patients (29.4%) by spine X-rays. The analysis of data showed the sensitivity of the examinations were lateral view of chest X-ray (100%), DXA (60%), and FRAX (60%). **Conculusion** Implementation of evaluation of fragile spine fracture usuing digital image of chest X-ray could be useful as a screening tool.

P2-096

Therapeutic effects of denosumab for bone loss and osteoporosis that exhibit resistance to bisphosphonates

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Conflict of interest: None

【Purpose】Although bisphosphonates (BP) are frequently used for osteoporosis, here are some cases with insufficient response. The effects of Denosumab (DMAB) on the bone mineral density (BMD) were studied when administered to the cases with % YAM less than 70% despite the treatment with BP, and analyzed the factors with its effects. 【Method】 Twenty-one patients (4 males, 17 females, 18 taking steroids) whose medication was switched to DMAB from BP were enrolled. We measured the BMD of the lumbar spine and femur 12 months after switching. We also studied about the factors such as age, sex, BMI, underlying diseases, or bone turnover markers (serum NTX, serum P1NP). 【Results】Average value of %YAM in lumbar spine and femur 12 months after switching was 72.1% and 65.6%, respectively. The rate of change in BMD in the lumbar spine and femur was 4.9±4.5% and 3.2±6.1%. However the reduction of BMD was found 3 patients in lumbar spine and 5 patients in femur. In lumbar spine, patients with decreased BMD had tendency to be older or with higher BMI as compared to those who showed improvement in BMD. Other factors had no relationship to the therapeutic effects on BMD. 【Conclusion】These results suggest that DMAB might be effective for bone loss and osteoporosis resistant to BP.

P2-097

Changes of bone metabolism markers in the course of ibandronate therapy with rheumatoid arthritis patients

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Conflict of interest: Yes

Purpose: To determine the changes of bone metabolism markers in the treatment of rheumatoid arthritis (RA) patients using ibandronate. Methods: In 18 RA patients, ibandronate was used for the treatment of osteoporosis. Bone metabolism markers; TRACP-5b and BAP, were measured before and 6 months after the administration of ibandronate. Results: TRACP-5b (average; mU/dl) changed from 498.7 to 337.9, and BAP (average; mg/L) changed from 17.6 to 13.9, respectively. There were no adverse effects of ibandronate therapy with RA patients. New

fractures were not observed in the course of the treatment with ibandronate. Conclusion: Preventing the bone absorption effects were observed in terms of bone metabolism. Ibandronate therapy with RA patients may be a useful strategy against osteoporosis.

P2-098

Current status of management of glucocorticoid-induced osteoporosis -Adherence to the updated JSBMR guidelines and related factors-

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Conflict of interest: None

We investigated the level of adherence to the Japanese Society of Bone and mineral Research (JSBMR) guidelines for management of glucocorticoid-induced osteoporosis (GIO) by age, prior fragility fractures, GC dose, and lumbar bone mineral density (BMD). The JSBMR has incorporated a new scoring method to assess fracture risk and updated on the basis of a score of 3 as the optimal cut-off score for drug therapy including bisphosphonates, teriparatide, and active vitamin D3 etc. We identified 119 patients with rheumatic diseases who are using or planning to use GC for more than 3 months. The mean age was 64.3 and 75% of the patients was female. Major underlying disease was rheumatoid arthritis. 77.3% of the patients met this criterion and among them, 60.9% received one of these drugs. More than 90% of patients with prior fractures received drug therapy. The low adherence level was associated with gender (male vs female=36.6 vs 70.6%) and age (<65 vs ≥65 = 30.4 vs 71.0%).The adherence level to the updated JSBMR guideline improved compared to that to the 2004 guidelines reported previously. Interventions to improve GIO management, especially targeting male and younger patients are needed.

P2-099

Evaluation of guidelines on the management and treatment of glucocorticoid-induced osteoporosis and ratio of prior fragility fracture between genders

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Conflict of interest: None

[Objectives] The aim of this study was to evaluate the risk factors of fracture in guidelines on the management and treatment of glucocorticoid-induced osteoporosis and the ratio of prior fragility fractures. **[Methods]** We analyzed the scores consisted of prior fragility fractures, age, glucocorticoid (GC) dose, lumbar bone mineral density (BMD in 300 patients (male 89 and female 241) who were treated with GC from January 2014 through December 2014 at our hospital. The patients divided 3 groups (Group L: under 49 years old, Group M: between 50 and 64 years old, Group H: over 65 years old). **[Results]** The averages of %YAM of male and female in the Group H were 89% vs 79%($p<0.05$). And the rates of prior fragility fractures of male and female in the Group H were 46% vs 75%($p<0.05$). **[Conclusion]** For rapidly reduction of BMD in female after menopause, the rates of prior fragility fractures in female over 65 years old were significantly increased compared with male.

P2-100

The Effects Of Monitoring On a Quality Indicator For glucocorticoid-induced Osteoporosis And Trends Of The Drug Variation In a Japanese Hospital

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Conflict of interest: None

[Object] To search the effect of Quality Indicator (QI) on Glucocorticoid Induced Osteoporosis (GIOP) care. **[Methods]** We studied all the patients with prescription of prednisolone as low as 7.5 mg daily or its equivalent for more than 3 months in our institution from 2010 to 2013. Patients were divided into 3 groups; Group A (male) and B (female<50yo) were recommended to take vitamin D analogues, and Group C (female>=50yo) was recommended to take bisphosphonates with vitamin D analogue, following ACR 2010 GIOP management recommendation. QI for GIOP was defined as the compliance rate of recommendation. Since 2011, we had monitored QI for GIOP, reported the result in the hospital wide QI meeting monthly. **[Results]** Pooled rate of QI improved from 45.76% in 2010 to 51.8% in 2011, and to 58.9% in 2013 ($p<0.05$), Subanalysis by group showed improvement in QI in group A and group C. Subanalysis by department demonstrated QI in 2012 was significantly different ranging from 76.1% to 13.6%. Subanalysis by type of bisphosphonates demonstrated allergy & rheumatology department had switched to the monthly type more rapidly than other departments. **[Conclusions]** Implementation of monitoring on a QI for GIOP significantly improves adherence to appropriate anti-osteoporotic drug prescription.

P2-101

Prognostic value of lumber spine quantitative computed tomography-based finite element method (QCT/FEM) in glucocorticoid-induced osteoporosis

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Conflict of interest: Yes

Object: The measurement of bone strength, including QCT/FEM and HAS (Hip structure analysis), has been highlighted in glucocorticoid-induced osteoporosis (GIO). We previously reported the predictive value of lumber QCT/FEM in the first 12 months during glucocorticoid treatment. Here we report that in the first 24 months. Methods: 43 Patients with autoimmune diseases who newly received glucocorticoids were enrolled. Prophylaxis for GIO was decided at the discretion of each doctor. Bone mineral density (BMD), QCT/FEM, HAS and biochemical markers were measured at 4, 12 and 24 months. Results: The incidence of morphological fractures was 20%. Bone strength by QCT/FEM at 4 months was significantly lower than the baseline level ($p=0.009$), but thereafter a little increased. On the other hand, the other parameters did not change significantly. There were no significant correlations between the incidence of morphological fractures and measured parameters. Bone strength by QCT/FEM in patients receiving vitamin D was significantly lower than that in patients receiving bisphosphonates at 4 months. Conclusions: Bone strength measured by QCT/FEM could have a possible predictive marker for fracture, but longer observation of larger number of patients are required to show its usefulness.

P2-102

Effects of denosumab on bone metabolic indices and bone mineral density in patients treated with glucocorticoid

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Conflict of interest: None

OBJECTIVES: We performed the prospective study to clarify the effects of denosumab on bone metabolic indices and bone mineral density (BMD) in 29 patients treated with GC, who had the fracture risk factors more than 3 points proposed by the Japanese Society for Bone and Mineral Research, for these disorders for 12 months. METHODS: In 29 patients, 14 patients had SLE, 6 patients RA, 10 patients other rheumatic diseases, and 2 patients renal diseases. Serum NTX and BAP were mea-

sured as bone metabolic indices. BMD of lumber spine (LSBMD) and femur head (FHBMD) was measured with dual-energy X-ray absorptiometry. There are no adverse effects. RESULTS: Both LSBMD and FHBMD values were significantly higher in 12 months after the denosumab therapy (91.5% to 95.0%(3.5%/year), 86.4% to 89.4%(3.0%/year)), although LSBMD and FHBMD values were slightly improved 1.36%/year and 0.96%/year in 16 patients treated with bisphosphonate. Denosumab significantly reduced serum NTX and BAP levels from the baseline during 12 months (19.2 nM BCE/L to 13.4 nM BCE/L, 11.9U/L to 9.2U/L, respectively). CONCLUSIONS: Denosumab is effective and safe to prevent BMD loss and bone resorption in patients treated with GC. The anti-osteoporosis effect of denosumab may be greater than that of BP.

P2-103

Efficacy and safety of denosumab for glucocorticoid-induced osteoporosis

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Conflict of interest: None

【Objectives】The data on the efficacy and safety of denosumab for the primary prevention of glucocorticoid-induced osteoporosis (GIOP) is still limited. We report the efficacy and safety of denosumab for the primary prevention of GIOP in patients with systemic autoimmune diseases who were treated with moderate to high dose glucocorticoid. 【Methods】 Denosumab was administered to 10 patients, requiring more than moderate doses of glucocorticoid (median 35 mg/day). Serum bone markers (TRACP-5b and BAP) were measured twice, at 0 month and 6-12 months after the administration of denosumab. The incidence of bone fracture in these patients was compared with 9 patients receiving bisphosphonates. 【Results】The bone fracture risk score of the cases receiving denosumab was high (median 8). Initial serum TRACP-5b levels (median 423 mU/dL) were high and significantly decreased after the administration of denosumab (median 172.5mU/dL). Serum BAP levels were decreased to within the normal range, but the decrease was not significant. Mild hypocalcemia was seen in 5 patients receiving denosumab. The incidence of bone fracture was not observed in any group. 【Conclusion】These results demonstrate the efficacy and safety of denosumab for the primary prevention of GIOP.

P2-104

Retrospective study on the usefulness of denosumab for the management of glucocorticoid-induced osteoporosis in patients with collagen diseases

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Conflict of interest: None

Purpose: To investigate the usefulness of denosumab (DSM) for glucocorticoid-induced osteoporosis (GIOP) in patients with collagen diseases (CD). **Methods**: We retrospectively reviewed the medical records of 24 CD patients (RA 14, SLE 4, SSc 2, DM 1, vasculitis 2, PMR 1) who had received steroid therapy and were prescribed DSM from January to October 2014. **Results**: Patients' profiles: male 4, female 20, median age was 73 years old, 19 patients had a history of fragile fracture, the median duration of glucocorticoid therapy was 134 months, the median prednisolone was 3 mg/day, and the mean lumber bone mineral density (BMD) value was 0.780 g/cm^2, its YAM value was 73.7 %. Previous therapy for GIOP; teriparatide 12, bisphosphonate 7, SERM 3, vitamine D alone 1. Mean lumber BMD and its YAM value were 0.790 g/cm^2(P=0.83) and 76.9 %(P=0.48) respectively after one year DSM therapy. New vertebral fracture developed in 2 cases, but non-vertebral fractures were not seen. There were several minor adverse events such as stomatitis 2, abdominal pain 2, loss of hair, gingival swelling, numbness of the limbs, myalgia and anorexia, but none of them led to cessation. **Conclusions**: In patients with CD receiving long-standing glucocorticoid therapy, DSM may be useful for the management of GIOP.

P2-105

Effects of glucocorticoid on Wnt signaling pathway in human osteoblasts

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Conflict of interest: None

[Object] Wnt signaling pathway plays an important role in bone formation. We measured serum levels of sclerostin and Dickkopf1 (Dkk-1), inhibitors of the pathway, in patients with systemic autoimmune diseases who received glucocorticoid (GC), and reported at JCR2015 that they were significantly increased at early phase of GC therapy. It was suggested that GC suppressed bone formation *via* Wnt/β-catenin signaling pathway *in vivo*. We then investigated the effects on the expression of sclerostin and Dkk-1 in human osteoblasts *in vitro*. [Methods] Human osteoblasts were incubated with or without dexamethasone (10^{-8}, 10^{-7}, 10^{-6} M) for 24 hours. The concentrations of sclerostin and Dkk-1 in the culture supernatants were measured by ELISA, and their mRNA expression were detected by PCR. [Results] Dexamethasone increased the concentration of Dkk-1 in the culture supernatants, and it also induced the expression of Dkk-1 mRNA in a dose-dependent manner. In contrast, we could not find any effects of GC on the mRNA and protein expressions of sclerostin. [Conclusion] GC-induced Dkk-1 expression in osteoblasts might possibly be a mechanism of suppressed bone formation by GC therapy *via* inhibition of Wnt/β-catenin signaling pathway.

P2-107

Denosumab as an osteoporosis treatment for patients suffering from rheumatoid arthritis

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Conflict of interest: None

[Object] It is reported that denosumab is useful for steroid-induced osteoporosis. Clinical results have varied due to: steroid dose, disease activity and the patient's medical history when using it for rheumatoid arthritis (RA). [Methods] 80 RA patients with similar backgrounds (age, sex, RA duration, BMI, disease activity and ant-RA drugs) and diagnosed with osteoporosis were divided into 2 groups and given different drugs to study their effectiveness. 40 patients were given denosumab (DENO group) and 40 patients were given bisphosphonate (BIS group). Bone mineral density (BMD), bone metabolic markers and newly occurring vertebral fractures were estimated pre- and post- medication. [Results] In the DENO group BMD increased by an average of 12% compared to 5% in the BIS group. TRACP-5b levels decreased by an average of 60% in the DENO group and 40% in the BIS group. Newly occurring vertebral fracture (s) occurred in only 1 case of the DENO group and in 2 cases in the BIS group. [Conclusions] BMD increased significantly more with denosumab than with bisphosphonate. Denosumab did not prove to be inferior to bisphosphonate in regards to newly occurring vertebral fractures.

P2-108

Efficacy of denosumab in Rheumatoid Arthritis by comparative study according to difference of disease activity

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Conflict of interest: None

Object The purpose of this study is to evaluate the efficacy of denosumab in Remission RA patients (R-Group) compared with in MDA and

HDA RA patients (MH-Group). A total 25 patients (all female) were administrated denosumab. At the baseline, the average age were 73.9 (+/-6.1) and 73.6 (+/-4.8) years old (p>0.05), average RA disease duration were 12.4 (+/-10.8) and 13.7 (+/-11.3) years,the average YAM (%) of the lumbar spine were 65.9 (+/-15.0)% and 68.2 (+/-14.5)%(p>0.05). Method At 6 month and 12 month after administration, the change in YAM were assessed at the total femoral neck and lumbar spine and the bone turnover markers which were PINP and TRACP-5b were evaluated between R-Group and MH-Group. Results At 6 month and at 12month, the average YAM at lumbar spine and femoralneck of R-Group and MH-group were significantly improved compared with at the baseline. There were no significant differences at 6 month and 12 month between R-Group and MH-Group. PINP and TRACP-5b were significantly decreased at 6 month and 12 month but there were no significant difference. Conclusion In this study, the RA disease activity did not affect YAM of RA patients with denosumab.

P2-109

Treatment outcome of denosumab therapy in patients with rheumatoid arthritis also presenting with osteoporosis

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Conflict of interest: None

Objective: To examine the treatment outcomes of denosumab therapy in patients with rheumatoid arthritis (RA) who also presented with osteoporosis at our hospital between April 2014 and October 2015.Methods: The effects and side effects of denosumab in patients who began treatment during the above period at our hospital were retrospectively investigated. Assessment variables included changes in markers of bone destruction and bone formation, changes in osteitis test results, and incidence of side effects. Additionally, changes in variables such as the Health Assessment Questionnaire, Simple Disease Activity Index, Crohn's Disease Activity Index, inflammatory response, and matrix metalloproteinase 3 were examined to evaluate the indirect effects of denosumab on RA.Results: The effects of denosumab treatment on osteoporosis were observed in patients with RA. Further examination is necessary to more thoroughly determine the effects on RA. **Discussion:** There are no large-scale reports on the outcomes of using denosumab in patients who present with both RA and osteoporosis, indicating that long-term follow-up, including evaluation of the drug effects, is necessary.

P2-110

Clinical characteristics of osteoporosis treatment for rheumatoid arthritis patient

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Conflict of interest: None

[Objectives] Treatment for osteoporosis (OP) was investigated in rheumatoid arthritis (RA) patient. [Methods] Patients who had been tested for osteoporosis, such as bone metabolism marker, and dual energy x-ray absorption scan, were recruited in this study. Patient was divided into four groups according to whether drug therapy is derived (O or nO), and whether RA patient (R or nR). Background for each group was collected and their average values were calculated. Statistical analysis was compared for each group. Anti-OP drug was also analyzed. [Results] O-R started in significant lower age for OP treatment than O-nR ($p<0.01$). O-R demonstrated significantly higher anti-citrullinated peptide anti-bodies titer, shorter disease history, higher joint deformity, higher disease activity (DA), lower ability of daily activities (ADL) level, and more concomitant gluco-cortical steroid usage than nO-R ($p<0.01$). Denosumab suppressed for bone erosion, however, it was significantly lower than biologic agent does ($p<0.05$). [Conclusions] RA is independent risk factor for OP. Especially, patient, in who has high DA, progresses more quickly in joint destruction, and is in low ADL level, is suggestive for necessity for OP treatment in early stage. In OP drugs, d-mab suggested higher affinity for RA.

P2-111

The effect of denosumab on progress of Sharp/van der Heojde score

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Conflict of interest: None

[Purpose/Background] In order to evaluate effect of demosumab (dMAB), a monoclonal antibody of RANKL, as an agent for osteoporosis treatment on progress of Sharp/van der Heijde score (dSHS), joint space narrowing (dJSN), and bone erosion (dBE) in rheumatoid arthritis (RA) patient. [Methods] 310 RA patients who are also been treated osteoporosis were recruited in this study. These patients were divided into four groups whether dMAB, is thrown, and whether biologic DMARD (bDMARD) is thrown. Mean value of each of the four is compared each other with Mann-Whitney test, and contribution of dMAB and bDMARD were evaluated with Chi Square test statistically. [Results] Average value of each group were -9.39, -2.28, -7.11 for group to whom dMAB and bDMARD were thrown, -1.48, +0.47, -1.95 for group with dMAB, -1.92, -0.23, -1.69 for group with only bDMARD, and -0.25, 0.24, -0.49 for group to whom none of these were thrown, in dSHS, dJSN, and dBE, respectively. dMAB was statistically significant on suppression of BE progress, and bDMARD has significantly suppressed all of the three element statistically (>0.01). [Conclusion] dMAB is effective on joint deformity progress especially on BE, not so evident as bDMARD, even with low dosage as for osteoporosis treatment.

P2-112

Effect of denosumab in osteoporosis in rhumatoid arthritis patients

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Conflict of interest: None

Objective: We attempt to confirm the effect of DMB (Denosumab) for RA patients complicated with osteoporosis. Method: Thirty-four patients (male: 2, female: 41, age 70.9±8.9 y.o.) with RA complicated by osteoporosis were enrolled. Bone mineral density (BMD) measurements were performed at the proximal femur, lumbar spine, hip and radius using DEXA. Bone specific alkaline phosphatase (BAP) and tartrate-resistant acid phosphatase 5b (TRACP-5b) were used as bone turnover markers. Results: Twenty patients in enrolled 34 patients reached the required criteria for analysis. In analysis of 20 patients, BMD at 6 months elevated significantly compared with the baseline data, while the bone turnover markers decreased significantly at same timing. However, we experienced some cases the measurement value of TRACP-5b in 6 months was more than 420 mU/dL which is the upper limit of reference value, indicated that the judgment of efficacy by TRACP-5b was difficult with the change of measurement value. Conclusion: In this study, we confirmed the clinical efficacy of BMD treatment by the evaluation of BMD and bone turnover markers in 6 months. We also suggested that further consideration was needed for appropriate measurement point of TRACP-5b by using the determination of clinical effect.

P2-113

Teriparatide preparations introduction patients with rheumatoid osteoporosis study

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Conflict of interest: None

[purpose] This time, once a week have stimulatory effects on bone formation of Teriparatide preparations (TPTD) and introduced the secondary osteoporosis patients with RA, examined the effectiveness of. Materials and methods: 8 patients with sequential injection drugs switched to antiresorptive agent, TPTD after 72 weeks has passed, age 50 to 80 years old (average age 67) was targeted. Before, during the administration of 24, 48, 72 weeks and measure the dose after 24 lumbar spine, proximal femur bone (%YAM value) and bone metabolic markers (P1NP, TRACP-5b, etc.), TPTD administration in the bone metabolism after ad-

ministration. Also examine the presence or absence of new fractures during the course. [Results] TPTD administration in the bone density of the lumbar spine, proximal femur did not change, but after the treatment is 24 weeks, each average of 70% from 66% to 72.8% and 70.8% increased. Results this time, once a week TPTD administration afteradministration of bone density changes of antiresorptive agent switched TPTD after effects may become evident, TPTD Administration considered effective in altering the bone metabolism of secondary osteoporosis.

P2-114

The predictors for 12 months efficacy of denosumab, an anti-RANKL antibody, on osteoporosis in patients with rheumatoid arthritis from multicenter study (TBCR-BONE)

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Conflict of interest: None

[Objectives] To investugate the 12months efficacy of denosumab (DMB) on opteoporosis in patients with rheumatoid arthritis (RA-OP) and predictors of efficacy from multucenter study (TBCR-BONE). [Methods] 64 female cases with RA-OP were included in this study. BMD of lumbar spine (LS-BMD) and total hip (TH-BMD) and bone turnover markers (P1NP and TRACP-5b) were measured at baseline and every 6 month. [Results] Mean age was 69 yo. Mean RA duration was 16y. Mean DAS28-CRP was 2.7. 44% of cases had the past history of fracture. Mean FRAX was 26%. Daly teriparatide was used in 12 cases before DMB treatment. LS-BMD at 6m and 12m was significantly increased compared with baseline (4.3% and 5.9%). TH-BMD at 6m and 12m was significantly increased compared with baseline (3.1% and 4.0%). Mean decrease in P1NP were 39.9% at 6m and 34.3% at 12m. Mean decrease in TRACP-5b were 31.5% at 6m and 27.2% at 12m. Higher baseline P1NP and higher LS-BMD increase at 6m were the predictors of better LS-BMD increase at 12m. Higher TH-BMD increase at 6m were the predictors of better LS-BMD increase at 12m. [Conclusion] DMB was effective in RA-OP. Early response of BMD and baseline P1NP were suggested to be the predictors of the efficacy of DMB in RA-OP.

P2-115

Anti-absorptive therapy in patients with rheumatic diseases

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Conflict of interest: None

[Object] To estimate persistence to anti-absorptive drugs in patients with rheumatic diseases and investigate factors associated with the persistence. [Methods] Data were obtained from our hospital database including prescription, diagnosis and patient characteristics. We selected patients newly prescribed with bisphosphonates and selective estrogen receptor modulators between June 1, 2007 and May 31, 2010. Persistence were estimated using Kaplan-Meier survival analysis. Multivariate Cox proportional hazard analysis was carried out to identify determinants of persistence. [Results] 557 patients (447 female, 80 male) were retrospectively analyzed. Persistence with anti-absorptive drugs was 71.9% after 1 year. Determinants associated with the persistence were patients with so-called collagen diseases and use of glucocorticoids. The most frequent reason for discontinuation of anti-absorptive drugs was adverse events (32.4%). [Conclusions] Persistence with anti-absorptive drugs was suboptimal, especially amang patients with collagen diseases and taking glucocorticoids.

P2-116

Sacral fracture in patients with rheumatoid arthritis

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Conflict of interest: None

[Purpose] Sacral fracture is relatively rare. We report 2 cases of sacral fracture in patients with rheumatoid arthritis (RA). [Case 1] An 81-year old woman with RA who had been treated with PSL 8 mg, SASP 1 g and MTX 8 mg had low back pain and numbness of both legs since a year ago. A diagnosis of lumbar spinal stenosis was made, but her symptoms did not reduce. Following CT disclosed sacral insufficiency fracture. Although the risedronate was added to her medication, her symptoms did not improve. Then, the risedronate was changed to the teriparatide. The treatment with the teriparatide for 3 months improved sacral pain and sclerotic change was observed by CT. [Case 2] A 60-year-old woman with RA who had been treated with SASP 500 mg, MTX 5 mg and TAC 1 mg fell from a chair 4 months ago and injured her hip. There were no abnormal findings by X-ray, following CT disclosed sacral fracture. Conservative therapy has improved her symptoms. [Discussion] We have experienced 2 cases of sacral fracture in patients with RA. Patients with RA are easily suffered from fractures even by mild injury and the fractures without dislocation can hardly be detected. Sacral fracture, as well as evaluation of osteoporosis, should be taken into account as a possible complication in RA.

P2-117

Bone mineral density of postmenopausal women with rheumatoid arthritis depends on disease duration regardless of treatment

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Conflict of interest: None

The aim of this study was to determine the associations of disease activity and disease duration with the bone mineral density (BMD) in rheumatoid arthritis (RA) patients. We also evaluated the associations of biological drugs with bone loss. A total of 138 postmenopausal RA patients were retrospectively assessed to identify the associations of disease activity, disease duration, and biological drug use with BMD. We assessed the associations of disease duration, disease activity score and the use of biological drugs with BMDs using univariate and multivariate linear regression analyses in bisphosphonate treatment and non-bisphosphonate treatment groups at 1 year of follow-up. The multivariate linear regression analyses showed that disease duration was significantly related to the BMD of the femoral neck and total hip regardless of bisphosphonate treatment. The use of biological drugs was not significantly associated with BMD. Hip BMD in postmenopausal women with RA depends on the disease duration regardless of bisphosphonate use. Biological drugs for RA treatment were not negatively associated with general bone loss.

P2-118

Pubic osteolysis with persistent effusion from biopsy site: report of a case with osteoporosis and rheumatoid arthritis

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Conflict of interest: None

[Object] To report a case of pubic osteolysis mimicking malignant or infective bone disease. [Case presentation] A 75-year-old woman with osteoporosis and rheumatoid arthritis presented with buttock and groin pain. Radiographs showed sacral fracture and osteolysis in the pubis. The administration of tocilizumab was suspended and bone biopsy was performed. The sample had pathologic feature of osteomyelitis. Two weeks later, she developed fever, drowsiness and swelling at the biopsy site. Laboratory data indicated hyponatremia, hypoalbuminemia, and highly

elevated CRP. Reincision and drainage was performed. Removed tissue was considered pathologically same as the initial. Drowsiness was improved after correction of hyponatremia. However, the effusion from the reincision site persisted for more than 2 months. The culture of the effusion was negative. Radiographs showed sclerosis of the eroded margins in the pubis and union of the sacral fracture. Following negative pressure wound treatment, the wound was closed in a few days. [Discussions] In this case, the osteolysis was self-limiting and considered to be due to sacral insufficiency fracture. The persistent effusions was thought to be due to hypoalbuminemia, caused by acute inflammatory responses after suspension of tocilizumab.

P2-119

Subsequent changes of bone turn-over markers and bone mineral density by treatment using denosumab in postmenopausal women with osteoporosis and osteopenia

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Conflict of interest: None

【Objectives】We estimated the efficacy of treatment by naïve or second-line use of denosumab in women with osteoporosis and osteopenia. 【Methods】75 women with osteoporosis and osteopenia were treated by denosumab. The average of the age was 73.7 years old. 22 patients with RA were included in this study. 22 patients were naïve, and 53 patients were switched. Subsequent changes of serum values in NTX, TRACP-5b, P1NP, ucOC, and homocysteine were examined. The bone mineral density of lumbar spines, femoral cervical neck and/or radius was analyzed both at the initial screening and 6 months later in each patients. 【Results】The mean value of serum NTX, P1NP and ucOC was gradually reduced. The mean value of serum TRCP-5b was unique, which was usually inhibited at 1 month later after each treatment by denosumab. The mean value of serum homocysteine was always maintained within the normal range. The bone mineral density of lumbar spines especially achieved increase of 3.9% at 12 months later after denosumab. Otherwise, that of radius was not significantly increased. The bone mineral density of lumbar spines in patients with RA was also increased. 【Conclusion】Treatment by denosumab was effective in women with osteoporosis and osteopenia, including RA.

P2-120

ADAM12 (Meltrin α) positively regulates chondroosteophyte formation

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Conflict of interest: None

【Introduction】 A disintegrin and metalloproteinase 12 (ADAM-12) is known to influence chondrocyte proliferation in osteoarthritis cartilage. The aim of this study was to investigate whether ADAM-12 is involved in the formation mechanism of the chondroosteophyte. 【Methods】 Expression levels of ADAM-12 were determined by real time PCR in ATDC5 cells in which experimentally chondrogenic differentiation had induced. We also investigated the protein localization pattern of ADAM-12 in the chondroosteophyte of human by immunohistochemistry and compared the results with the expression of proliferating cell nuclear antigen (PCNA) and type X collagen for the identification of proliferative and hypertrophic chondrocyte phenotypes, respectively. 【Results】 We found the gene expression of ADAM-12 by ATDC5 cells as a dual mode, both before the expression of type X collagen and after hypertrophic differentiation. The immunoreactivity of ADAM-12 was observed in chondrocytes of proliferative and hypertrophic zones in the chondroosteophyte of human. 【Discussion】 These results of the present study suggest ADAM-12 might have a role in formation mechanism of chondroosteophyte to allow chondrocyte proliferation and hypertrophy.

P2-121

Difference of lateral femorotibial angle and Hip-knee-ankle angle to evaluate coronal alignment in Japanese patients with anatomic variations

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Conflict of interest: None

Purpose: Lateral femorotibial angle (FTA) is popular in Japan, and Hip-knee-ankle angle (HKAA) is popular in USA and Europe. The difference between two parameters was assessed in 100 Japanese patients before total knee arthroplasty (TKA). Method: FTA and HKAA and anatomical variations were measured on radiographs in 100 Japanese patients before TKA. The effect of anatomic variations on values of FTA and HKAA was then assessed. The effect of difference between FTA and HKAA on the coronal alignment of the lower extremity after TKA was also assessed. Results: The patients had anatomic variations such as lateral bowing of the femoral shaft, proximal tibia vara and medial shift of the tibial articular surface. The mean distance from anatomical axis of the tibia to the center of the tibial spines notch was 6.8mm. FTA cannot express exact varus alignment in cases with lateral bowing of the femoral shaft. HKKA underestimates varus deformity in cases with medial shift of the tibial articular surface. Discussion: Both FTA and HKAA cannot express the exact varus deformity in knees with anatomic variations. Attention should be paid when the coronal alignment is assessed in implanted knees with varus deformity and with medial shift of the tibial articular surface.

P2-122

Quantitative analysis of moving distance of the patella during knee flexion in normal knees

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Conflict of interest: None

Purpose: Quantitative analysis of moving distance of the superior pole of the patella and the most antero-superior point of the tibia was done during knee flexion in 12 normal knees. Methods: Lateral radiograph of the knee was taken at 0, 30, 60, 90, 120 and 150 degree flexion in each knee. Contours of the femur, tibia and patella were drawn on the drawing tool soft Adobe Illustrator. The superior pole of the patella and the most antero-superior point of the tibia were marked. The contours of the bones at every flexion angle were superimposed and the contour of the femur was matched. Then the moving distance of the two points were measured. Flexion angle of the patella and the patella tendon was also assessed. Results: The flexion angle of the patella and the patellar tendon linearly increased during knee flexion. The moving distance of the two points was minimum since 60 degree to 90 degrees flexion. Discussion: Because of the sliding and rolling of the femoral condyle during knee flexion, the moving distance was different among early flexion, flexion and deep flexion. With this method, the detailed analysis of the moving distance of the patella and the tibia during flexion can be assessed in OA knees and implanted knees.

P2-123

Development of rheumatoid arthritis (RA) hand/finger simulation equipment.

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Conflict of interest: None

OBJECTIVE: It is difficult to predict the decrease of ADL due to hand/finger deformity in RA patients. Therefore, if we are able to simulate the RA hand/finger, it may help us predict the outcome of RA patients who refuse early treatment intervention and could be a good education material for RA patients. Accordingly, we developed the RA hand/finger simulation equipment (RSE) to assess the comparability of this equipment to RA patients. **METHODS**: RSE is an open fingertip type apparatus that can be equipped to each finger accommodating various deformity. We investigated the role of RSE for evaluating hand function. Healthy volunteers (HV) equipped RSE (RSE group), HV (HV group) and RA patients (RA group) were assessed using the Simple Test for Evaluating Hand Function (STEF). **RESULTS**: The number of cases for each group was: RA patients 4 (8 hands), HV 5 (10 hands). Mean scores of STEF were RA group 91.0, RSE group 94.2 and HV group 99.7, respectively. The score of STEF in RA group were significantly lower than HV group. However, no significant difference in the score of STEF between RA and RSE group. **CONCLUSIONS**: No statistical differences were observed in the scores of STEF for RA and RSE group. This indicates that there is possibility for simulation of RSE of RA hand/finger.

P2-124

The difference between disease specific quality of life of patient with rheumatoid arthritis (RA) and that of patients with osteoarthritis (OA)

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Conflict of interest: None

【Object】 This study is aim to clarify the differences and courses between patients with RA and those of OA from Japanese knee osteoarthritis measure (JKOM) and elderly status assessment set (E-SAS). 【Methods】 The subjects are 15 cases (RA; 5cases, OA; 10cases) were included in this study, who were performed primary TKA from Aug. 2014 to Aug. 2015 at Saitama medical university hospital. There were examined the knee function before TKA and 5 months after TKA. In this study, we were investigated age and BMI at operation, E-SAS, knee ROM and muscle strength, the single leg standing time at 5months after operation, JKOM before and 5months after operation. Also, investigated to the improvement rate in each item of JKOM. All items of two groups were calculated by Mann-Whitney test. 【Results】 The pain score of JKOM and age at operation day of RA were significantly smaller than those of OA. Furthermore, the improvement rate in health score of JKOM of RA were higher than those of OA both before and 5monts after TKA. On the other hands, there was no significant difference of improvement of JKOM between two groups. 【Conclusions】 Although there was no differences of improvement of JKOM between RA and OA, RA's feeling health in both before and after surgery are lower than those of OA.

P2-125

The usefulness of ceramic therapy in the treatment of rheumatoid arthritis (RA) at the outpatient level

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Conflict of interest: None

[Objectives]Occupational therapy includes various handicrafts and manual arts, and our hospital has employed beadwork and Japanese paper crafts as therapy for RA at the outpatient level. The objective of this study is to report on the usefulness of ceramics as rehabilitation in RA patients. [Methods]The participants were 10 outpatients being treated for RA at our clinic. In the analysis of the results of therapy, VAS, FACE scale, and self-rating depression scale (SDS) were measured before and after the ceramic therapy and results were compared. A questionnaire was also administered to the participants to assess how they felt about the therapy. [Results]The m-HAQ and CRP score for the participants were 0.4 ± 0.3 and 0.9 ± 1.6. Scores on the FACE scale and SDS decreased from 4.7 ± 3.6 to 2.9 ± 3.3 and 41.2 ± 11.8 to 37.1 ± 9.4, showing improvements compared to before the therapy. In the questionnaire, many participants commented that it was fun to make the ceramics and a joy to use them. This demonstrates that making ceramics is an ongoing therapeutic activity which has effects on daily life. [Conclusions]In addition to improving the physical condition and depression symptoms of RA patients, ceramics was useful as a therapeutic activity producing change in the quality of life.

P2-126

The effect of mindfulness-based stress reduction for rheumatoid arthritis

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Conflict of interest: None

[Object]Clinical trials have shown that mindfulness-based stress reduction (MBSR) improves the pain, anxiety and depression for many chronic disease. Recently,the effect has also been reported for rheumatoid arthritis.We examined the the effect of MBSR for rheumatoid arthritis in japan. [Methods]We recruited seven patients (5 rheumatoid arthritis patient, adult onset still disease patient and antiphospholipid antibody syndrome patient). Patients comprised 6 females and 1 male with a mean age of 57 years. The MBSR was 6-week programme in a group session. Anxiety and depression were assessed Hospital Anxiety and Depression Scale. Pain and fatigue were assessed Visual Analogue Scale (VAS). [Results] Pre-treatment Anxiety score (As) was average 7.3 and Depression score (Ds) was average 8.7. At As and Ds, 3 people were 8 points or more (positive). Two of the seven dropped out. As of five people who were treated to the last was changed to 6.4 →5 and Ds was changed to 8.2 →9. It was no improvement in the treatment before and after. Pain VAS was changed to 22.2 →17.2 and it showed a trend of improvement (P=0.089). Fatigue VAS was changed to 32 → 31 and it was no improvement. [Conclusions] It is necessary to further investigate the effect of MBSR for rheumatoid arthritis in Japan.

P2-127

Disease activity and the effects of rehabilitation in Rheumatoid Arthritis(RA) (2nd Report)

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Conflict of interest: None

[Object] We have rehab program of RA in our hospital from 1987. The aim is acquisition of rehabilitation to keep or increase ADL/QOL and education. We checked 1)the changing measures of QOL that are Face Scale (FS), Visual Analogue Scale (VAS), and modified Health Assessment Questionnaire (mHAQ) around the program, 2)the difference of effect according to disease activity and duration on admission. Last year we reported about 4 weeks hospitalization, so this year about 2 weeks. [Methods] We analyze the changes of measures that are FS, VAS, mHAQ, and C-reactive protein (CRP) level after hospitalization among 20 patients which classified by the disease activity and duration from 2009 to 2013. [Results] The group of low disease activity reached to functional remission, but high activity group didn't reach. The group of under 10 years duration reached to clinical remission, but over 10 years group didn't. [Conclusions] If your patient has been controlled as low disease activity by medicine, we suggest that rehabilitation should be started as early as possible, even for short duration like 2 weeks. So it will be achieved the functional remission which got difficultly only by the medication.

P2-128

Effects of rheumatoid arthritis patients' functional impairment and disease activity on kinesthetic motor imagery

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Conflict of interest: None

[Purpose] Noting the involvement of the brain function of kinesthetic motor imagery (KMI) in the performance of exercise, we investigated whether the KMI ability of rheumatoid arthritis (RA) patients affects QOL. [Material/Method] The subjects were 15 RA patients. The endpoints were DAS28CRP as an index of disease activity, SF-36v2 as an index of QOL, and KVIQ-10, iTUG, and HLJT as indices of KMI ability, all measured at the time of initial hospitalization. [Results] The status of disease activity was reflected in the status of functional impairment and chronic pain, and the higher disease activity was, the more KMI ability decreased. Moreover, the lower the KMI ability, the more QOL declined. [Discussion] KMI ability is thought to decrease in RA patients because the plasticity changes in brain function which accompany symptoms. that damages the neural pathways that compose exercise programs. The resulting inadequacy in exercise program composition makes it difficult to perform exercise, which in turn compromises QOL. [Conclusions] The results of this study suggest that high levels of disease activity in RA patients bring about declines in KMI ability, with a deleterious effect on QOL. Therefore, there is a need for rehabilitation approach to KMI ability to RA patients.

P2-129

Upper limb function reflected QOL of rheumatoid arthritis patients

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Conflict of interest: None

[Objectives]The objedtive of this study was to examine the factors influenced by the upper limb function of the patients with rheumatoid arthritis (RA) using The Simple Test for Evaluating Hand Function (STEF). [Methods]121RA patients (29men and 92women) were tested.The average age was 60.7years.The average morbidity period was 78.6 months. From Larsen Grade classification (LG)of hand x-ray,all cases were classified to LG0:83hands,LG1:46hands,LG2:32hands,LG3:19hands,LG4:36hands,LG5:26hands. In all cases STEF was tested in each hands,and the relation between the sum of the STEF in both hands and SDAI,DAS28,mHAQ were considered. [Results]No significant correlation was seen between SDAI,DAS28 and the sum of the STEF in both hands. Negative correlation was admitted between the mHAQ and the sum of the STEF in both hands Considered the relation between mHAQ and STEF in each hand, many cases with high mHAQ score were observed progression of bony destructive change on hand x-ray and STEf score were low. [Discussion] Upper limb function of the RA patients didn't influenced on disease activity. In the cases with high bony destrucition of the hand, upper limb function of the RA patients fell,and QOL were low. [Conclusion] Upper limb function reflected QOL of the RA patients.

P2-130

Pneumatosis cystoides intestinalis (PCI) in two patients with systemic lupus erythematosus (SLE) complicated with internal organ calcification-Report of two cases

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Conflict of interest: None

We present here two cases of PCI in SLE patients with internal organ calcification. Patient 1: A 37-year-old woman developed SLE (Raynaud's phenomenon, polyarthritis and pleuritis with anti-DNA Ab) at the age of 33. The starting dose of prednisolone (PSL) was 40 mg, which was tapered to 10 mg, when she developed lupus enteritis (diarrhea, intestinal edema, frequent urination, bilateral hydronephrosis). After 4 weeks of 40 mg PSL therapy, she developed abdominal distension (PCI) and was successfully treated with cyclosporine. Patient 2: A 35-year-old woman had a history of Raynaud's phenomenon and photosensitivity from the age of 15. At the age of 31, she developed SLE (fever, malar rash with anti-DNA Ab) and was treated with 20 mg PSL. She was taking a maintenance dose of 7 mg PSL, when she developed abdominal pain and diarrhea (PCI with intestinal edema) and was successfully treated with 60 mg PSL. PCI is presumed to be vasculitis and is usually accompanied by active lupus enteritis. Of note, our patients had calcification (basal ganglia and cerebellum in patient 1; spleen in patient 2). Since the etiology of calcification in SLE is also presumably vasculitis, we consider it possible that our patients had subclinical GI vasculitis before developing PCI.

P2-131

Marked improvement of pulmonary arterial hypertension associated with systemic lupus erythematosus with immunosuppressive therapy and pulmonary vasodilators

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Conflict of interest: None

A 31-year-old female was presented to our hospital with shortness of breath and lower leg edema lasting for 6 weeks. NT-proBNP elevated to 1103 pg/ml. Echocardiography showed elevated estimated systolic pulmonary arterial pressure (esPAP) of 87mmHg. Right heart catheterization showed elevated mean pulmonary artery pressure (mPAP) of 44 mmHg, elevated pulmonary vascular resistance index (PVRI) of 1626 dyn s cm^{-5} m^{-2} and impaired cardiac index (CI) of 1.8 l/min/m^2. She was diagnosed as pulmonary arterial hypertension (PAH) associated with systemic lupus erythematosus (SLE) on the basis of skin rush, alopecia, oral ulcer, cytopenia, hypocomplementemia, positive antinuclear antibody and positive direct Coombs test. Prednisolone 1 mg/kg and six fortnightly intravenous cyclophosphamide (IVCY) 500mg/body followed by tacrolimus were started. After 6 weeks NT-proBNP improved to 188.6 pg/ml and esPAP improved to 67mmHg and pulmonary vasodilator therapy with tadarafil, ambrisentan and beraprost was started. After 5 months NT-proBNP, esPAP, mPAP, PVRI and CI improved to 30.4 pg/ml, 40 mmHg, 23 mmHg, 248 dyn s cm^{-5} m^{-2} and 4.19 l/min/m^2, respectively. WHO functional class improved from III to II. After 1 year her condition was stable without exacerbation of PAH and SLE.

P2-132

SLE associated with the acquired coagulation XIII deficiency

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Conflict of interest: None

A 47 years old woman,who presented to our hospital with back pain in December 2014. She suspected of renal hemorrhage. In March 2015, fully examinations which were performed by our urologists due to the appearance of the left back pain showed subctaneous hemorrhage and mascular walls hemorrhage. Further evaluations for hemorrhagic tendency have performed, which include the clotting factor assay. It revealed decreased activity of coagulation factor XIII(cF13). Additionally, ANA and the antiDNA antibody had positive results and proteinuria was also found. As she had photosensitivity and oral ulceration as well, she was assumed to have SLE complicated with cF13 deficiency. She started to immunosuppressive therapy on the 2nd day of addmission. To defferenci-

ate the cause of cF13 deficiency, specialized examinations were performed by, and they showed that the deficiency was suspected to be the acquired. Owing to the treatment, activity of SLE decreased and made satisfactory progress. However, regarding the cF13, activity level still remained low. She was discharged our hostital without any new hemorrhage during hospitalization. Recentry, activity level are on an upward trend and she has followed a good clinical course. This study was supported by a Health and Labour Sciences Research Grant.

P2-133

A case of refractory autoimmune hepatitis with SLE for which infliximab was effective

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Conflict of interest: None

Case: A 48-year-old woman was found to have liver dysfunction based on blood tests (T-Bil 4-5 mg/dL) in 1998, and was diagnosed with autoimmune hepatitis (AIH) on liver biopsy. SLE was simultaneously diagnosed. Despite treatment with PSL and additional treatment with various immunosuppressants, the patient experienced recurrent AIH due to side effects and an insufficient response. During recurrence, increases in transaminase levels were accompanied by increases in anti-dsDNA antibody levels, suggesting an association with the disease activity of SLE. In late July 2014, the patient developed to liver cirrhosis. During outpatient follow-up with PSL 15mg/day and MMF 2g/day, an exacerbation was seen in May 2015 as follows: AST 191U/L; ALT 102U/L;T-Bil 2.6mg/dL. Infliximab (IFX) 400mg was initiated for refractory AIH. Following initiation of IFX therapy, AST, ALT, and T-Bil decreased to 31U/L, 11U/L, and 1.7 mg/dL. Anti-dsDNA antibody levels, however, increased from 65IU/ml prior to IFX initiation to >300IU/ml after IFX initiation. Discussion: IFX has been reported to be effective for AIH in a number of cases, but it was highly effective for comorbid SLE and AIH in the present case. An increase in anti-dsDNA antibody levels thought to be due to IFX therapy was observed, however.

P2-134

A case of thrombocytopenia associated with systemic lupus erythematosus (SLE) effectively treated with splenectomy

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Conflict of interest: None

[Case] 48-year-old woman [chief complaint] purpura [history] 31-year-old: allergic purpura, 34-year-old: depression [current medical history] She was diagnosed as SLE with low complement, proteinuria, leukopenia and thrombocytopenia in 1997. Platelet count was about 20,000 under treatment with 10mg/day of prednisolone (PSL) and cyclosporineA (CyA). In 2011 thrombocytopenia was exacerbated, so romiplostim was initiated and CyA was changed to tacrolimus (TAC) because of its side effect. In spite of the treatment with romiplostim, PSL and TAC, platelet count had been about 20,000μL. Anal canal cancer was detected and TAC was discontinuated in May 2014. After chemotherapy and radiation therapy were performed, significant bone marrow suppression was recognized and frequent blood transfusions were needed in September. Romiplostim was changed to eltrombopag and TAC was resumed, but platelet count was about 10,000μL. Splenectomy was undergone after intravenous immunoglobulin therapy (IVIG) and platelet count was kept from 40,000 to 100,000μL without platelet transfusion in December. [Conclusion] Splenectomy in combination with IVIG is expected treatment to refractory thrombocytopenia which resists to immunosuppressants and thrombopoietin receptor agonists.

P2-135

A case of 45 years old woman headache by lupus meningitis improved after treatment of cyclophosphamide

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Conflict of interest: None

A 45 years old woman was admitted complaining headache for 2 weeks that was not improved with Loxoprofen. At the age of 37, she had been diagnosed with systemic lupus erythematous and nephritis (class IV). When she was admitted, she took 7mg of prednisone. Cerebrospinal fluid examination revealed that the amount of monocyte and protein increased. A CSF culture and mycobacterium culture was negative. A CSF PCR of herpes simplex virus and Varicella zoster virus and cryptococcal antigen were negative. ADA of CSF was under the cutoff level. Cytology of CSF revealed no tumor cell. She took indomethacin as virus meningitis. Her symptom improved and she was discharged. But, her symptom became worse and the amount of CSF monocyte and protein increased again. She was admitted 1month after. The amount of prednisone was increased toward 20mg as lupus meningitis. But her symptom didn't improve. She had femur head necrosis, so it was difficult to increase the amount of prednisone. So intravenous cyclophosphamide (500mg/m2/month) was started. Her symptom was improved and the amount of CSF monocyte and protein decreased. There were few reports of lupus meningitis and cyclophosphamide treatment, so I report this case.

P2-136

Sixty-seven-year-old female with systemic lupus erythematodes (SLE) presented with systemic lymph nodes swelling and splenomegaly resembling Angioimmunoblastic T-cell lymphoma (AITL)

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Conflict of interest: None

Sixty-seven-year-old woman was seen complaining of the swelling of the submandibular lymph node. Biopsy of the right axillary lymph node was performed. Pathological diagnosis of paracortical hyperplasia was made. However; a slight atypicality in the cells, proliferation of the small high endothelial venules and few CD45RO positive cells were recognized in the biopsied lymph node. These findings could not rule out the initial stage of AITL completely. CT scan showed systemic lymph node swelling and splenomegaly. She had positive ANA, positive anti-DNA antibody, hypocomplementemia and leukopenia, was diagnosed as SLE according to SLICC criteria. Prednisolone was started with the dose of 50mg /day. The titer of anti-DNA antibody was reduced and hypocomplementemia was improved with the therapy. The dose of prednisolone was tapered to 25mg /day. She was discharged and under outpatient careful follow-up. (Discussion) SLE may cause the swelling of the lymph node, and the differentiation with other diseases may be difficult. The patient was lacking typical symptoms, but diagnosed with SLE by the serological tests, while findings of biopsied lymph node could not rule out AITL completely.

P2-137

A case of SLE relapsed with Guillain-Barre-like symptoms

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Conflict of interest: None

24-year-old woman visited our hospital by enterogastritis. At 2000 (10 years old) SLE was onset. Initial symptoms were the butterfly erythema, joint pain and lupus nephritis (Type IV). The highest value of anti-

DNA antibody value was 78IU / L. The first treatment dose of PSL was 1mg / kg. Then it was decreased. No relapse had been seen for 14 years. She was administered 3 mg / day of Tacrolimus and 4 mg / day of PSL. On July 31, she visited our hospital because of persistent upper abdominal pain from July 26 2015. She was admitted. But, then swallowing difficulty begins from August 8. Lumbar puncture was holed, but no abnormality was seen. Axonal hindered neuropathy was found by electrophysiological method. It is in a non-typical type but is the Guillain-Barre-like symptoms associated with SLE. The level of C3 decreased in serum. Although 40mg prednisolone was administered, symptoms were impaired. Dyspnea and level down resulted of CO2 narcosis, were seen on August 15. PCO2 was 102 mmHg. NIPPV was used. The steroid pulse was carried out for two courses, but did not recover muscle strength. We saw the recovery of muscle strength after administrated gamma globulin. It was a rare case that relapsed SLE developed by Guillain-Barre-like symptoms.

P2-138

A case of antiphospholipid antibody syndrome mimicking pregnancy-induced hypertension

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Conflict of interest: None

【Background】Antiphospholipid antibody syndrome (APS) can be the cause of pregnancy morbidity.【Case】A 28-year-old Japanese woman presented with hypertension and proteinuria at 16 weeks of gestation. She noted persistent headache and vomiting, and was diagnosed as pregnancy-induced hypertension (PIH). Blood test showed acute kidney injury (Cr 1.3mg/dl) and thrombocytopenia ($6\times10^4/\mu L$), without schistocytes. Liver function test was normal. She was admitted and underwent an emergency Caesarean section at 38th week of gestation. Despite of placental expulsion, kidney function and thrombocytopenia got worse. Nephrology was consulted and kidney biopsy was performed; There were thrombi at the vascular pole, without mesangial or endocapillary proliferation. A careful review of the history revealed 2 times miscarriage in the past. With positive antiphospolipid antibody, she was diagnosed as APS nephropathy. Anticoagulation therapy was initiated, and she was discharged on hospital day 25.【Conclusions】In this case, it was difficult to differentiate APS from PIH because baseline platelet count was undefined. We report this case with some literature review.

P2-139

Portal vein thrombosis in a patient with antiphospholipid syndrome associated with *Fusobacterium nucleatum* bacteremia: A Case report

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Conflict of interest: None

Case A 71-year-old man with a history of systemic lupus erythematosus presented with back pain and fever for three days. His past medical history included peripheral artery disease resulting in ischemia of the second digit of his right foot and asymptomatic coronary artery stenosis. He had been on aspirin and clopidogre for drug eluting stents put in left anterior descending artery. A lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL) were positive without previous thrombotic events. He underwent abdominal CT with contrast which showed filling defects suggestive of portal vein thrombosis in the anterior segmental branch of the portal vein. Blood cultures grew *Fusobacterium nucleatum*. LAC, aCL, and anti-beta2-glycoprotein antibody (anti-beta2-GPI) were positive. We treated him with piperacillin/tazobactam and meropenem for three weeks, and switched to oral sitafloxacin and metronidazole for three weeks. He had been on dalteparin during admission and was discharged with warfarin. Conclusion We report a 71-year-old man with thrombosis of the portal vein associated with bacteremia due to *Fusobacterium nucleatum* and superimposed on antiphospholipid syndrome. No potential COI to disclosure.

P2-140

Clinical characteristics of clinically amyopathic dermatomyositis (CADM) in six patients who started treatment at our department

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Conflict of interest: None

[Objectives] We investigated the characteristics of patients who started treatments as CADM at our department. [Methods] Nine patients had the first onset of dermatomyositis after January 2010. Of these nine patients, we retrospectively compared six with a CK level below 150 U/I at the first visit. [Results] The subjects were four women and two men, with a mean age of 49.3 (range, 38-59) years. One patient was anti-PL-7 antibody positive, and one was anti-PL-12 antibody positive. Anti-MDA5 antibody was not measured. Five patients had skin symptoms at the first visit, including heliotrope rash in two, Gottron's sign in two, and Gottron's papules plus Gottron's sign in one. The remaining patient had joint symptoms for approximately one year, followed by the onsets of heliotrope rash and Gottron's papules. Five patients had interstitial pneumonia, and one had a rapidly progressive lung disorder. Four patients were treated with steroids in combination with immunosuppressants, and two others were given steroids plus high-dose intravenous immunoglobulin treatment. [Conclusion] Anti-ARS antibody positive patients exists a certain number in dermatomyositis, which was considered CADM.

P2-141

Two cases of refractory polymyositis accompanied with steroid myopathy

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Conflict of interest: None

Polymyositis (PM) is an inflammatory muscle disease characterized by chronic inflammation in skeletal muscle. Although most patients with PM respond to corticosteroids, some cases show an unsatisfactory response. Furthermore, glucocorticosteroid (GC) toxicity leads to a significant disability known as steroid myopathy, particularly in elderly patients. Here we report two patients with refractory PM. Combined treatment with high-dose GCs, tacrolimus, and intravenous immunoglobulin resulted in beneficial effects against myositis. But, muscle weakness and the disability progressed due to steroid myopathy, and subsequent oral intake became impossible because of swallowing disturbance in these two patients. Nutritional intervention, including branched-chain amino acids (BCAAs) and rehabilitation, was undertaken in addition to treatment against myositis. These treatments finally improved the muscle weakness and activities of daily living. The high-dose GC treatment caused elevation of serum levels of amino acids, including BCAAs, but these amino acids were subsequently declined. These findings suggest that the catabolic effects of the glucocorticoid treatment impair the balance of amino acids, including BCAAs, within the muscle, leading to steroid myopathy.

P2-142

A retrospective review of PM/DM associated interstitial lung disease with anti-glycyl tRNA synthase(EJ) antibodies

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Conflict of interest: None

Polymyositis/dermatomyositis (PM/DM) patients with Anti-ARS an-

tibodies (Abs) have association with interstitial lung disease (ILD), arthritis, and skin changes. Some reports showed difference in clinical symptoms exist between each of the anti-ARS Abs. Aanti-EJ Abs is a form of anti-ARS Abs with a 15~35% prevalence.Espeacially in the case of PM/DM-associated ILD (PM/DM-ILD),anti-EJ Abs is most common Abs. Aim of this study is to identify long term survival of patients of PM/DM-ILD with anti-EJ Abs. We enrolled 7 patients of PM/DM-ILD with anti-EJ Abs at our facilities. The demographic and clinical characteristics, laboratory values (PaO2,KL-6), and pulmonary function test (PFT) results, CT findings were retrospectively obtained from the medical records over the course of 1 years. No patients revealed reduction of PaO2 level and PFT value, whereas follow up CT scan showed new abnormality area in 2of 6 (33.3%) patients. 2 of 7 (28.5%) patients readmitted by ILD progression among observation term. Distribution of treatment were as followed; no treatment in 1 case, PSL only in 2 cases, PSL+immunosupressor in 4 cases,and combination of pulse therapy were showed in 4 cases. Our study showed that strong therapy may be required in patients of PM/DM-ILD with anti-EJ Abs.

P2-143

Clinical information of 4 cases with anti-ARS antibody (ELISA) positive at the clinic

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Conflict of interest: None

[Method] I screened 234 RA patients, 18 SSc pts and 6 PMDM pts. There were 4 positive patients with anti-ARS antibody (ELISA). And, I reviewed clinical information about these 4 cases. [Case 1] 57 year old Female, SSc+RA+IP, Raynaud (+), polyarthritis, sclerodactylia, digital pitting scar, RF (+), ACPA (+), ANA×640 (NU), anticytoplasmic antibody (+). [Case 2] 62 year old Female, PM+IP, preceded IP, fever, myopathy, mechanic's hands, ANA (-), anti-cytoplasmic antibody (-), KL-6 (+). [Case 3] 84 year old Female, RA+BO, Raynaud (+), polyarthritis, RF (+), ACPA (+), ANA (-), anti-cytoplasmic antibody (+). [Case 4] 69 year old Male, RA+IP, polyarthritis, RF (+), ACPA (+), ANA×40 (SP,NU), anti-cytoplasmic antibody (+). [Result and Discussion] In these 4 cases, 3 had polyarthritis and 3 had IP. But, typical anti-synthetase syndrome was case 2 only. I checked the 4 cases using RNA immunoprecipitation (IPP) assay. Case 1 was anti-KS antibody positive, Case 2 was anti-EJ antibody positive, but Case 3 and Case 4 were anti-ARS antibody negative using RNA-IPP assay. Carefully interpretation of anti-ARS antibody (ELISA) test results is important for us.

P2-144

The examination for Polymyositis and Dermatomyositis in our hospital

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Conflict of interest: None

Objectives We examined for PM/DM in our hospital. Methods We extracted the patient who made a definite diagnosis of PM/DM based on the criteria of Bohan & Peter from September, 1995 until October, 2015 in our hospital. We examined about sex, onset age, serum creatinine kinase, ferritin level (peak level), antiJo-1 antibody, malignancy, interstitial pneumonia (IP), dysphagia, heart disease and treatment. Results Eighty-three cases (PM 42, DM 41 cases) were enrolled,and the onset age was 62.8±13.9 years old (female:61 (73%), male:22 (27%);PM/DM with IP:39 (47%), PM/DM with malignancy:23 (28%), PM/DM with dysphagia:9 (11%),heart disease:3 (4%)). Anti Jo-1 antibody positive was 9 cases (11%). The peak serum CK level was 3352.8±493.5 IU/L, and ferritin was 601.0±187.9 ng/ml. Forty cases (48%) were treated for steroid pulse therapy.Fifty-three cases (65%) survived and 28 (35%) died. In comparison in survival group (L) and the death group (D), L group was significantly high in the serum ferritin level (L261.8±63.3 ng/ml vsD1279.2±511.1 ng/ml:*p=0.01*). Also percentage of with malignancy was significantly high in aged and DM patients. Conclusion We confirmed that the prognostic factors of PM/DM in our hospital were serum ferritin level. We should fully care for malignancy in Aged DM patients.

P2-145

A case of amyopathic dermatomyositis associated with hemophagocytic syndrome

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Conflict of interest: None

We report here a rare case of amyopathic dermatomyositis associated with hemophagocytic syndrome. A 73 year-old man suffered from painful erythema on elbows and hands for 1 month and visited our clinic. The erythema resembled Gottron's sign of dermatomyositis and he was admitted to our hospital. Physical examination revealed no musclar symptom and his serum levels of myogenic enzymes were not elevated. Serum anti-MDA5 antibody was positive, and we diagnosed him as amyopathic dermatomyositis. Laboratory data (L/D) also revealed hyperferritinemia and liver dysfunction. He was treated with 60mg/day of prednisolone and cyclosporine. Erythema gradually resolved, but thrombocytopenia emerged on 18th hospitalized day. Furthermore, L/D revealed leukocytopenia and sustained hyperferritinemia. Pathological findings of bone marrow specimens revealed hemophagocytosis. Then additional intravenous corticosteroid pulse therapy was not effective and high dose intravenous cvclophosphamide therapy was started. Thereafter thrombocytopenia, leukocytopenia and hyperferritinemia gradually resolved.

P2-146

A case of anti-aminoacyl tRNA synthetase antibody syndrome during pregnancy

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Conflict of interest: None

Two months before the admission, a 20s'-year-old woman developed dry cough, general malaise and a fever of over 37 degrees at twelve weeks of gestation. She also developed proximal dominant muscle weakness and femur muscle pain. Her muscle symptoms got worse gradually. A month before the admission, she couldn't walk on her own. Her laboratory data were CK 22930 IU/L, AST 364 IU/L, ALT 187 IU/L, LDH 1669 IU/L. She was admitted to our hospital at nineteen weeks of gestation. On admission, manual muscle testing indicated 1-2 in proximal upper and lower limbs. Magnetic Resonance Imaging confirmed myositis in the limbs. Lung computed tomography indicated interstitial pneumonia. Anti-PL-7 antibody, which is the one of myositis-specific autoantibodies, was positive. We diagnosed her as anti-aminoacyl tRNA synthetase (ARS) antibody syndrome, and started with methylprednisolone pulse therapy followed by oral prednisolone therapy. Thereafter, the muscle symptoms, CK level and interstitial pneumonia were recovered. This is very rare case with myositis during pregnancy.

P2-147

A case of refractory dermatomyositis successfully treated with rituximab

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Conflict of interest: None

A 65 year old female was admitted to the hospital because of one month weakness. A physical examination revealed weakness of proximal

extremities, Gottron's sign of elbows and erythema of back. Laboratory tests showed remarkable elevation of muscle enzymes. We diagnosed as dermatomyositis by electromyography, MRI, muscle biopsy and skin biopsy. She had interstitial lung disease in the peripheral lower lobes and no malignancy disease.We started 40mg/day prednisolone (PSL) on the seventh hospital day, and added IV-methotrexate (MTX) 20mg/week. On the 23th hospital day, we increased PSL 60mg/day because of dysphasia. On the 31th hospital day, her interstitial lung disease worsened. We discontinued MTX, and started Trimethoprim/Sulfamethoxazole and ganciclovir, and added IV immunoglobulin. Regardless of the therapy, her respiratory status was deteriorated on the 36th hospital day, and she needed mechanical ventilation. We added methyl-PSL 500mg/day for three days followed by PSL 60mg/day. Although she was able to be extubated on the 43th hospital day, her respiratory status was worsen again and her muscle enzymes elevated. We started rituximab (RTX) 375mg/m^2/week on the 46th hospital day. After RTX therapy, her respiratory status recovered and muscle enzymes decreased continuously.

P2-148

A Case of anti-SRP myopathy with interstitial pneumonia and malignant tumor

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Conflict of interest: None

A 71-year-old woman showed leg pain, dyspnea on exertion. The value of serum creatine kinase was 4,630IU/l. Drug-induced rhabdomyolysis was suspected because of history of statin. The drug was discontinued, but there was no improvement in muscle pain. Polymyositis is suspected because proximal muscle weakness was dominant. She was admitted to our hospital. Chest CT showed ground-glass opacities in both lower lobes and a nodule shadow to the right mammary gland, she was diagnosed as the breast cancer.Later the antibody against signal recognition particle (SRP) was detected by means of immunoprecipitation. The biopsied specimen of the deltoid muscle showed necrotic fibers scattered in fascicles. We diagnosed immune-mediated necrotizing myopathy. The myopathy often shows the severe muscle disorder. With many reports of steroid-resistance, effective intravenous immunoglobulin (IVIG) is reported. IVIG in addition to prednisolone showed muscle strength improvement. Generally the complications of malignant tumor and interstitial pneumonia to this myopathy is rare.We report those rare case of anti-SRP myopathy with literature review.

P2-149

Effective plasma exchange therapy for anti-MDA5 antibody positive dermatomyositis

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Conflict of interest: None

A 62-year-old man had been suffering from fever, cough, dyspnea, eruption and arthralgia for three weeks. He was referred to our hospital because his symptoms were not improved by antibiotic therapy at a clinic. At first presentation he showed cutaneous manifestations including Gottron's sign, heliotrope erythema, periungual abnormality and mechanic's hands, elevated serum creatine kinase (CK) and serum ferritin, and interstitial pneumonia (IP), which led to a diagnosis as dermatomyositis. Anti-MDA5 antibody turned out to be positive later. High dose steroid therapy, intravenous cyclophosphamide pulse therapy and tacrolimus were given, then clinical symptoms gradually improved. However, his hypoxia due to IP progressed on 47th day, thus plasma exchange therapy (PE) was performed. His respiratory function improved and serum ferritin level decreased from 4236ng /L to 1119 ng/L, therefore, PE was finished on 159th day (15 times in total). On 169th day, however, iliopsoas abscess was revealed, although treated with antibiotics, he died with CO2 narcosis on 212th day. We conclude that PE should be considered as a treatment option for anti-MDA5 antibody positive dermatomyositis, especially for the case refractory to immunosuppressive therapy.

P2-150

Deforming arthropathy associated with anti-Jo-1 antibody in dermatomyositis

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Conflict of interest: None

We experienced the rare case of deforming arthropathy associated with anti-Jo-1 antibody in dermatomyositis. The patient was 60-year-old woman. Her hands were gradually deforming for the past 6 years. Moreover, she recently felt muscle pain and fever and got worse. So she visited to our hospital. She was diagnosed with the combination of dermatomyositis and systemic lupus erythematosus, and was treated with corticosteroids.Her dominant right hand extremely contractured, dislocated with second to fifth MP joints, had z-shaped deformity of the thumb and ankylosed with some DIP and PIP joints. First, arthroplasty of the thumb was performed. And then artificial finger joint replacement of second to fifth MP joints and arthrodesis to fourth and fifth PIP joints were performed 7 months later. Deforming arthropathy associated with anti-Jo-1 antibody in dermatomyositis sometimes misdiagnosed with rheumatoid arthritis.

P2-151

Two cases of refractory Polymyositis(PM)/Dermatomyositis(DM) with anti-ARS antibody positive successfully treated with calcineurin inhibitor and azathioprine

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Conflict of interest: None

Case 1] A 21-year-old woman was admitted to our hospital, because of fever and proximal muscle weakness with the marked elevation of serum CK. She was diagnosed with PM and interstitial pneumonia, and received steroid pulse therapy. After steroid pulse therapy, PSL 50mg/day and TAC 4mg/day was started, but were effect insufficiency and she realized pneumomediastinum. Then we used IVIG and added AZA 50mg/day. Serum CK level was normal and interstitial pneumonia and pneumomediastinum was improved. [Case 2] A 62-year-old woman was admitted to our hospital, because of rash and proximal muscle weakness with the marked elevation of serum CK. She was diagnosed with DM and interstitial pneumonia, and received steroid pulse therapy. After steroid pulse therapy, PSL 60mg/day and TAC 4mg/day was started, but were effect insufficiency and the consentraion of TAC was very high. We used IVIG and switched TAC to AZA. But IVIG and AZA were effect insufficiency. Then we added CsA 100mg/day. Serum CK level was normal and interstitial pneumonia was improved. [Conclusion] Anti-ARS antibody positive PM/DM may be resistant to treat. We estimate that the combination of calcineurin inhibitor and AZA will be one of the treatment options for refractory PM/DM.

P2-152

A case of anti SRP antibody associated necrotizing autoimmune myositis which showed rapid response to steroid therapy

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Conflict of interest: None

The patient is a 56-year-old female who admitted to her local doctor because of fever, general fatigue and finger edema at March 2015. Loxoprofen and oral antibiotics were prescribed, but these symptoms were remained. Gradually, systemic myalgia was appeared. Moreover, erythema was emerged to her neck, body and hands at next month. Her physician referred her to our hospital as dermatomyositis. After the admission, since loxoprofen withdrawal vanished her rash, it was diagnosed as the drug eruption. She had positive anti SRP antibodies and muscle biopsy findings of necrotizing muscle fibers. Thus we diagnosed her as anti SRP antibody associated necrotizing autoimmune myositis, and started the 1mg/kg of prednisolone (PSL). Surprisingly, the MMT of upper and lower limbs rapidly improved from 2-3 to 4-5 in 5 days of medication. However, her creatine kinase (CK) level did not fall below 2000 IU/L even after that. Therefore, 100mg/day of azathioprine was added, resulting in a decrease of CK and reduction of PSL. Anti SRP antibody associated necrotizing autoimmune myositis has the character of steroid resistant refractory myositis. However, this patient was rare case which rapidly improved muscle symptoms with PSL only, even though the immunosuppressive agent was needed finally.

P2-153

Six cases of rapidly progressive interstitial lung disease complicated with clinically amyopathic dermatomyositis

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Conflict of interest: None

[Purpose] Rapidly progressive interstitial disease (RP-ILD) with clinically amyopathic dermatomyositis (CADM) is a poor prognosis. We report six cases of RP-ILD with CADM in our hospital [Patients and Methods] Among patients with DM in these five years in our hospital, we identified patients with none or slight of muscular manifestation as CADM. We examined age of onset, KL-6 and ferritin levels, kinds of therapies between death group and survival group. [Results] Among fifty-five cases of DM, the six cases were CADM with RP-ILD. All six cases were anti-MDA5 antibody positive. The three cases died and the mean duration of death from onset were four months. The age of onset in death group was older than survival group. The mean levels of KL-6 in death group and survival group were 879.3U/ml and 1605U/ml. Those of ferritin in each group were 660.1ng/ml and 4283.6ng/ml. Five of six cases were treated with corticosteroids, Calcineurin inhibitors (CNI) and intravenous cyclophosphamide (IVCY). Only one of survival group was treated with corticosteroids and CNI without CY. The mean duration of therapeutic intervention from onset were about four months in both groups. We thank to Kyoto University for tests of anti MDA5 antibody.

P2-154

Clinical findings in 5 cases of dermatomyositis with anti-melanoma differentiation-associated gene 5 antibody (anti MDA-5 antibody)

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Conflict of interest: None

[Objectives] Anti MDA-5 antibody is known as a dermatomyositis-specific antibody. Anti MDA-5 antibodies are predominantly positive in clinically amyopatic dermatomyositis (CADM), which is often complicated with rapidly progressive interstitial lung disease (RPLPD). The present study aimed to clarify the clinical features of DM with anti MDA-5 antibody. [Methods] 5 DM cases (2 men) that admitted to our hospital from 2012 to 2015 were analyzed retrospectively. We investigated clinical characteristics and treatments. [Results] The median age of disease onset was 45±11 years old. All cases had gottron's sign. 4 cases had heliotrope eyelids and periungual erythema. Serum CK was not elevated in 3 cases and serum ferritin revealed >1,000 ng/ml in 2 cases. Titer of anti MDA-5 antibody revealed <100 U/ml in 2 cases and >400 U/ml in 2 cases. All cases had ILD and high dose steroid with calcineurin inhibitors were used for initial therapy. In spite of those therapies, 3 cases remained progressive and 2 cases further developed DAD and 1 case was died. DAD cases were male who revealed serum ferritin >1,000 ng/ml that were resistant to those therapies. [Conclusions] We confirmed that high ferritin levels and male sex were poor prognosis factors for anti MDA-5 antibody positive DM with ILD.

P2-155

A case of rheumatoid arthritis complicated with polymyositis during tacrolimus treatment

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Conflict of interest: None

A 63-year-old female who had rheumatoid arthritis (RA) had been treated with 1mg of oral tacrolimus per day for more than 3 years. She didn't notice any muscle weakness, but a mild elevation of serum creatine kinase (CK) levels had continued for nearly 2 years. This June, thirty-six months after beginning of tacrolimus administration, laboratory investigations showed much higher levels of CK (1621IU/L) than before. The diagnosis of polymyositis was made because of positive anti-Jo-1 antibodies, CK (and aldolase) elevations, no skin lesion and the result of an open biopsy of the vastus lateralis muscle. She showed a good clinical response to oral prednisolone therapy with 1mg of tacrolimus per day. Prednisolone was able to be tapered from 30mg/day to 17.5mg/day in 11weeks without relapse. There are few case reports about patients who were diagnosed as polymyositis during tacrolimus treatment, so we report this case with a review of cases that were previously reported.

P2-156

Dermatomyositis (DM) with positive anti-melanoma differentiation-associated gene 5 (MDA5) antibody - report of the five cases

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Conflict of interest: None

Background: Anti-MDA5 antibody was shown to be associated with clinically-amyopathic dermatomyositis (CADM), complicated by rapidly-progressive interstitial lung disease (RP-ILD). Methods: Retrospective chart review of 5 cases of DM with positive anti-MDA5 antibody. Results: The age of the onset was 61, 71, 69, 75 and 47 years old. Serum ferritin level on admission was 3060, 507, 263, 1010 and 513 ng/mL, and the peak level was 12600, 1740, 1930, 2860, and 1060 ng/mL each. The former four cases were CADM with RP-ILD. Their respiratory status deteriorated despite of methylprednisolone (mPSL) pulses, combination therapy of cyclosporin A, intravenous cyclophosphamide and rituximab. They died on 21st day, 51st day, 17th day and 21st day after the administration. The last case, a 47-year-old male, did not have ILD initially, and presented with myositis. He treated with mPSL pulse, followed by high-dose oral glucocorticoid. But slowly-progressive ILD had emerged, and treatment with the combination therapy of immunosuppressant and rituximab was initiated. Conclusion: DM with positive anti-MDA5 antibody may take various clinical courses, and novel therapeutic strategy is strongly needed for the treatment of CADM with RP-ILD.

P2-157

A Case of Eosinophilic Granulomatosis with Poliangiitis (EGPA) complicated by Central Retinal Artery Occlusion (CRAO)

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Conflict of interest: None

[Case]A 40-year-old female with a history of bronchial asthma and allergic rhinitis developed sudden bilateral visual loss. Ophthalmoscopy showed an ischemic change of retina with "cherry red spot sign". Ophthalmologist diagnosed bilateral central retinal artery occlusion (CRAO) based on the finding of Fluorescent fundus angiography. The blood tests showed eosinophil 2636 /μl, CRP 4.92 mg/dl, IgE 278 IU/ml, and MPO-ANCA 181 EU. Nerve conduction velocity study showed multiple mononeuropathy. Chest computed tomography (CT) scan showed granular shadow. We diagnosed Eosinophilic Granulomatosis with Poliangiitis (EGPA) complicated by CRAO based on clinical course. Immediately, she received treatment combined with hyperbaric oxygen therapy and intravenous methylprednisolone (mPSL: 1000 mg/day for 3 days) followed by oral PSL and cyclophosphamide. After 5 weeks treatment, the levels of eosinophil and CRP were normalized, but only a slight improvement in visual disturbance was observed.[Conclusion]EGPA should be included as differential diagnosis in acute visual disturbance. We discuss clinical features of EGPA complicated by CRAO with some literature review.

P2-158

A case of ANCA-related otitis media,which happedned to occur the eye symptoms

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Conflict of interest: None

[Case] 76 years old, women [Chief Complaint] left eye blepharoptosis,movement disorders [Clinical History]In 2014,because of refractory otitis media and elevation of MPO-ANCA,she received a diagnosis of ANCA-related otitis media.She noticed left blepharoptosis and the movement disorders in 2015,so she was in hospital for the suspicion of the association with the vasculitis.In physical examination,there were the blepharoptosis and movement disorders of all directions.In head MRI,hypertrophic pachymeningitis and the orbital apex syndrome secondary to it were found.We thought it was associated with the vasculitis because of the past history of ANCA-related otitis media and the elevation of ANCA.We started methylprednisolone 500 mg/day bolus for three days and followed by 1mg/kg/day prednisolone. After that,CRP showed a downward tendency and the symptoms were improved.[Discussion] There are several reports about the association between ANCA-related vasculitis and hypertrophic pachymeningitis. We report it including those discussion from the literatures.

P2-159

A case of EGPA onset and relapse with cardiovascular events

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Conflict of interest: None

The patient was 62-year-old man. He developed Asthma in December 2011. He was developed angina attack and admitted to **cardiovascular medicine** of another hospital in January 2012. He was suspected to be eosinophilic granulomatosis with polyangiitis (EGPA) from WBC18,000 (Eosino 67.5%), pleural effusion, and peripheral neuropathy. His symptom was improved by 30mg of prednisolone (PSL). He came to our hospital after this treatment. During tapering 2mg of PSL, he had a pyrexia on September 21, 2014. He was developed angina attack and admitted to **our** hospital on October 1. He was diagnosis of EGPA from because of WBC17,600μl (Eosino 50%), ESR23mm/h, CRP 2.76mg/dl, IgE 1936IU/ml, MPO-ANCA (-), PR3-ANCA (-), pleuritis peripheral neuropathy, coronary vasospasm, nasal eosinophil infiltration, and sputum eosinophilia. After administrating 60mg of PSL, his symptoms were improved. EGPA shows a various symptoms that contain neuropathy, vascular symptoms and allergic symptoms. Vasculitis of coronary artery develops first and second angina attack. EGPA complicate 40% of cardiovascular lesions, but there is little frequency of the coronary arteritis.

P2-160

A case of microscopic polyangitis with Sjogren's syndrome who died of acute exacerbation of interstitial pneumonia

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Conflict of interest: None

An 81-year-old female had been treated with glucocorticoid (GC) because of microscopic polyangitis (MPA) diagnosed with p-ANCA and interstitial pneumonia (IP) in 1998. She was also suffered from Sjogren's syndrome (SjS) and manifested dry mouth and double positive for anti SS-A and SS-B antibodies. She had maintained remission of MPA with 5 mg of prednisone until 2013 when she developed purpura and elevation of MPO-ANCA titer then she was treated with add-on azathioprine. Two weeks after improvement of *Pseudomonas aeruginosa* pneumonia in 2014, dyspnea and hemosputum appeared. Computer tomography showed multiple grand glass appearance and consolidation dominant in hilar regions and partial traction bronchiectasis. Exacerbation of MPA was suspected and high-dose GC and rituximab were initiated but she died 36 hours after her admission. Pathological examinations showed no finding of vasculitis but diffuse alveolar damage indicating the exacerbation of IP. It is well known that IP is common in Japanese MPA patients while IP is also common in patients with SjS and 3% of SjS patients were nonspecific ANCAs positive. It was difficult to diagnose the cause of respiratory failure as whether vasculitis or not in the present case.

P2-161

A case of complete remission of Granulomatosis with Polyangitis / rapidly progressive glomerulonephritis (GPA/RPGN) treated with IVCY and PSL

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Conflict of interest: None

A 55-year-old man presented with numbness of upper and lower limbs, a nose bleeding, chronic cough and fever persistent for more than two months. A CT scan revealed severe infiltration in both sides of lung. Physical examination showed a mononeuritis multiplex of upper and lower limbs and subcutaneous nodule of the elbow (epithelioid cell granuloma). Laboratory tests revealed high-titer of serum PR3-ANCA. He was diagnosed with vasculitis-related granulomatous disease (GPA) and then he underwent Steroid pulse therapy (mPSL 1 g 3 days, PSL 1 mg / kg/day) combined with Cyclophosphamide pulse therapy (IVCY 15 mg/kg) resulting in remarkable remission of his lung disease and mononeuritis multiplex. However, he developed subacute renal failure: urine protein 1.5 g/gCre and urine occult hematuria. Kidney biopsy showed a necrotizing crescentic glomerulonephritis. Total five courses of IVCY therapy made his renal failure completely remitted. Many cases were reported MPO-ANCA-positive ANCA-associated Vasculitis treated with steroid monotherapy effectively. On the other hands, some cases required combined therapy of steroid and IVCY as shown in this case who has GPA with PR3-ANCA-positive that is rare in Japan.

P2-162

A case of granulomatosis with polyangitis complicated with abdominal aortic aneurysm improved by internal medical treatments

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Conflict of interest: None

A 58-year-old man was admitted to our hospital due to fever up, back pain, and paranasal sinusitis. On admission, pulmonary infection was suspected because of multiple module shadows in both lungs, however, antibiotics treatment was not effective for his symptoms. Laboratory tests indicated a positive reaction of proteinase 3 (PR3)-antineutrophil cytoplasm antibodies (ANCA), and findings of his lung biopsy revealed necrotizing giant-cell granulomatous inflammation. Furthermore, abdominal aortic aneurysm was detected by CT scan examination. Based on these findings, he was diagnosed with granulomatosis with polyangitis (GPA) associated with abdominal aortic aneurysm. He was treated with steroid pulse therapy (500mg/day for 3 days) and followed by oral prednisolone (1mg/kg daily), and then intravenous cyclophosphamide therapy (IVCY; 750mg/day). Aneurysm is a rare, but life-threatening, complication of GPA. This case was improved by only internal medical treatments without operations. We report this case with literature considerations.

P2-164

A case report of microscopic polyangitis (MPA) associated with epididymitis

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Conflict of interest: None

[Case report] An 87-years-old man noted scrotal pain and fever, and had a diagnosis of acute orchitis in July, 2015. He was treated with antibiotics including CTRX and MEPM for one month. However, the treatment had been ineffective. To make a diagnosis, right testis extirpation was performed. The histopathological analysis showed vasculitis of small-sized blood vessels with the fibrinoid necrosis in the epididymis. Laboratory data showed remarkable elevation of MPO-ANCA (1524 u/ml) and moderate renal dysfunction of eGFR 35 ml/ml with microscopic hematuria, proteinuria and Erythrocytic cast.From these findings, he was diagnosed as microscopic polyangitis with epididymitis involvement. He was treated with moderate doses of predonisolone of 30 mg daily, and his symptom quickly improved. [Discussion] MPA tends to involve various organs including the kidneys, lungs, skin, and peripheral nerves, but it was rare that initial manifestation was scrotal pain due to epididymitis. We present here a rare case of MPA with epididymitis with review of literature.

P2-165

Clinical evaluation of 21 cases with IgG4-related diseases

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Conflict of interest: None

[Objectives] To elucidate clinical characteristics and outcomes of IgG4-related disease (IgG4-RD). [Methods] We retrospectively reviewed 21 cases diagnosed with IgG4-RD between 2003 and 2015. [Results] Among 21 cases, 19 were males. The mean age was 64.1 years, and the mean serum IgG4 level was 685.2 mg/dl. The organ involvements were retroperitoneum (13 cases), salivary and lacrimal glands (8), lung (5), kidney (5), pancreas (3) and bile duct (2). Prednisolone (PSL) was used in all cases and the mean initial dose was 0.63 mg/kg/day. The mean PSL dose for maintenance therapy was 4.8 (range, 2.5-6) mg/day. 4 relapses in 3 cases occurred during a mean follow-up period of 3.9 years. In a case with autoimmune pancreatitis, first relapse occurred after self-discontinuation of PSL and second occurred during maintenance therapy (PSL 5mg/day). The remaining 2 cases with retroperitoneal fibrosis received no glucocorticoid (GC) therapy at the time of relapse. 6 cases (28%) developed malignancies during follow-up. [Conclusion] In this study, most cases remained in remission during administration of low-dose PSL, while some relapses were observed in the absence of GC treatment, suggesting that long-term maintenance therapy with low-dose GC are required for patients with IgG4-RD.

P2-166

Targets of treatment in 39 Patients with IgG4-Related Disease

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Conflict of interest: None

[Objective]The optimal treatment for IgG4-related disease (IgG4-RD) has not been established. All patients with symptomatic, active IgG4-RD require treatment, some urgently. A subset of patients with asymptomatic IgG4-RD also requires treatment. This study was undertaken to report the trend of treatment for IgG4-RD patients in our department. [Methods]39 IgG4-RD patients who satisfied Umehara criteria (including probable, possible) were reviewed regarding onset age, organ involvement, receiving treatment or not, and the targets of treatment. [Result]Of the 39 patients, 23 were receiving treatment. The frequent targets of treatment were lachrymal glands (26%), orbit (17.4%), heart (17.4%). [Conclusion]The most frequent targets of treatment for IgG4-RD was in the ophthalmological region.

P2-167

A case report of IgG4 related disease and rheumatoid arthritis with pneumoconiosis

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Conflict of interest: None

A 67-year-old man who is a mason showed polyarthralgia and cough. He had previously been diagnosed with pneumoconiosis (PNC) since 2009. In 2013, polyarthralgia occurred, and was aggravated from 2014. Around the same time, he had been suffering from a cough. Therefore, he was admitted to our hospital. From the polyarthritis, rheumatoid factor positive and satisfying 2010 ACR/EULAR classification criteria, we diagnosed rheumatoid arthritis (RA). Furthermore, he had the observations suggesting IgG4 related disease (IgG4-RD) such as elevated serum IgG4 levels and biomarker for the tubule-interstitial renal disease. His interstitial pattern of chest CT image confused with PNC, RA and IgG4-RD. The biopsied specimen of the renal showed the pattern of IgG4-RD. Additionally, we performed trans-bronchial lung biopsy. The specimen of upper lung field showed the pattern of PNC and that of lower field showed the pattern of RA related lung disease. RA associated with PNC is known as Caplan's syndrome. Moreover, it is reported that the relationship between asbestosis and retroperitoneal fibrosis. In conclusion, we report a rare case of IgG4-RD with RA and PNC.

P2-168

A Case of IgG4-Related Retroperitoneal Fibrosis Associated With Polyarthritis ~IgG4-Related Arthritis or Rheumatoid Arthritis?

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Conflict of interest: None

【Case】A 71-year-old man developed polyarthritis and was diagnosed with RF-positive rheumatoid arthritis (RA) a year ago. Methotrexate 6mg/week and adalimumab were started, and low disease activity was kept. A month ago, both drugs were stopped because of AKI (Cr 5.87mg/dl). Abdominal US/CT revealed bilateral hydronephrosis and thickening soft tissue surrounding the aorta to common iliac artery, suggesting postrenal failure. He underwent bilateral ureteral stent, and renal function immediately improved. Laboratory findings showed high levels of serum IgG and IgG4 (1758mg/dl and 328.0mg/dl, respectively). Laparoscopic biopsy from retroperitoneal lesion demonstrated the strong infiltrations of IgG4-positive plasma cells and striform fibrosis, indicating IgG4-related retroperitoneal fibrosis (RPF). PSL 0.6mg/kg/day was started, and RPF was dramatically reduced and high IgG/IgG4 and polyarthritis also immediately improved.【Conclusion】Firstly, RA was diagnosed in our case, however high IgG level was also revealed. Furthermore, retrospectively assessing bone scintigraphy at the time of diagnosis as RA, retroperitoneal lesion was revealed. In such a case, it is significant to study whether IgG4-related arthritis or RA associated with RPF, and we report with review of literature.

P2-169

IgG4-RD with serositis; A possible case of overlapping SLE

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Conflict of interest: None

We report the case of a 74 year old man with Raynaud phenomenon, polyarthralgia, hypocomplementemia, increased serum level of IgG and IgG4, and positive ANA as well as anti-DNA antibodies. Bilateral renal swelling was identified by CT imaging and Ga scintigraphy showed accumulation of ^{67}Ga within the submandibular gland. Renal biopsy revealed tubulointerstitial nephritis (TIN) with storiform fibrosis and infiltration by high numbers of IgG4-positive plasma cells, and showed no evidence of immune complex mediated glomerulonephritis. After five months later, he developed acalculous cholecystitis and serositis. Recently, the cases of IgG4-RD with pericardial involvement were reported. The pathological the relationship between IgG4-RD and serositis should be investigated.

P2-170

A case report of IgG4-related disease (IgG4RD) with intractable urinary frequency and dysuria due to prostate involvement

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Conflict of interest: None

[Case report] A 69-year-old man was admitted to our hospital because of urinary frequency and dysuria, which symptoms had not been effective for the treatment of prostatic hypertrophy. The histopathological analysis of prostate revealed the fibrous connective tissue with massive invasion of IgG 4 positive plasmocyte to prostatic glandular tissue. Laboratory data showed elevation of serum IgG4 level to 976 mg/dl with IgG 3751mg/dl. CT scan showed prostatic hypertrophy, thickening of aortic wall, hypertrophy of urinary bladder and a mass of right maxillary sinus. From these findings, he was diagnosed as IgG4RD with the involvement of prostate, and treated with prednisolone (30 mg/day). His dysuria improved in 3 days after the treatment. In addition, aortic wall thickening and the mass in the sinus seen on the CT scan were also disappeared in two weeks. [Discussion] IgG4RD is a relatively novel clinical disease entity which involved a variety of organs including salivary glands, pancreas, kidney, and lung. Although it was rare that initial manifestation was urinary frequency and dysuria in IgG4RD, it is important for us to keep in mind that IgG4RD sometimes cause intractable dysuria. We present here a rare case of IgG4RD-related prostate involvement with review of literature.

P2-171

A case of IgG4-related skin disease associated with Mikulicz disease

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Conflict of interest: None

【Case】The patient, a 65-year-old man with a 6-month history of bilateral neck swelling and eruption with itching, referred to Otolaryngology. Biopsy specimens from swollen submandibular gland and lymph node showed IgG4-related chronic sclerosing sialadenitis. The biochemical profile demonstrated elevated levels of IgG4/IgG (209/1073mg/dl) and IgE (729IU/ml), suggesting Mikulicz disease. He was started to treat with prednisolone (PSL) 10mg daily. Submandibular and lymph node swelling were improved, but eruption remained. Then, indurated eruption with itching expanded to neck, forearm and precordia. Skin biopsy revealed several nodular infiltrations constituted by IgG4 positive plasma cells and eosinophil in dermis with discreet fibrosis. The positive ratio of IgG4/IgG was 40% and IgG4 positive plasma cells over 10 counts/high-power field, suggesting IgG4-related skin disease. Oral fexofenadine 120mg daily and topical clobetasol propionate in addition to oral PSL improved IgG4-related skin lesions. 【Conclusion】Recently, IgG4-related disease is widely noticed and IgG4-related skin disease is rarely reported. It is reported to be 7 types of skin lesions in IgG4-related disease and we report with literatures.

P2-172

IgG4-related Hypophysitis with adrenal insufficiency

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Conflict of interest: None

In recent years, some IgG4-related Hypophysitis have been reported. We herein report a case of IgG4-related Hypophysitis with adrenal insufficiency. A 66-year-old man treated with steroid for retroperitoneal fibrosis, finished steroid 5 months ago on admission. With fever and vomiting, he was admitted for suspect of gastrointestinal obstruction. CT inspection showed no gastrointestinal obstruction, but worsened retroperitoneal fibrosis. His symptom of polyuria and polydipsia, and laboratory data showing hyponatremia and hypoglycemia, suggested adrenal insufficiency and diabetes insipidus. Head MRI test in T1-weighted image showed swelling pituitary stalk and signal loss of posterior pituitary. We diagnosed pan hypopituitarism and diabetes insipidus due to IgG4-related hypophysitis. After he was treated with moderate dose of steroid, his symptom was diminished and abnormal laboratory data was improved. Retroperitoneal fibrosis was also improved. Hormone test of Pituitary showed normal function of anterior pituitary, but decreased function of posterior pituitary. We had difficulty diagnosing pan hypopituitarism and diabetes insipidus due to hypophysitis, when IgG4-related disease was exacerbated.

P2-173

Which came first, "IgG4-related diseases" or "ANCA-associated vasculitis"? : A case of IgG4-related retroperitoneal fibrosis concomitant with MPO-ANCA associated vasculitis

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Conflict of interest: None

A 70-year-old woman presented with 2 weeks history of diarrhea, 10 days history of proximal myalgia, and weight loss of 2 kg. Physical examination findings were unremarkable except for tenderness of bilateral hip and shoulder. Laboratory data showed CRP 7.81 mg/dl, and MPO-ANCA 188.5 IU/ml. Renal function and urinalysis were normal. Contrast-enhanced CT revealed subpleural curvilinear shadow in the lower lung field, increased number and size of mesenteric vessels (comb sign), and a dorsal prevertebral lesion from Th8 to Th12. Upper and lower endoscopy, and small-bowel series showed unremarkable. We underwent CT-guided biopsy of the dorsal prevertebral lesion, and tissues showed inflammatory granulation. Immunostaining for IgG4 and IgG revealed increased IgG4 positive cells and lgG4+/IgG+ ratio at 50%. Additional laboratory data showed serum-IgG4 of 241mg/dl. She was started on 45 mg/day of prednisolone and 16 mg/week of methotrexate. Her symptoms rapidly disappeared. Previous studies reported increased IgG4-positive cells in the tissues that obtained from cases of granulomatosis with polyangiitis. However, IgG4-positive retroperitoneal fibrosis concomitant with MPO-ANCA associated vasculitis is rare. Further studies are warranted to make clear a relationship between ANCA and IgG4.

P2-174

Successful steroid sparing by add-on azathioprine in a patient with steroid-dependent IgG4-related disease

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Conflict of interest: None

Case report: A 74 year-old man with IgG4-related disease (IgG4RD) was admitted for proteinuria and rapidly progressive renal function deterioration. Four years before admission, weight loss, steatorrhea, bilateral submandibular gland swelling, and elevation of urinary β2-MG and serum IgG4 developed. Because abdominal CT scan revealed pancreatitis and renal biopsy showed the interstitial nephritis, he was diagnosed as IgG4RD. Predonisolone (PSL) 20 mg/day was started with satisfactory improvement of symptoms and was tapered to 8 mg/day 14 months later. However, symptoms were aggravated again, and PSL was increased up to 15 mg/day. Then symptoms were disappeared, and PSL was discontinued 9 months later. Six months after discontinuation of PSL proteinuria and rapidly progressive renal function deterioration developed. Because renal biopsy revealed severe TIN, relapse of IgG4RD was confirmed. PSL 20 mg/day with azathioprine 50 mg/day was started with the satisfactory improvement of renal function and the uneventful tapering of steroid. **Summary:** The add-on azathioprine could serve as the steroid sparing strategy in the patients with steroid-dependent IgG4RD, and we report this case with literature review for the treatment of IgG4RD.

P2-175

Two cases of IgG4-related disease (IgG4-RD) complicated with atypical eye lesions

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Conflict of interest: None

【case1】A male diagnosed with the ocular myasthenia gravis (OMG) in 64 year-old had diplopia, his right eye movement to lowerawrd was disorderd. and the antibodies against the acetylcholine receptor (AchR-Ab) was positive. He had been observed without treatment. Six years later, he was aware of persistent diplopia and the enlargement of lacrimal and salivary glands. He was diagnosed with IgG4-RD rather than MG because of the low titer of AchR-Ab, the negative ice pack test. and high serum IgG4 concentrations and the result of lacrimal glands biopsy. Four years later, MRI demonstrated pseudo- tumor around his optic nerve and enlargement of extraocular muscles. These conditions quickly improved with corticosteroids. In this caes it was difficult to distinguish G4RD from MG.【case 2】A female was aware of abnormality in the visual field in 53-year-old and was diagnosed with IgG4-RD due to high IgG4 concentration and orbital pseudotumor in MRI.. Her symptoms improved by corticosteroids temporally,but four times of recurrences were seen after reducing these drugs. Rrituximab administration in 63 year-old, improved her eye symptom without any recurrence. Rituximab may be useful for the eye lesions of G4-RD not affected with corticosteroid such as this case.

P2-176

A case of suspected IgG4-related tumorous lesion in central nervous system

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Conflict of interest: None

【Case】A 65-year-old Japanese woman presented with prolonged right neck tumor and right upper limb pain. Biopsy specimen from right neck tumor 8 years ago has showed inflammatory pseudotumor. One year ago, she was firstly revealed a tumor (35 x 12mm) on the right side of the medulla oblongata on MRI. FDG-PET/CT demonstrated high FDG uptake in tumors of medulla oblongata, brachial plexus and sciatic nerve. Laboratory finding showed elevated levels of serum IgG4 (633mg/dl) and IgG (1971mg/dl). Re-biopsy from right neck tumor was performed, and biopsy specimen showed IgG4/IgG>50% and IgG4-positive plasma cells infiltration >10/HPF, suggesting IgG4-related disease. The biopsy sample performed 8 years ago was also re-stained with IgG4 and showed similar results. PSL 0.6mg/kg/day 30mg was started as diagnostic treatment. After treatment, her symptoms and serum IgG4/IgG level dramatically improved. Medullary tumorous lesion was also reduced on MRI.【Conclusion】IgG4-related tumorous lesion in central nervous system is very rare, however our case might remind to consider IgG4-related diseases as a rare cause of tumor in the regions of central nervous system.

P2-177

Rituximab treatment to a case of IgG4-related disease associated with autoimmune hemolytic anemia and membranous nephropathy

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Conflict of interest: None

Although rituximab is frequently used for treatment to patients with IgG4-related disease (IgG4-RD) in USA, it's rationale is controversial. We report a 63 year-old male case in the first admission in 2011, having a swelling of right submandibular gland. He was diagnosed as IgG4-RD because of findings of autoimmune pancreatitis in CT-scan, IgG 3867mg/dl, IgG4 1260mg/dl, and pathological findings of submandibular gland. Furthermore, he had autoimmune hemolytic anemia (AIHA) of Hb 7.7g/dl, positive direct and indirect Coombs tests, then he has been treated by prednisolone at starting dose of 30mg/day. Though mass lesions were decreased, serum IgG4 remains high. In 2015, he had marked bilateral legs edema and hypoalbuminemia when he was taking 12mg daily prednisolone. Diagnosis of membraneous nephropathy (MN) with IgG4-RD was made by kidney biopsy. On admission, he had marked bilateral pretibial edema, proteinuria, Hb 12.2g/dL, Cr 0.93mg/dL, TP 6.5g/dL, Albumin 2.4g/dL, LDH 506U/L, IgG1794mgdL, and IgG4 842mg/dL. Rituximab was administered 375mg/m2 once a week, four times, however particular effectiveness has not been confirmed. We tried rituximab treatment to a patient with refractory IgG4-RD associated with AIHA and MN, thus we report the clinical course of this case.

P2-178

A case of IgG4-related disease manifesting as pancytopenia and pharyngeal ulcer

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Conflict of interest: None

A 71-year-old man with a history of early laryngeal cancer, and atrial fibrillation was admitted for dyspnea. One year ago, he had elevated serum IgG4 (350 mg/dL),and his inguinal lymph node and prostate biopsy demonstrated IgG4-related disease. On admission, his laboratory data showed anemia (Hb 5.3 g/dL), leukocytopenia (WBC 2160 μ/L), and serum IgG4 level was 935 mg/dL. Anti-nuclear antibody was positive, but anti-DNA antibody, anti-Sm antibody, rash, and renal involvement were negative. Direct and indirect coombs' test, anti-neutrophil antibody, and anti-platelet-associated IgG antibody were positive. In his course, agranulocytosis and thrombocytopenia were occured. Bone marrow biopsy demonstrated neither hematopoietic maturation disorder nor malignant tumor. Pain and swelling of pharynx were getting worsen, and the biopsy specimen showed pharyngeal ulcer with infiltration of IgG4 positive plasma cell. He was succesfully treated with predonisolone (40mg/day). [Clinical significance] We discuss about hematologic and pharyngeal involvement of IgG4-related disease with literature review.

P2-179

Clinical evaluation of IgG4-related diseases (IgG4-RD) in our department

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Conflict of interest: None

[Aim] The fine characteristics and pathogenesis of IgG4-RD have not been well-known. In this study, we examined patients with IgG4-RDs in our department in order to show characteristics of this disorder. [Methods] Twenty-nine patients were diagnosed as definite, probable or possible disease using the Comprehensive diagnostic criteria for IgG4-RD 2011. The clinical symptoms and laboratory data were retrospectively reviewed based on the medical records. [Results] Patients were 21 males and 8 females. The average age at the diagnosis was 63.3 years old. The average serum IgG4 level before treatment was 444.0 (50.8~1570) mg/dl. Affected organs at onset were salivary glands; 10, lacrimal glands; 2, upper pharynx; 1, pancreas; 2, retroperitoneum; 3, abdominal aorta; 4, superior vena cava; 1, lymph nodes; 2, colon; 1, and others; 3. Prednisolone (PSL; average 24.6mg/day) as initial therapy was administered in 24 cases. PSL or other glucocorticoids (GCs) were effective in all cases, except 3 cases that needed immunosuppressants to control the disease. The size of lesions was reduced in 20 of 24 cases. Serum IgG4 levels were decreased in 12 and normalized in 7 cases. The mean maintenance dose of PSL was 5.7mg/day. [Conclusion] GCs were effective and could be tapered in most of our cases.

P2-180

A case of IgG4 related renal disease complicated with systemic lupus erythematous

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Conflict of interest: None

A case of IgG4 related renal disease complicated with systemic lupus erythematous Rheumatology and Allergy department, Kameda medical center ○Akira Jibatake, Tamao Nakashita, Yuto Hamada, Koutaro Matsumoto, Shinji Motojima Introduction:IgG4-related disease must be differentiated with Sjogren syndrome, but there is no case that IgG4-related renal disease complicated with systemic lupus erythematous (SLE) has been repored before. Case:the patient is a 77 years old female who developed organizing pneumonia had got better with cortesteroid, but purpura in lower extremities, fever and right knee arthritis occurred with steroid tapering. She was diagnosed with SLE with the specific antibody, hypocomplementemia, positive coombs test. Hydroxychloroquine was begun but urine protein became positive in the meanwhile. The renal biopsy showed IgG4 positive plasma cells more than 10/HPF and the diagnosis of IgG4 related renal disease was made. Steroid was increased and the urine protein disappeared. Conclusion:Both of SLE and IgG4-relatd disease have hyperglobulinemia and hypocomeplementemia, so we have to make a diagnosis of SLE with caution when the plasma IgG is high.

P2-181

A case of anti PL-12 antibody positive interstitial pneumonitis in case with IgG4-related disease

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Conflict of interest: None

[Case] 71-year-old man [Chief complaint] dyspnea [Present history] A year before the admission, the patient was presented with retroperitoneal fibrosis that caused swelling of bilateral legs, hydronephrosis and lymphadenopathy. The biopsy of a lymph node along with the elevated serum concentration of IgG4 (240mg/dL) confirmed the diagnosis of IgG4 related disease. He was treated with prednisone of 40 mg daily that resolved retroperitoneal fibrosis. Prednisone was gradually tapered to 6 mg daily. With a week history of shortness of breath, he was admitted to the hospital with a hypoxia due to interstitial pneumonitis that showed diffuse ground glass opacities in both lung fields. Anti PL-12 antibody, an antibody towards aminoacyl tRNA synthetase, was positive, but there was no muscle or cutaneous manifestations that relate to inflammatory myositis. The interstitial pneumonitis did not respond to methylpredonisone 80mg daily, later gradually improved by the addition of cyclosporine. [Discussion] This is the initial case report of coexistence of IgG4 related disease and anti tRNA synthetase syndrome. The presented case illustrates a possible association of anti PL-12 antibody positive interstitial pneumonitis with IgG4 related disease.

P2-182

A case of Mikulicz disease suspected with eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

The patient was a 73-years old man. He suffered from polyarthralgia since February 2015. The swellings of his lachrymal and submandibular glands appeared with fatigue and anorexia. He was suspected with eosinophilic granulomatosis with polyangiitis (EGPA) because of his eosinophilia and elevation of PR3-ANCA. He was referred to our hospital in October 2015. His history of asthma and allergic rhinitis, hypereosinophilia (9513/μl), mild renal injury, interstitial pneumonitis and the elevation of PR3-ANCA suggested the diagnosis of EGPA, but it was not conclusive. In addition to his swelling of salivary glands, he had the elevations of IgG and IgG4, and hypocomplementemia. His submandibular gland biopsy showed sialadenitis with the extensive infiltrations of IgG4 positive plasmacytes (120/HPF, IgG4/IgG>80%). We diagnosed him as Mikulicz disease. After his treatment was started with moderate dose of corticosteroid (PSL 40 mg/day), his symptoms were rapidly improved. We report a case of Mikulicz disease suspected with EGPA. Because both of diseases link with allergy, this case is suggestive for the diagnoses and pathogenesis of them.

P2-183

A case of IgG4-related disease presented with masked diabetes insipidus of infundibulo hypophysitis after treatmemt of prednisolone

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Conflict of interest: None

A 78 year-old man with a medical history of chronic sinusitis, chronic otitis media and tumor of the parotid gland was admitted to our hospital for arthralgia and fever.Serum IgG4 level was elevated (406mg /dl) and the pathological findings of paranasal sinuses showed increased IgG4-positive plasma cells.Thus IgG4-related disease was diagnosed.After 30mg of prednisolone (PSL) was started, all his symptoms improved, but a few days later polyuria appeared.Endocriological findings revealed diabetes insipidus with anerior pituitary dysfunction.Pituitary MRI showed enlargemnt of pituitary gland and stalk.These results suggested IgG4-related infundibulo hypophysitis and masked diabetes insipidus. Desmopressin administration improved the urine volume. IgG4-related disease affects multiple organs.When we diagnose IgG4-related disease, a search for pituitary involvement is necessary even if there is no apparent symptom.of hypopituitarism.

P2-184

A case which the differential diagnosis of IgG4-RD or EGPA was difficult to make

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Conflict of interest: None

A 61-year-old woman. She had been diagnosed with bronchial asthma since around the age of 50. She was admitted our hospital because of pain, numbness, muscle weakness with scattered erythema on the lower extremity. The blood test showed marked eosinophilia (25840/μl) with high titer of IgG4 (261mg/dl). PR3-ANCA and MPO-ANCA were both negative. No obvious abnormalities in cerebrospinal fluid examination, head and neck MRI, peripheral nerve conduction velocity were found. The PET-CT showed strong FDG uptakes in multiple mediastinal lymph nodes as the level of malignant lymphoma, but transesophageal lymph node biopsy was not performed for absence of her consent. The skin biopsy of the lower extremity revealed only eosinophil infiltrations. Thus, the diagnosis of whether IgG4-RD or EGPA couldn't be made clearly. High dose of prednisolone improved eosinophilia promptly, symptoms and the titer of IgG4 were improved gradually. [Clinical significance] IgG4-RD and EGPA are both associated with cytokines of Th2 type which mainly play a role in allergic reactions. This case is supposed to be noteworthy in consideration of the mechanism and the management.

P2-186

Action for development and early practical use of biomedicines in the child in Japan

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Conflict of interest: Yes

[Background] By remarkable improvement of the diagnosis technology in inflammology and rheumatology, the good prognosis can be expected without carrying over some organ dysfunctions in adulthood, when the early diagnosis and treatment intervention for the inflammatory condition are performed to the patients. It is not exaggeration that it was caused by the appearance of the biomedicines. The four biomedicines (tocilizumab, etanercept, adalimumab, palivizumab) were approved in pediatric rheumatology in Japan, and greatly changed "CARE" to "CURE". [Purpose and method] In order to realize that development, approval and early practical use of biomedicines in the child in Japan, we investigated the present process from development to approval for the biomedicines. [Result] It was recognized that it could shorten the examination period when PMDA spent on both clinical trial preparations and approval in comparison with the past. Conclusively, it showed that the rate-limiting step in the child was rather supposed to the enforcement time of clinical trial. [Conclusion] For more shortening the enforcement period of clinical trial, the necessary key words might be "registry", "collection of facilities" and "international cooperation" for promotion of the future biomedicine development..

P2-187

Prognosis of 128 patients who developed arthritis under 16 years of age registered in NinJa 2014

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Conflict of interest: Yes

[Object] To evaluate the prognosis of patients who developed arthritis under 16 years of age. [Methods] Among 15,023 RA patients registered in NinJa 2014, 128 patients who developed arthritis under 16 years of age were entered this study. Their data were compared with those of other groups categorized by age of onset. [Results] Compared with other groups, they had the lowest mean age (44.3 years), the longest mean disease duration (33.0 years), the lowest mean values of DAS28-ESR (2.71), and the highest rate of DAS28 remission (51.4%). The rate of Stage IV (54.9%) and Class 4 (7.8%) and the mean values of mHAQ were higher. The rate of MTX use was low (51.6%), but that of biologics use was highest (42.2%), instead that of steroid use was lowest. The rate of drug-free was highest in this group. In women, this group showed lower height (153.2 cm) and lower body weight (48.4 kg). [Conclusions] This study showed the actual situation and prognosis of patients who developed arthritis under 16 years of age. For better understanding of transition medicine in rheumatic diseases, further studies are needed in this field.

P2-188

Continuation rates of the biological disease modified anti-rheumatic-drugs for the juvenile idiopathic arthritis: a retrospective single center study

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Conflict of interest: None

[Object] To investigate continuation rates of biological modified anti-rheumatic-drugs (bDMARDs) in juvenile idiopathic arthritis (JIA). [Methods] We investigated retrospectively continuation rates of bDMARDs in JIA patients and cause for withdrawal of bDMARDs in Osaka Medical College Hospital from April 2002 to September 2015.[Results] Eighty cases (12 systemic arthritis, 24 RF-positive polyarthritis, 9 RF-negative polyarthritis) were included, and avegage age was 7.2. Patients were treated with 23 adalimumab, 18 etarnercept, 52 tocilizumab and 15 infliximab. On the whole, 4-years continuation rate was 60.0%. When studying withdrawals due to treatment failure insufficient effect, 4-years continuation rate was 76.1%. Continuation rates in oligoarthritis and RF-positive polyarthritis patients tended to low, although it was not significantly. [Conclusions] Four-years continuation rates of bDMARDs for JIA were 60-70%. This study indicated that some oligoarthritis patients may not be good treatment response.

P2-189

Interleukin-33 as a marker of disease activity in juvenile idiopathic arthritis

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Conflict of interest: None

To assess the clinical significance of serum IL-33 levels in juvenile idiopathic arthritis (JIA), we measured serum levels of IL-33 in 7 patients with rheumatoid factor positive polyarticular JIA (RF+ poly-JIA), 8 patients with RF negative polyarticular JIA, 19 patients with oligoarticular JIA, and 30 age-matched healthy controls (HC). We determined their correlation with measures of disease activity and severity. Serum IL-33 levels in RF+ poly-JIA patients were significantly elevated compared with those in patients with other JIA subtypes and HC. Serum IL-33 levels were significantly elevated in patients treated with biological DMARDs compared to others. Serum IL-33 levels were positively correlated with serum RF titers in patients with RF+ polyJIA. Serum IL-33 levels sustained elevated in patients with refractory clinical courses but were normalized after remission. These results indicate that serum IL-33 levels correlated with disease activity, suggesting a potential role of IL-33 as a promising indicator of disease activity for JIA.

P2-190

Initial treatment and two-year outcome in juvenile systemic lupus erythematosus

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Conflict of interest: None

[Object] Treatment strategy of juvenile SLE is similar to that in adult. However, steroids should be avoided in children because of growth impairment. Therefore, certainty of induction of remission and prevention of recurrence are important. [Methods] We retrospectively studied 16 patients (M5, F11) with juvenile SLE who have been observed more than 2 years in our institute since 2008. We examined the recurrence, daily dose of prednisolone (PSL), SLEDAI at 2 years from the onset. [Results] ISN / RPS classification of lupus nephritis of 16 patients were; class I (n=2), II(n=2),III(n=5),IV(n=4),V(n=3). Regarding to remission induction therapy, 5 patients [III(n=3), IV(n=1),III+V(n=1)] were treated with methylpredonisolone pulse therapy (MPT), intravenous cyclophosphamide (IVCY) combined with mycophenolate mofetil (MMF). They were treated with MMF as maintenance therapy. Other 11 patients were treatment with MPT. Two year from initiation of therapy, no patients treated with MPT+IVCY+MMF had relapse, but 9 patients had relapse in another 11 patients (p=0.0046). [Conclusions] Regarding to remission induction therapy, MPT and IVCY combined with MMF was excellent. As remission maintenance therapy, MMF was excellent. MMF would change the future outcome of juvenile SLE.

P2-191

Factors associated with late diagnosis of juvenile dermatomyositis (JDM)

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Conflict of interest: None

[Aim] JDM is an autoimmune disorder characterized by typical rashes and muscle weakness. Early diagnosis is necessary to prevent death and sequelae, but often delayed. We analyzed the factors associated with delay in the diagnosis. [Methods] Medical records of patients with JDM who have admitted to our hospital between 1995 and 2015 were retrospectively reviewed. [Results] Twenty-three patients were enrolled. Nine patients were diagnosed with JDM after 4 or more months after the onset of any symptoms. One patient was diagnosed with amyopathic JDM. Two with severe muscle weakness were misdiagnoses as congenital myopathy. Three patients presented with arthralgia and were initially suspected as JIA. The other 2 patients had mild rash and muscle weakness which caused delay in the hospital visit. Six patients showed normal levels of serum CK at the presentation. However MRI showed abnormal findings in all but one patient with ADM. Myositis-specific antibodies (MSA) were positive in 5 patients; anti-MDA5 Ab in 2, anti-TIF1g Ab in 2, and anti-Jo-1 Ab in 1. [Conclusion] Diagnosis of JDM is likely delayed in cases of mild clinical symptoms or too severe weakness, and arthritis similar to JIA. Both MRI and MSA should be tested even in the patient with normal serum CK levels if indicated.

P2-192

Risk factors of subcutaneous calcification in 41 patients with juvenile dermatomyositis

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Conflict of interest: None

Fourty-one patients with juvenile dermatomyositis who visited at Kagoshima University Hospital from January 2000 to November 2015 were included in this study. Gender ratio: female 22 (53.4%), age of disease onset was 6.1 (median, range 0.4-15.1). Cumulative drug free remission rate at 5 and 10 years was 25.5% and 52.2%, respectively. Subcutaneous calcification was seen in 12 pts (29.3%), and the risk factors of it were episodes of relapsing myositis ($p<0.05$) and persistent muscle pain over 12 months (sensitivity 63.6%, specificity 77.3%, $p<0.05$). Tight disease control is important to prevent subcutaneous calcification.

P2-193

Long-term outcome of juvenile dermatomyositis with severe skin ulcers: a case report

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Conflict of interest: None

Case: A 14-month-old girl was referred to our hospital for muscle weakness and skin ulcers. She showed heliotrope discoloration, Gottron papules, and high serum creatine kinase levels. Muscle biopsy revealed myositis. Accordingly, she was diagnosed with juvenile dermatomyositis (JDM). Although methylprednisolone pulse therapy (MPT) was administered, the ulcers gradually increased in size. Skin biopsy revealed vasculitis. She was treated with intravenous cyclophosphamide pulse therapy followed by MPT concomitant with methotrexate (MTX) and high-dose prednisolone (PSL). Subsequently, her symptoms gradually improved, and MTX and low-dose PSL were continued. The ulcers had epithelized at 2-year-old. The medication was stopped at 7-year-old. However, at 8-year-old, although no ulcerations developed, she had muscle weakness and flares, for which MPT was administered and her symptoms improved. She again started receiving both MTX and PSL. She has not developed flares since then. The medication was stopped at 15-year-old. **Clinical significance:** This is the first report on the long-term outcome of JDM with severe skin ulcers. Early aggressive immunosuppressive therapy may improve the prognosis of JDM with severe skin ulcers.

P2-194

Evaluation of WISC-IV in Juvenile fibromyalgia

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Conflict of interest: None

Objective: To evaluate the trend of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) in Juvenile fibromyalgia (JFM). Method:WISC-IV was applied to 20 patients who were newly diagnosed with JFM in our hospital from April 2013 to March 2014 and analyzed these data. Results:Full scale IQ was 104.36±13.2 and each composite score were the following: VCI 107.4 ±15.72, Perceptual Reasoning Index 97.5 ±16.00, Working Memory Index 98.45±12.14, and Processing Speed Index 103.95±13.23. Among the composition scores, it revealed that VCI score was significantly higher than other composition scores in the majority of patients. Conclusions: This result, despite having ample vocabulary, may suggest the possibility of: poor communication skills; lack of visual information processing and working memory, the ability of processing speed, and faculty to adjust to the surroundings. It also implicates the trend of a bias in the perception characteristics of the JFM children. It is necessary to accumulate additional cases in order to lead to effective approaches of the treatment.

P2-195

Acute leukemia presenting with bone pains and normal hemogram

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Conflict of interest: None

Case 1:A 6-year old girl was introduced our hospital because of neutropenia. After four months, she was suffered from remittent fever with right shoulder pain.Afterward she experienced right knee pain, left knee pain, left upper leg pain one by one. Each pain underwent spontaneous remission within one week.Gallium scintigraphy showed abnormal uptake in right shoulder, left upper leg and right tibia pain.Bone marrow study showed a hypocellular marrow with over 80% blasts. Surface marker analysis revealed a pre-B cell phenotype. The final diagnosis was pre-B-acute leukemia.Case 2: A 4-years old boy was introduced our hospital because of pleuritis. After one month, she was suffered from fever with left upper leg pain, left ankle pain. Bone marrow study showed a hypocellullar marrow with blasts. the final diagnosis was acute leukemia. In conclusion, our case serves as a reminder that hematopoietic disease diagnosis should be considered for all patients with unexplained bone pain, bone lesion or other musculoskeletal manifestations, even if the hemogram is normal.

P2-196

A juvenile case of overlap syndrome of polymyositis and systemic sclerosis with pulmonary lymphoid hyperplasia

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Conflict of interest: None

A 14-year old man was admitted to our hospital because of scleroderma, muscle weakness and swelling in the parotid gland. His laboratory data showed that serum creatine kinase was elevated and anti-Scl-70, anti-SS-A, and anti-SS-B antibodies were positive. Myositis-associated autoantibodies were negative. Electromyography showed myopathic pattern, and subsequent muscle biopsy showed necrosis and regeneration of muscle fibers. High-resolution computed tomography (HRCT) of the lungs demonstrated ground-glass opacities (GGO) and multiple pulmonary nodules. Video-assisted thoracoscopic surgery was performed for diagnosis. Lung biopsy specimen showed the aggregation of lymphoid follicles and plasma cell hyperplasia. We diagnosed overlap syndrome of polymyositis and systemic sclerosis with pulmonary lymphoid hyperplasia. The parotid gland biopsy showed also lymphoid hyperplasia, but he was not diagnosed with Sjogren syndrome. He was treated with prednisolone (40 mg/day), after which serum creatine kinase and muscle weakness were improved. Chest HRCT showed reduction of nodules and GGO. There are few reports of polymyositis and systemic sclerosis with pulmonary lymphoid hyperplasia. Thus, we speculate that anti-SS-A and anti-SS-B antibodies induce pulmonary lymphoid hyperplasia.

P2-197

Regularly examination of serum cytokine (IL-18 and IL-6) levels is useful biomarker for treatment of two patients with acute phase of systemic-onset juvenile idiopathic arthritis

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Conflict of interest: None

[Object] Systemic-onset juvenile idiopathic arthritis (sJIA) is a systemic inflammatory disease characterized by arthritis, spiking fever and a skin rash. And proinflammatory cytokines interleukin (IL)-18 and IL-6 are critical role of the inflammatory processes in sJIA. Although serum levels of IL-18 and IL-6 may be useful as predict disease course of sJIA, reports of its usefulness as a regularly biomarker are limited. [Methods] We present a case series of two pediatric patients with acute sJIA. Patients #1 a 5-month-old girl with sJIA with high levels of IL-18 and IL-6 was treated with high-dose methylprednisolone. She developed pre-MAS but was successfully treated with dexamethasone palmitate (DEX-P), cyclosporin A by monitoring serum IL-18 and Il-6 levels.. Patients #2 an 11-year-old girl with sJIA who developed severe MAS but was successfully treated with DEX-P, cyclosporin A, and plasma exchange by monitoring serum IL-18 and IL-6 levels. [Conclusions] Serum IL-18 and IL-6 levels are a useful cytokine for monitoring the activity of sJIA and MAS. And especially serum IL-18 level can be used as a regularly predictor for the effectiveness of treatment and the regulation of immunosuppressive therapy.

P2-198

A boy with acute type neuro-Behcet's disease

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Conflict of interest: None

Neuro-Behcet disease (BD) is rare in children. This case report describes a boy with juvenile-onset neuro-BD successfully treated with corticosteroids and anti-TNF antibody (infliximab). Case report. A 15-year-old boy was admitted to our hospital because of fever lasting for 10 days and oral ulcers. Urinary retention, flaccid paralysis and paresthesia of lower limbs, and dysarthria developed 3 days after admission. He showed meningeal irritation (pleocytosis and elevated level of protein in the CSF). Brain MRI revealed many minute high signal intensities on DWI at right basal ganglia et al. and high signal intensities on T2-WI and FLAIR at brainstem and thoracic spinal cord et al. Methyl-PSL pulse-therapy did not improve paralysis of the lower limbs and again he complained of blurred vision due to uveitis. He was diagnosed as having neuro-BD, incomplete form; stage IV with HLA B51-positivity. CSF oligoclonal bands and anti-aquaporin 4 antibody were negative. Two weeks after pulse therapy, infliximab was introduced into the treatment. Then paralysis and MRI findings have gradually improved. Clinical implication. Infliximab looked quite effective in the amelioration of neurological damage. Detailed case series study remains to be done.

P2-199

A Case of Childhood-Onset Neuro-Behçet Disease with Hearing Loss and Uveitis as the Onset Manifestations

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Conflict of interest: None

Onset of Behçet disease before puberty is rare and neurologic involvement is uncommon. Here we report a girl who had hearing loss and uveitis as the first manifestations of neuro-Behçet disease. A 5-year-old girl arrived with intermittent fever, headache, vomiting, and wobbling toward her right side. She had a family history of probable Behçet disease. Her laboratory data showed elevated WBC and CRP (10800/μL and 7.9mg/dL, respectively) that did not respond to antibiotics. She was noticed to have bilateral sensorineural hearing loss and it was improved after PSL 1mg/kg administration. After PSL was tapered off, fever relapsed and CRP elevated. She felt numbness in her legs and pain on her ankle occasionally. Her hearing loss exacerbated and she developed uveitis after 1 month after her first visit. Autoantibody tests were all negative and HLA typing was positive for A24, B52, and DR15. She had abnormal electroencephalography and nerve conduction study, but no abnormal MRI findings nor oral aphthae, genital ulceration and skin lesions. We diagnosed her as Behçet disease probable and started steroid pulse therapy. Symptoms improved and PSL was tapered gradually. CRP elevated transiently but was improved by oral colchicine and she is now stable without a relapse.

P2-200

Two cases of post streptococcal cardiac complication without previous streptococcal infection and rheumatic fever episode

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Conflict of interest: None

[case 1] 5years old girl, she had no significant past history. She was found a systolic heart murmur on regular health check. Mitral regurgitation was demonstrated by cardiac ultrasound examination. In addition, serum ASO, ASK, anti-DNaseB antibody titer were elevated. We diagnosed she developed post streptococcal cardiac complication. [case 2] 7years old girl, she had no significant past history. She was pointed out that her restless and writing disorder. She was developed Sydenham's chorea and mitral regurgitation. Serum ASO, ASK were elevated. We diagnosed, she developed post streptococcal complications. [Discussion] Two cases developed post streptococcal cardiac complication without obvious streptococcus infection and rheumatic fever episode before. We have to reconsider about how to find out latent streptococcal complications and secondary prophylaxis.

P2-201

Clinical Features and Treatment of Patients with Psoriatic Arthritis

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Conflict of interest: None

【Objective】The aims of this study were to clarify the clinical features of patients with psoriatic arthritis (PsA).【Methods】We retrospectively assessed clinical characteristics, laboratory findings, and treatments in PsA patients who had attended our department from January 2014 to January 2015.【Results】27 patients were included in this study. The mean age at onset of PsA was 45.8 years and the sex ratio (M:F) was 18:9. Of 27 patients, 18 patients (66.7%) developed arthritis after skin lesion. 4 patients (14.8%) developed arthritis along with skin lesion. Only one patient (3.7%) developed arthritis before skin lesion. All patients had peripheral arthritis. 10 patients (37.8%) had enthesitis, 5 patients (18.5%) had axial joint involvement. RF and anti-CCP antibody were positive in 14.8% and 3.7% of patients respectively. The number of patients treated with NSAIDs, MTX, PSL, and biologics was 63%, 59%, 14.8%, and 33.3% respectively. Although many PsA patients received aggressive treatment, 6 patients (22.2%) voluntarily discontinued their treatment.【Conclusion】The rate of discontinuation of treatment seemed to be high in patients with PsA. We therefore should consider their social background and psychological status for treatment of PsA.

P2-202

Acute onset of peripheral Spondyloarthritis with sacroiliac arthritis on magnetic resonance imaging developing after the non-chlamydial urethritis: a case report

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Conflict of interest: None

A 20-year-old male belonging to the cycling team of his university was suffered from urethritis. Though his urethral symptoms were cured with azithromycin, fever and right knee arthritis newly appeared. He received arthrotomy and the other antibiotics therapy for a month in orthopedic hospital, but arthritis spread to his shoulder, elbow and finger joints, so he entered our hospital. He has no medical and family history of inflammatory bowel disease, psoriasis, uveitis and spondyloarthritis (SpA). In addition to the previous urine culture and polymerase chain reaction, the serum antibody tests could not show the gonococcal or chlamydial infection. Besides, HLA B27 was positive and MRI could indicate the non-radiographic sacroiliac arthritis, though he had no back pain. Consequently, he was diagnosed with peripheral SpA based on the ASAS classification criteria. Sequentially adding of the prednisolone, salazosulfapyridine and methotrexate gradually improved his symptoms. It may be controversial to consider this case either as reactive arthritis after the non-chlamydial urethritis or as acute onset of non-radiographic axial-SpA because of the sacroiliac arthritis. Finally, we are deeply grateful to Dr. Shigeto Kobayashi who provided helpful comments and suggestions.

P2-203

Three cases of crystal-induced arthritis presented Achilles, sternoclavicular and spinal involvements ~the significance of differentiation from peripheral SpA~

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Conflict of interest: None

【Case 1】A 62-year-old man presented with neck pain and Achilles enthesopathy. CRP 3.6 and uric acid 10.9 mg/dl were revealed. Bone scintigraphy and ultrasonography (US) showed spondylodiscitis and Achilles tendonitis, indicating enthesitis with low-echoic lesion and calcification. Numerous urate crystals was identified. He was diagnosed with gouty arthritis.【Case 2】A 78-year-old man, who had psoriasis, presented polyarthralgia with CRP 4.9mg/dl. Bone scintigraphy demonstrated calcified lesions of sternoclavicular, ischial tuberosity, greater trochanter and Achilles tendon, indicating crystal deposition by US. He was diagnosed with CPPD.【Case 3】A 79-year-old man, who had psoriasis, presented polyarthralgia with CRP 5.9mg/dl. Bone scintigraphy demonstrated calcified lesions of cervical spine, sternoclavicular, knee and Achilles tendon, indicating crystal deposition. He was diagnosed with CPPD. 【Results】After the treatment with PSL, colchicine and NSAID, their symptoms and CRP levels were improved. 【Conclusion】The Achilles tendon, sternoclavicular joint, spine and ischial tuberosity are rare and notable sites of involvements in crystal-induced arthritis. When the patient was noted to have back pain and enthesopathy, we should always recognize crystal-induced arthritis.

P2-204

Gout causes acute monoarthritis in early stages, but Gout also causes chronic polyarthritis when the disease duration longer----The latter will be struggling to distinguish from rheumatoid arthritis

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Conflict of interest: None

We report 3 cases with polyarthritis seen on gouty arthritis,.Case1, A 64y.o.M was admitted for right gonalgia. 1 day before admission (BA), right gonalgia appeared. On admission (OA), rt knee arthritis,uric acid (UA)6.0mg/dl. He was treated with prednisolone 20mg/day. With tapering below to 5mg, a flare of rt cox, both shoulders and jaw joints pain was observed.Case 2,A 75y.o.M was admitted for left first metatarsophalangeal joint (1MTPj) pain. Two day BA, left 1MTPj pain appeared. OA, left swollen red foot,UA4.8mg/dl. He was treated with diclofenac over the following 2 weeks, he obtained a responce. After 2 months, he was treated with febuxostat. After 4 months, both ankles and 1,5MTPj swelling appeared. Case 3, A 50y.oM was admitted for back pain. He had been diagnosed with gout for 6 y. 4days BA, back pain appeared, 3 days before gastrocnemius pain, both knees and ankles pain appeared. OA,UA6mg/dl. He was treated with celecoxib, he obtained a responce. 1 month later, painful swelling of the 1, 2 Metacarpophalangeal joint,both ankle and 1, 5 MTPj. appeared.Discussion: It is little known that longer disease duration of gout causes poliarthritis called Chronic tophaceous gout. Value of Uric acid OA was struggling to differentiate from rheumatoid arthritis because it was normal.

P2-205

A case of palmar fascitis and polyarthritis syndrome associated with ovarian cancer

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Conflict of interest: None

A 68-year-old Japanese woman suffered arthritis of small joints of both hands, lateral upper and lower limbs muscle pain and rapidly progressive contracture of both palms and fingers. As ground glass opacity was recognized in chest X-Ray and anti ARS antibody was positive by ELISA, anti-ARS antibody syndrome was suspected. On the other hand, abdominal CT and MRI revealed an ovarian cancer and lymph nodes metastasis, and we detected adenocarcinoma by biopsy from the swollen cervical lymph node. Arthritis and fasciitis of the palm were detected by MRI of the hand. We diagnosed her as palmar fasciitis and polyarthritis syndrome (PFPAS) induced by ovarian cancer. Anti-ARS antibody was negative from her serum by immunoprecipitation. Anti-ARS antibody syndrome was denied. Palmar fasciitis and polyarthritis syndrome (PFPAS) is a rare paraneoplastic presentation and has been mainly reported for ovarian cancers. PFPAS mimic other rheumatic diseases. Investigating the possibility of a cancer is recommended when treating elderly patients and patients with atypical arthropathy, especially with palmar fasciitis.

P2-206

Successful treatment of sarcoidosis-related hypercalcemia in a patient with rheumatoid arthritis by abatacept

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Conflict of interest: None

The abnormality in calcium metabolism in sarcoidosis is due to the uncontrolled synthesis of calcitriol by activated mononuclear cells, mostly macrophages in granulomas. We report a rare case of a 74-year-old female with long-standing history of rheumatoid arthritis and sarcoidosis, associated with uveitis, lung nodules, arthropathy, hypercalcemia, and nephrocalcinosis. Upon commencement of treatment with abatacept for her highly active RA, she showed a remarkable, unexpected improvement of hypercalcemia/hypercalciuria and renal dysfunction. In addition, the elevated serum ACE has been normalized after the administration of abatacept. Pathological examination of bone tissues taken during her left total knee arthroplasty, demonstrated non-caseating granulomas. The present case suggested possible beneficial effect of abatacept on abnormal calcium metabolism in sarcoidosis.

P2-207

Castleman's disease associated with Henoch-Schonlein purpula (IgA vasculitis) successfully treated by Tocilizumab; a case report

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Conflict of interest: None

A 40 year old man was referred to our hospital because of unresponsiveness to 10mg of predonisolone for polygammaglobulinemia. On admission at the age of 41, it was evident that he had continuous fever of 37 degrees Celsius, splenomegaly, polygammaglobulinemia (IgG 3136 mg/dl, IgA 596 mg/dl), inflammation (CRP 6.3 mg/dl) and anemia (Hb 11 mg/dl). Diagnosis of Castleman's disease was made from 20 mm swollen axillary lymph node biopsy. Five months later, painful multiple 5 mm purpula developed in his lower leg, accompanied by arthalgia in his wrists, ankles, and knees. The eruptions gradually spread to arms, legs and trunk. Skin biopsy revealed leukocytoclastic vasculitis with IgA deposition on dermal vessel showing complication of IgA vasculitis. Clinically judging the situation exacerbation of Castleman's disease, we administered intravenously 8 mg/kg of tocilizumab (anti-IL-6 receptor antibody) every four weeks. Remarkable improvement on purpula, arthalgia, fever, and above stated laboratory abnormalities were observed, besides that serum IL-6 level increased significantly from 18.7 ng/l to 376 ng/l. Various exanthema are reported to complicate Castleman's disease, and we report complication of anaphylactoid purpura with IgA deposition with Castleman's disease.

P2-208

A case of Neuro Sweet disease with meningitis and optic neuritis

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Conflict of interest: None

The patient was a 19-year man whose complaints were fever and headache, nausea. By treatment with acyclovil and methyl-prednisolone (mPSL) pulse, intravenous immunoglobulin, he recovered once. However soon he recurred, so he was transferred to our hospital. His temperature was 37.6℃, and he had stiff neck. Laboratory test revealed CRP2.0mg/dl, ESR35mm/hr. Cerebrospinal fluid (CSF) examination showed cell count of 720/μl (60 % monocytes and 40% polymorphs), and IL-6 level was 66000pg/ml. Brain magnetic resonance imaging (MRI) demonstrated T2 hyper intensity lesions in brain stem, hippocampus, corpus callosoum, and thalamus. His human leukocyte antigen testing reveal B54 and Cw1. We diagnosed neuro Sweet disease (NSD). He was treated with mPSL pulse followed by PSL 60 mg/day. His symptoms were gradually improved, and the CSF cell count decreased. After 2 years, he lost left eyesight, and he was admitted to our hospital. The fundus of his left eye demonstrated optic nerve edema. Brain MRI with gadolinium demonstrated hyper intensity in left optic nerve. We gave his diagnosis of a relapse of NSD. He was treated with mPSL pulse followed by PSL 60 mg/day, and his left eyesight was improved.

P2-209

Granulomatous periostitis and tracheal involvement in sarcoidosis

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Conflict of interest: None

【Case】A 66-year-old Japanese woman presented with a 1 month history of continuous fever, upper leg pain, voice change and cough. There had been no response to antibiotics. The biochemical profile showed elevated levels of CRP (6.1mg/dl), but calcium and ALP levels were normal. Tests for ANA, ANCA and angiotensin-converting enzyme were negative or normal. Blood cultures, the tuberculin reaction and HIV antibody were negative. Notably, fluorodeoxyglucose (FDG)-PET/CT revealed a swollen trachea and periosteum of sclerotic femoral bone with high uptake. Bronchoscopy showed mucosal edema, erythema and nodules in the trachea, suggesting granulomatous lesions. CT-guided needle biopsy of the left sclerotic femur demonstrated non-caseating granulomas with Langhanstype giant cells. The patient was diagnosed with sarcoidosis and treated with prednisolone 40mg and AZA 50mg daily. After treatment, her symptoms and CRP level improved and the high FDG in the tracheal and periosteal lesions completely resolved. She was discharged without further complications.【Conclusion】Periosteal or upper airway involvement in sarcoidosis is quite rare. We should remind to consider sarcoidosis as a rare cause of fever of unknown origin or of periosteal and tracheal lesions found on imaging.

P2-210

A case of cryoglobulinemia with successful treatment for HCV infection

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Conflict of interest: None

A case of female with 69 years old is reported. She had polyarthralgia and morning stiffness in 1999. As positive reactions of serum rheumatoid factor and anti-centromere antibody were found, she was diagnosed having limited scleroderma at another hospital. While she received nonsteroidal anti-inflammatory drugs, her symptoms sustained. She admitted to our clinic in 2002. Although joint swelling and scleroderma were not found, laboratory data showed positive reaction of cryoglobulin along with high titer of hepatitis C (HCV) antibody, HCV-RNA (7.0LIU/ml) and C1q binding immune complexes. Then, she received treatment for HCV infection. She had combination therapy of oral ribavirin 600mg per day and interferon α-2b injection from July, 2002 to January, 2003. This treatment temporarily suppressed her symptoms. However, polyarthralgia developed again. Then she had combination therapy of oral ribavirin and peginterferon α-2b injection from February, 2004 to April, 2006. Finally, HCV-RNA was detected only in 1.5 LIU/ml and cryoglobulin was negative. At the present time, her symptoms are acceptable after such treatments. Treatment for HCV infection is considered to be successful to patients with cryoglobulinemia by HCV infection.

P2-211

2 cases with development for syndrome of inappropriate antidiuretic hormone secretion during the intravenous cyclophosphamide

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Conflict of interest: None

[Case 1] A 76 year-old female and microscopic polyangiitis. The treatment of prednisolone (PSL) 1mg/kg and intravenous cyclophosphamide (IVCY) 400mg/4 weeks (4w) was started. IVCY was conducted 6 times with 400mg. We continued IVCY with the increased amount 500mg for the 7th time. We recognized a lowering in conscious level on the next day. We diagnosed it as syndrome of inappropriate secretion of antidiuretic hormone (SIADH) from serum Na117mEq/L, a lower osmotic pressure, and a measurable antidiuretic hormone (ADH). [Case 2] A 43 year-old female and dermatomyositis. The treatment of PSL 1mg/kg and IVCY 500mg/4w was started. We continued IVCY with the increased amount 500mg for the second. She had headache and vomit on the next day. We diagnosed it as SIADH from serum Na 126mEq/L, a lower osmotic pressure, and a measurable ADH. [Discussion] SIADH may be developed with CY as a rare case. SIADH may be developed after the first/second IVCY administration in many cases, but it was developed after the seventh administration in Case 1. When SIADH is developed by water loading through IVCY side effect prevention, it possibly become more severe, and would be necessary to focus on the symptom after multiple administrations particularly at the time of dose increase.

P2-212

A case of systemic lupus erythematosus associated with pancytopenia due to persistent infection of human parvovirus B19

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Conflict of interest: None

[Case] 43-years-old woman In 2012, she was diagnosed systemic lupus erythematosus (SLE) because of positive anti-nuclear antibody, positive anti-ds-DNA antibody, serositis, nephropathy, and leukopenia. She was treated with 45 mg/day of prednisolone (PSL) and immunosuppressants (cyclophosphamide, tacrolimus and Mizoribine), and her SLE improved. In September 2015, she admitted to our hospital because of general fatigue. Laboratory findings showed acute anemia (Hb 5.0mg/dL) and low reticulocyte (undertectable). There were no physical signs of viral infection, and SLE recurrence was suspected. Additional treatments of increasing PSL (50 mg/day) and cyclosporine were initiated. However, the pancytopenia, the hemolysis, and the huge proerythroblast in bone marrow were observed. Because human parvovirus B19 (HPV-B19) DNA was detected in peripheral blood, and the conditions due to HPV-B19 were suggested. Therefore we tapered PSL and discontinued cyclosporine. Although, her anemia, leukopenia, and hypocomplementemia were improved by additional treatment with repeating intravenous high-dose immunoglobulin, thrombocytopenia and hemolytic findings were remained. [Conclusion] We report a case that human parvovirus infection during SLE treatment course and review of literature.

P2-213

Screening for Thyroid Dysfunction in a rheumatology outpatient clinic

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Conflict of interest: None

【Background】Several study has reported association rheumatic disease with thyroid dysfunction.【Objective】This article focuses on whether it is useful to order a thyroid function test for patient who visit rheumatology department for the first time.【Method】From April 2006 to September 2015, We compared prevalence of abnormality of TSH Rheumatology department with Endocrine department and NINGEN DOCK in our hospital.【Result】 Rheumatology department; 13.9%, Endocrine department: 27.2%, health center: 16.3%【Conclusion】There are no significant effective of screening thyroid dysfunction in a rheumatic patient. But more study about data of all rheumatic patient, consideration of cut-off value of TSH.

P2-214

A case of SLE associated with miliary tuberculosis without any clinical symptom

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Conflict of interest: None

A 21 year-old woman from Myanmar suffered from sore throat and fever. She consulted 4 clinics in total and was prescribed several kinds of antibiotics as pharyngitis, but her symptoms did not improve. Then she visited our clinic, laboratory data revealed elevated serum level of ferritin, and she was admitted to our hospital. On admission, she had remittent, polyarthralgia and systemic lymphadenopathy. Laboratory data revealed leukocytopenia/lymphcytopenia, positive ANA, and positive anti-Sm antibody, and she was diagnosed as SLE. The result of QFT was indeterminant. Pathological finding of cervival lymphnode was necrotizing lymphadenitis and that of bone marrow was hypocelluar marrow. She was treated with 40mg/day of prednisolone (PSL) p.o, but suffered from allergic fever. Then corticosteroid was switched from PSL to methylprednisolone (mPSL) 32mg/day. Thereafter, her symptom disappeared and dose of mPSL was gradually decreased. Six weeks after start of treatment, she had no symptom, but chest X-p and CT revealed multiple nodular shadows. Her sputum examination revealed tubercle bacilli, she was diagnosed as miliary tuberculosis and started to take antitubercular agents.

P2-215

Eleven collagen disease patients complicated with gastrointestinal perforation in our hospital

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Conflict of interest: None

[Objective] Few studies reported in gastrointestinal perforation with collagen disease about the background and prognosis. We examined this problem. [Methods] Eleven collagen disease patients complicated with gastrointestinal perforation among 2592 inpatients were examined about primary disease, drug, symptom at the perforation and site, treatment and prognosis, retrospectively. Gastrointestinal perforation was defined by CT and excluded the intramural emphysema. [Results] The mean age was 67.5 ± 21.1 years old, and 6 male and 5 female were examined. The diseases were vasculitis (4), DM (3), SLE (2), RA (1) and PM (1). The median days from the starting treatment to perforation was 71 days. In the perforation site, an upper gastrointestinal tract was 4 cases, and a lower digestive tract was 7. As for 3 of 11 (27.3%) was asymptomatic at the perforation. The mean dosage of PSL for primary disease was 30.5 ± 15.5 mg/day at perforation. Eight patients were used pulsed mPSL, 7 were used immunosuppressive drug and 2 were used NSAIDs. As for the treatment for the perforation, surgery was 7 cases. [Conclusions] It is needed to pay attention for the case that is under the medical treatment in vasculitis and DM for gastrointestinal perforation, with or without clinical symptom and use of NSAIDs.

P2-216

A case of systemic lupus erythematosus with headache and speech disturbance that diagnosed with cryptococcal meningitis

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Conflict of interest: None

A 68-year-old woman was admitted to our hospital for evaluation of systemic lupus erythematosus (SLE). She had been diagnosed as SLE based on the presence of oral ulcers, lymphopenia and positive anti-dsDNA antibody. She had been treated with steroid pulse therapy for interstitial pneumonia at a local hospital. On admission, she complained of a mild headache, but was absent for neurologic abnormality. On the 12th day of admission, she developed severe headache and speech disturbance. Lumbar puncture was performed and fungi are detected in her cerebrospinal fluid. Cryptococcal antigen in cerebrospinal fluid was over than 512 titer. She was treated with 3mg/kg/day of liposomal amphotericin B and 100mg/kg/day of flucytosine, and her speech disturbance improved promptly. The finding of her cerebrospinal fluid normalized gradually. In the present case, the patient manifested few symptoms specific for meningitis. Since SLE is not rarely complicated with cryptococcal meningitis, it is crucial to differentiate infections meningitis from neuropsychiatric SLE. We discuss the importance of prompt cerebrospinal fluid examination in SLE.

P2-217

Efficacy of biologics in the treatment to renal AA amyloidosis secondary to rheumatoid arthritis

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Conflict of interest: None

The principal aim in treating rheumatoid arthritis (RA) patients with amyloid A (AA) amyloidosis is to switch off serum amyloid A protein (SAA) production, by controlling RA inflammatory processes. Biologics, such as etanercept, tocilizumab, and abatacept, can reduce serum SAA levels in RA patients with AA amyloidosis, improving rheumatoid disease activities. AA amyloid fibrils may be turned-over under the biological therapeutic conditions due to immunologic mechanisms. The number of CD68-positive cells surrounding the AA amyloid fibrils in the biopsied specimen obtained from upper gastrointestinal examinations correlated with the amelioration in RA disease activity, renal dysfunction, and levels of serum albumin ($P<0.05$). It was suggested that macrophages would play an important role in the regression of AA amyloid fibrils from the deposition foci within RA patients with AA amyloidosis.

P2-218

Prevalence of sarcopnea in rheumatoid arthritis

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Conflict of interest: None

Background: Primary sarcopenia is usually due to aging. Although secondary sarcopenia occurs due to chronic inflammatory disease, the prevalence of sarcopenia in rheumatoid arthritis (RA) is well not known. Objectives: We clarified the prevalence of sarcopenia in RA patients. Methods: Consecutive patients with RA were recruited. Sarcopenia was diagnosed with European Working Group on Sarcopenia in Older People (EWGSOP) diagnostic criteria. The skeletal muscle was measured by Bioimpedance Analysis (BIA) and grip power and walking speed were measured as muscle strength. Analyzed variables included age, disease duration and disease activity score (DAS) 28. Statistical analysis was performed using SPSS version 21. Results: Twenty-nign RA patients treated with disease-modifying antirheumatic drugs (DMARDs) and/or biologic DMARDs, were recruited. Five patients fulfilled EWGSOP diagnostic criteria. Although prevalence was 28.6%(4/14) in the group of above 65 years of age, prevalence was 0.07%(1/15) in the below 65 years of age. Sarcopenia did not correlate with disease duration and DAS28. Conclusions: Sarcopenia increases from 0.07% in those age of below 65 years, to 28.6% in those age of above 65 years. There is no significant correlation between sarcopenia and RA disease duration.

P2-219

A case of Felty's syndrome successfully treated with tacrolimus

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Conflict of interest: None

Felty's syndrome is a rare condition, characterized by rheumatoid ar-

thritis, neutrocytopenia and splenomegaly, with poor prognosis. Although its treatment strategy has not been established, some reports have shown the efficacy of methotrexate. However, it is also known that patients with Felty's syndrome often complicates with interstitial pneumonia, regarded as a relative contraindication to methotrexate. Here, we describe a case of Felty's syndrome resistant against corticosteroid, successfully treated with oral tacrolimus. In this case, the introduction of tacrolimus 3 mg/day improved all of arthritis, neutropenia, interstitial pneumonia. This shows the potential of tacrolimus as a new treatment strategy of Felty's syndrome with interstitial pneumonia.

P2-220

Two cases of enteropathic arthritis, successfully treated with adalimumab

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Conflict of interest: None

We report two cases of enteropathic arthritis, successfully treated with adalimumab (ADA). (Case 1) A 54-year old male developed ulcerative colitis (UC) and peripheral arthritis in April 2014. He was given mesalazine and corticosteroid, but intestinal and articular symptoms were aggravated from May 2015. ADA was administered and the clinical symptoms significantly improved. He is now in the remission. (Case 2) A 44-year old male who developed UC in 2001 and was treated with mesalazine.Multiple peripheral arthritis occured in 2009 and gradually worsened. Infliximab was administered in January 2011 and then articular symptoms had disappeared by 6 weeks after starting treatment and remained in remission for 22 months. However, articular symptoms worsened again, ADA was administered from August 2014. ADA improved his articular symptoms and the remission was achieved at 28 weeks. These cases suggest that ADA may be highly effective against enteropathic arthritis associated with UC.

P2-221

A case of intestinal perforation due to secondary amyloidosis associated with rheumatoid arthritis

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Conflict of interest: None

A-65-year-old woman with RA was admitted to hospital on September 9, 2015 because of abdominal pain and diarrhea. Bucillamine was started, but her disease activity had been high. A CT scan revealed thickness of small and large intestine. On the colonoscopy, the mucosa of most of the colon was edematous and erosive. Because vasculitis was suspected, PSL was increased to 20mg/day. On September 18, she complained about severe abdominal pain. A CT revealed intestinal perforation. She underwent emergency operation. The perforation 3mm in a diameter was noted at ileum. Histological examination of the specimen showed amyloid deposition around intestinal vessels. A diagnosis of secondary amyloidosis was made. Her abdominal symptom gradually improved because of the control of bowel movement and tocilizumab (TCZ). The intestinal perforation due to amyloidosis was rare but life-threatening complication of RA. In this case, the patients recovered because of successful surgery and TCZ.

P2-222

Clinical features of 8 cases of autoimmune-associated hemophagocytic syndrome

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Conflict of interest: None

Objective Few patients with connective tissue disease (CTD) are complicated by hemophagocytic syndrome, thus the clinical features of autoimmune-associated hemophagocytic syndrome (AAHS) in our patients were examined. **Methods** We reviewed CTD patients admitted to our hospital from January 1, 2013 to September 30, 2015. Eight patients matched proposed AAHS criteria. **Results** The eight patients with AAHS comprised two men and six women with a mean age 38.8 years. Three patients had systemic lupus erythematosus, two had dermatomyositis, and one each had mixed connective tissue disease, adult-onset Still's disease and microscopic polyangiitis. Five patients had fever and splenomegaly, and three had lymphadenopathy and skin rash. Median lab values were: white blood cells 4,750 /μl; hemoglobin 12.2 g/dl; platelets 97,500 /μl; lactic acid dehydrogenase 614 U/l; ferritin 4,482 μg/l. All six patients who underwent bone marrow aspiration had hemophagocytes in bone marrow smear. AAHS was diagnosed in two patients after four weeks of CTD treatment. Additional immunosuppressants were required in six patients, but all patients were cured. **Discussion** CTD patients who do not recover despite treatment should be checked for AAHS; these patients need more aggressive immunosuppressive therapy.

P2-223

Articular manifestations of gout in Japanese patients

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Conflict of interest: None

Background: Gout is one of the most common form of inflammatory arthritis. The characterization of articular symptom in Japanese patients with gout has not been extensively studied. Object: To characterize the articular manifestations in Japanese patients with gout. Methods: 864 patients (men/women: 853/11) with gout were included in the study. The articular manifestations at the first visit were analyzed retrospectively. Results: The mean age of gout onset was 43.7 years. The mean duration of gout at the first visit was 6.0 years. At first gouty attack, the most involved joint was the first metatarsophalangeal joint (1MTP) (50%), followed by ankle (24%) and knee (6%). The frequencies of involvement on 1MTP, ankle and knee at the first visit were 61%, 41% and 16%, respectively. In female patients, the mean number of affected joints was 3.3 and the joints in the upper limbs were affected in half of the patients. Discussion: The first gouty attack occurred on the 1MTP joint in half of the patients. The 1MTP joint was most frequently affected however, significant proportion of the patients experienced gouty attacks on ankle joint. The total number of affected joints and the involvement of upper limb were higher in women than in men, suggesting that females were more severe than males.

P2-224

Impaired glucose tolerance in patients with rheumatic diseases treated with corticosteroid

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Conflict of interest: None

Objective: To investigate the short-term impaired glucose tolerance in patients with rheumatic diseases treated with corticosteroid. **Patients and methods:** Fifty-eight patients (male:16, female 42, median age: 58 years old) with rheumatic diseases were retrospectively accessed their glucose tolerance in 10 days after the beginning of treatment with prednisolone (5mg or more). Patients with known history of diabetes were excluded from the study. If they have fasting or anytime blood sugar levels of 126mg/dl and 200mg/d or higher, respectively, they were considered

to have impaired glucose tolerance (IGT). **Results:** Twenty-one (36%) of 58 patients had IGT in 10 days of treatment of prednisolone. Fourteen of them (67%) showed IGT in 5 days of treatment. As patient characteristics, gender, rheumatic diseases, amount of prednisolone, level of HbA1c before treatment, CRP, Body Mass Index, and history of lifestyle disease were not different between patients developed IGT and non-IGT; however, older age showed statistical difference $p<0.001$). Oral hypoglycemic agent for 3 patients and insulin for 6 patients were necessary in addition to diet therapy. Conclusion: IGT appeared soon after the treatment of corticosteroid like in 10 days. Older age was suggested to be the risk factor for IGT.

P2-225

Clinical Features of Intractable Fibromyalgia

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Conflict of interest: None

[Purpose]To grasp the clinical features of intractable fibromyalgia (FM) and to determine abnormalities in labo date and the efficacy of pharmacotherapy.[Subjects] An intractability refers to patients with disabilities in daily life and who require assistance. They had undergone pharmacotherapy for 1 year or more but had not seen any improvement. [Method]As background for clinical features, medical history. In addition, focusing on the site and degree of pain, neuropsychiatric symptoms. were listed.In clinical examination, inflammation and autoantibodies were considered. Regarding treatment, present prescriptions were categorized according to drug efficacy and the validity was considered. [Results]1) In a complex social environment, external physical stress and physical neuropsychiatric stress are felt, resulting in hyperalgesia. Disorder of the autonomic nervous system causes a so-called dysautonomia.2) No inflammations or autoantibodies are manifested.3) Early diagnosis/ early treatment do not apply, resulting in doing the rounds of multiple departments without any clear diagnosis. Various treatments are carried out.4)Main constituents of pharmacotherapy are pregabalin, duloxetine, various drugs added.5) Does not lead to remission and remains within the bounds of pain relief.

P2-226

Two Cases of Malignant Mesothelioma that was Mimicked Difficult to Distinguish from Collagen Vascular Disease

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Conflict of interest: None

We have experienced 2 cases of malignant mesothelioma (MM) that was mimicked difficult to distinguish from collagen vascular disease. [Case 1] A 47-year-old man with FUO. Screening for occult cancer showed no apparent lesions. He was tentatively diagnosed as with AOSD. Methylprednisolone pulse therapy was effective but maintenance therapy with oral glucocorticoid and cyclosporine (CyA) was not. Finally, tocilizumab was introduced. Four months later, he was re-hospitalized because of acute abdomen with massive ascites. Peritoneal biopsy confirmed the diagnosis of MM. [Case 2] An 80-year-old woman with left pleural effusion. As anti U1 RNP antibody was positive, she was diagnosed with MCTD complicated with serositis, although the effusion was unilateral. As mesothelial cells were detected repeatedly from the effusion and slightly thickened pleura was revealed by chest CT scan, pleural biopsy was performed and MM was diagnosed. In this case, cell block cytology in the pleural effusion also did not confirm the diagnosis. In both cases, the levels of hyaluroninc acid in the effusion were very high. In such cases with difficult diagnosis, proactive aggressive approaches, such as biopsy, are necessary to differentiate MM from and other diseases.

P2-227

Two cases of patients with hematologic disease who were previously diagnosed as connective tissue diseases and treated

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Conflict of interest: None

Introduction: We encountered two patients with hematologic diseases who had been previously treated as connective tissue diseases. It is difficult to make a differential diagnosis when the autoantibody is negative or weak positive. **Case 1:** The 57-years-old woman was diagnosed as microscopic polyangitis 15 years ago in the previous hospital because of her anemia and high blood levels of C-reactive protein (CRP) and perinuclear anti-neutrophil cytoplasmic antibody. Despite the use of prednisolone (PSL), anemia became severe 2 years ago so she visited our hospital. The blood level of soluble interleukin-2 receptor (sIL-2R) was high and she had adenopathies. We diagnosed as Castleman disease after the lymph-node biopsy. **Case 2:** The 78-years-old man had a fever from 50 days ago. Chest X-ray showed a consolidation. Blood tests showed an elevation of CRP and antinuclear antibody was positive, so he treated with PSL in previous hospital. After that, he had anemia and thrombocytopenia so he visited our hospital. He had erythema and blood levels of IgG and sIL-2R were high. We diagnosed as diffuse large B-cell lymphoma after the skin biopsy. **Conclusion:** When blood tests reveal elevations of IgG or sIL-2R and when steroid is not effective, we should suspect of non-connective tissue diseases.

P2-228

A case report of RS3PE associated with lung squamous cell carcinoma

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Conflict of interest: None

【Background】RS3PE can be classified as a VEGF associated disorder.RS3PE is a rare disease,but it is easy to make a diagnosis based on knouledge and a treatment.There is no report of the considering measurement of plasma VEGF level in japanese practical clinics. 【Case Report】72-year-old,female.I have diagnosed her from the inspection value (CRP 13.6,RF71,ACA9.7,VEGF146,CYFRA8.2,ALP345,sputum cytology class V)as RS3PE due to lung cancer with idopathic pulmonary fibrosis,although she had been trated by PSL 10mg /day based on the diagnosis of RA associated with bucillamin induced pneumonitis.For the case,PSL has been increased to 20mg/day by the terminal lung cancer. 【Discussion】It was possible to diagnose her as RS3PE by the VEGF measurement.She has been sero-positive.High level VEGF after long term of steroid therapy may forecast the bad prognosis in this case.The rise of VEGF plays usefull and important role for diagnosing RS3PE ,such as the different method of the treatment of Elderly- onset RA and diagnosis about tumor.

P2-229

A case of Graft versus host disease (GVHD) associated arthritis long after peripheral blood stem cell transplantation

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Conflict of interest: None

A 35-year-woman developed chronic myeloid leukemia and received allogeneic peripheral blood stem cell transplantation in August 2000. After transplantation, chronic skin graft versus host disease (GVHD) had developed, and treatment with immune-suppresive drugs was started, but skin lesion didn't improved. Because of the polyarthralgia, she was ad-

mitted in our hospital in January 2015. Laboratory data reveled high level of CRP and positive test for RF, but not for anti-CCP antibody. Synovitis was identified by ultrasonography and MRI. Because of persistent skin lesions due to GVHD and positive test for anti-nuclear antibody, she was diagnosed as GVHD associated arthritis. Thereafter, treatment with MTX was initiated and her symptoms gradually improved. GVHD has pathological condition like auto immune diseases, and can show skin, eye and liver lesions. GVHD associated joint disorder is often attributed a limitation in range of motion like SSc, and rarely involved arthritis. In our case, arthritis was developed with GVHD long after allogeneic transplantation.

P2-230

A case of HLA-B39/B52-positive ankylosing spondylitis associated with Takayasu aortitis

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Conflict of interest: None

A 24-year-old man began to feel faintness and pain in jaws while receiving methotrexate (MTX) at 4mg/week for his ankylosing spondylitis (AS). Bilateral radial artery pulsations were decreased and arterial bruit was audible at cervix. Ultrasonography revealed homogeneous, midechoic, and circumferential wall thickening of bilateral common carotid arteries. Three-dimensional CT showed the wall thickening and luminal narrowing of both carotid and subclavian arteries. The diagnosis of Takayasu aortitis (TAK) was added to the patient. HLA-typing revealed HLA-B39/B52 positive and subtyping of the alleles revealed HLA-B 39:02 and B 52:01. Oral prednisolone (PSL) at 30 mg/day was started and MTX was increased to 6 mg/week. PSL dosage was decreased gradually without relapse. He became fully asymptomatic and laboratory studies showed no abnormalities after 4-year therapy, and PSL and MTX were discontinued. In addition to the significant association of HLA-B39 with HLA-B27-negative AS, the close association of the susceptibility to TAK and HLA-B39 or B52 is reported in the Japanese population. By presenting a case of HLA-B39/B52-positive AS associated with TAK, we would like to have an insight into the roles of HLA-B antigens in the pathogenesis of the disorders.

P2-231

A case of rheumatoid arthritis which developed after the onset of Coombs-negative autoimmune hemolytic anemia during pregnancy

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Conflict of interest: None

A 32 year-old-woman of childbearing 19 weeks had been admitted to the department of obstetrics in our hospital for severe anemia. The main laboratory findings on hospitalization were as follows: hemoglobin 5.3g/dl; LDH 3424IU/ml; total bilirubin 2.1mg/dl; haptoglobin <1mg/dl; negative Coombs' test. Coombs-negative autoimmune hemolytic anemia was suspected, but the anemia was improved after 4 weeks without any treatments except blood transfusions. Then the swelling of fingers and polyarthritis appeared, and she consulted us. First we diagnosed as Sjögren syndrome. While the value of serum CRP and MMP-3 kept within normal limits, the titer of anti-CCP antibodies was 6950 U/ml and that of rheumatoid factor was 357 IU/ml. Arthritis was gradually worsen and 2010 ACR/EULAR classification criteria was fulfilled, so the complication of rheumatoid arthritis was suspected. At 30 weeks pregnancy 5mg/day predonisolone was added. The value of DAS28-CRP on administrating predonisolone was 3.84, and that decreased to 2.16 at 40 weeks. After delivery the articular symptoms improved more and at 4 weeks postpartum that decrease to 1.28. The changes of hormone and immune balance which was induced by pregnancy might cause the temporary hemolytic anemia and actualized artiritis.

P2-232

A case of SLE-like clinical condition with the myelodysplastic syndrome (MDS) exhibited pancytopenia

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Conflict of interest: None

The case is a 57-year-old man. He had history of alcoholism and followed at psychiatry and was hospitalized until consultation a half year ago. He abstained from alcohol, but took the unbalanced diet. They received hyperuricaemia and psychiatry medications. He got a check-up at our hospital due to stomachache. The symptom seemed to be due to the constipation, but the blood exam showed severe pancytopenia. It was suspected of drug or malnutirition induced cytopenia. After the cancellation of the suspicious medicine and the nutrition care for one month, cytopenia did not improve, and change to our department for inspection. The bone marrow aspiration revealed the refractory anaemia and anti Sm antibody was positive. The insomnia and the violent behavior were persisted, we performed the cerebrospinal examination. The IL-6 level showed 4.76pg/ml, mild increase in cerebrospinal fluid. We thought about likelihood of the SLE, but cytopenia and the psychiatric symptoms improved without treatment and obtained the negative conversion of the anti Sm antibody and cerebrospinal fluid IL-6. The abnormalities of bone marrow remained by the reexamination three months later. By having discontinued several kinds of drugs, MDS-like cytopenia with immunological abnormalities seemed to be improved.

P2-233

A case of the RS3PE syndrome which caused agranulocytosis by esomeprazole

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Conflict of interest: None

【Case】The patient was 85-year-old woman. She was treating hypertension in nearby doctors. She was prescribed edema of both legs, tightening of both hands. Rheumatoid factor was negative. Symmetric arthritis of both hands and feet was detected by the contrasting MRI. We considered RS3PE syndrome, but we put off steroid introduction due to repeated urinary tract infection. She was diagnosed pneumonia, and admitted to our hospital. Pneumonia was cured by antibiotics, but high fever lasted. So we gave 15 mg of prednisolone. Her fever, tightening of both hands and edema of both legs were improved. Before starting to give prednisolone, we gave non steroidal anti-inflammatory drugs and esomeprazole. WBC level was decreased from 6620/μl to 2610/μl, so we stopped to give esomeprazole. WBC and neutrophils level were 2130/μl and 0/μl, and we gave G-CSF. After stopping of G-CSF, WBC and neutrophils level were 7780/μl and 5170/μl. 【Clinical significance】Esomeprazole is proton pomp inhibitor and optical isomer of omeprazole. Side effect incidence of esomeprazole is 45 of 3,394 cases in a use results investigation. Two cases WBC decreased were reported, but there was not the report of the agranulocytosis. We should carry out a blood test early, after starting to give esomeprazole.

P2-234

Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 cases in Japan

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Conflict of interest: None

[Object] Tocilizumab (TCZ) is used for the treatment of rheumatic diseases; however, concerns remain regarding its safety during and after

pregnancy. [Methods] Data from Chugai's safety database with TCZ use (April, 2005 to October, 2014) was retrospectively analyzed. [Results] In the study period, 61 pregnancies of 53 women were reported and outcome data was available for 50 pregnancies. TCZ therapy was continued during pregnancy in 2 cases, discontinued before conception in 9 pregnancies, in the first trimester in 28 pregnancies and timing of exposure were unknown in the remaining 11 pregnancies. There were 14 abortions (9 spontaneous, 5 induced) in 50 pregnancies and 1 fetal abnormalities (caudal regression syndrome) was reported among the induced abortion pregnancies. A total of 36 live births without abnormalities were reported, but 5 cases of low birth weight infants (3 cases of fetal growth retardation) and 1 neonatal asphyxia were found. In 2 cases, TCZ resumed during lactation, with no subsequent adverse events. [Conclusions] In this largest scale retrospective analysis, no increased rates of spontaneous abortion or congenital abnormalities were found after TCZ administration. However, because the number of women exposed to TCZ is limited, further studies are required.

P2-235

Rheumatoid arthritis patients treated with Certolizumab pegol in pregnancy and lactation

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Conflict of interest: None

【BACKGROUND】Recently, the treatment of rheumatoid arthritis (RA) has gradually improved, which has been expanded with the contribution of biological therapies or DMARDS. However, if pregnancy is desired, some drugs such as methotrexate must be stopped, and then the symptoms showed worsening. Certolizumab pegol (CZP) is less placental transfer property, it has also been reported as difficult to be migrated in the breast milk. It is considered to be relatively safe and effective drug among the TNF inhibitors upon use for that reason pregnancy and lactation. We reported four cases treated with CZP in pregnancy and lactation in our hospital. [Case] Case 1: A 41 years old RA patient was admitted early pregnancy to joint symptoms worsen, she was administered prednizolone (PSL), and the symptoms were improved. But after delivery as her symptoms showed worsening, She started treatment with CZP. Case 2: A 38 years old patient diagnosed with RA admitted joint pain from late pregnancy. She started treatment with CZP when pregnancy 31 weeks because of the high disease activity.【Conclusion】CZP treatment may be an useful strategy for management of active RA resistant to conventional DMARDs in women who desire to bear children.

P2-236

Two SLE patients with antiphospholipid syndrome nephropathy (APSN) gave birth without exacerbation and pregnancy induced hypertension

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Conflict of interest: None

Case1: SLE onset was at age 20, with lupus nephritis at age 22. She was in remission with low-dose prednisolone. She had four miscarriages at 7-20 weeks. Anti-CL antibody (aCL) and LAC were negative, but anti-PS/PT was positive. We suspected APSN by renal biopsies. At age 38, we treated with antithrombotic therapy and intravenous immunoglobulin after pregnancy was noted. However she had a threatened abortion and intrauterine infection at 15 weeks, gave birth to a 858 g boy at 25 weeks and 2 days. Case2: SLE onset was at age 10 with deep vein thrombosis at age 22. She had a miscarriage and stillbirth at 13 and 23 weeks at age of 24. ACL and LAC were positive. At age 28, she developed hypertension and renal dysfunction (Cr1.2mg/dl). Renal biopsy showed arterial wall thickening, so considered APSN. At age 32, we treated with antithrombotic therapy and plasma exchange after pregnancy was detected. She could not stand due to low back pain starting at 23 weeks, so gave birth to a 804 g girl at 26 weeks and 6 days. Conclusion: APSN is reportedly associated with positive antiphospholipid antibodies, hypertension, and renal dysfunction. However pregnancy outcomes with APSN are unclear, we consider these two cases without exacerbation and pregnancy induced hypertension to be educational.

P2-237

Transient osteoporosis of the hip in pregnant woman with Rheumatoid arthritis : A case report

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Conflict of interest: None

Transient osteoporosis of the hip (TOH) is an uncommon condition that cause temporary bone loss in the upper portion of the femur. Now we report a case of TOH in a pregnant woman with rheumatoid arthritis (RA) who treating with etanercept.The patient is 39-years-old with established RA, Steinblocker Stage IV, class 2, had been treated with etanercept and predonisolone. The bilateral coxalgia occurred in 33rd week of pregnant and developed in right hip. It revealed that bone marrow edema at left femoral head and neck in magnetic resonance imaging after delivery. According to history, physical examinations and image finings, TOH was diagnosed spontaneous pain relief occurred in three months.TOH is a rare, self-limited syndrome, characterized by sudden onset of joint pain followed by local osteopenia after several weeks, with spontaneous healing. The etiology of this disorder is unclear. It has been considered to be associated with hormonal change in pregnancy and obstruction of small blood vessels but not have been reported the relationship between RA and TOH. When RA patient with high inflammation or treated with corticosteroid, it may be hard to exclude infection or femoral head avascular necrosis. It is necessary to diagnosis carefully to avoid overtreatment for hip pain in RA.

P2-238

Clinical features of patients with rheumatoid arthritis classified by a novel assessment measure (joint index vector): A multicenter observational study based on the *NinJa* (National database of rheumatic diseases by IR-Net in JAPAN)

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Conflict of interest: None

Background: Joint index vector, Vji (x, y, z) is a novel assessment measure for RA. $|V|(=\sqrt{x^2 + y^2})$ represents disease activity, and z indicates functional disability.**Aim:** To examine the clinical features of patients with RA classified by Vji.**Methods:** Joint index (JI) of upper/large (UL), upper/small (US), lower/large (LL), and lower/small (LS) was defined as previously described[1]. Vji (x, y, z) for each patient enrolled in *NinJa* database was calculated as $x = JI_{UL} + JI_{US}$, $y = JI_{LL} + JI_{LS}$, and $z = JI_{UL} + JI_{LL} - JI_{US} - JI_{LS}$. Patients were classified into four groups by |V| and z values (G1: $|V| \leqq 0.1$, G2: $|V| > 0.1$ $|z| \leqq 0.2$, G3: $|V| > 0.1$ $z < -0.2$, G4: $|V| > 0.1$ $z > 0.2$).**Results:** Patients in G4 were the oldest and had the longest disease duration among the four groups. Class, Patient VAS, Physician VAS, and HAQ increased from G1 to G4 in order, while DAS28, SDAI, and MTX dose increased in the order of G1, G2, G4, and G3. Upper joint superiority ($x > y$) in G2, G3 and G4 was related with high level of SDAI, and lower joint superiority ($x < y$) in G2 was related with long disease duration and high level of HAQ.**Conclusion:** RA patients were classified into four clinical different groups by 3-dimensional joint index vector. **Reference:** 1. Nishiyama S, et al. Rheumatol Int. 2012:32;2569-71

P2-239

Development of the bone and joint tissue bank of patients with rheumatoid arthritis registered in Ninja data base (network-tissue-bank) to elucidate unknown pathophysiology in damaged joint

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Conflict of interest: Yes

[Objective] The technological development and the newly developed therapeutic agents against rheumatoid arthritis (RA) give us the chance to research the unknown pathophysiology using the tissue sample with new methodology symbolized by omics. So, the importance of study using tissues taken in orthopaedic joint surgery from damaged joint in RA is growing steadily. This study aimed to develop the bone and joint tissue bank of patients with RA registered in NinJa data base (network-tissue-bank). [Methods] Patients were recruited among the patients with RA already registered National Database (NinJa) at 5 hospitals of National Institute of Hospital. Synovial tissues resected in surgeries of elbow, hip, and knee joint from 102 patients who gave informed consent were stored in each hospital and sampling information was registered in NinJa. The synovium samples were assessed by hematoxylin and eosin (HE) staining using Rooney's score, which were analyzed for its relation with clinical data. [Results & Conclusion] We have successfully developed network-bank of synovial tissue stored in each hospital using NinJa system effectively. Sampling site variation in synovial tissue and inter-observer variability, however, should be improved for further development.

P2-240

RA patients with high levels of anti-CCP antibody and treated with high dose glucocorticoid frequently fall: five years of the TOMORROW study

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Conflict of interest: None

[Object] The aim of this study was to prospectively investigate factors influencing falls in patients with rheumatoid arthritis (RA) compared to controls for 5 years. **[Methods]** We started a prospective cohort TOMORROW study in 2010. We compared the frequency of falls in 208 RA patients and 205 age- and sex-matched volunteers from 2010 to 2015 and analyzed risk factors for falls in patients with RA using multivariate regression analysis. **[Results]** No significant difference in the rate of fallers was evident between RA and control group for 5 years. However, the incidence rate of falls was significantly higher in patients with RA (0.39/person-year) than controls (0.21/person-year, P=0.002). Linear multiple regression analysis revealed that anti-cyclic citrullinated peptide antibody (CCP) at entry and mean values for glucocorticoid dosage (GC) over the 5 years were apparently related to the number of falls in RA patients (β = 0.295; $p < 0.001$; $\beta = 0.160$, $p = 0.024$, respectively). **[Conclusions]** The incidence rate of falls was significantly higher in RA patients than controls. RA patients with a higher titer of anti-CCP and higher dose of GC frequently fall.

P2-241

Correlation between sleep disturbance and health status including psychological states in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To assess the correlation between sleep disturbance and health status and psychological status in patients with RA. Methods: Sleep disturbance was evaluated with PSQI, while health status was examined utilizing with SF-36. Psychological status such as depression and anxiety was assessed utilizing CES-D, STAI and HADS. The data were analyzed utilizing Spearman's rank correlation coefficient. Results: 112 RA patients (18 males and 94 female) were enrolled. Patient characteristics were as follows: average age: 54.8, duration: 11.4 years, PGA: 23.2mm, EGA: 16.2mm, SJC: 2.7, TJC: 2.2, Pain-VAS: 22.3mm. There is no statistically significant difference between PSQI and age, disease duration, SJC, TJC and EGA, while statistically weak correlation was shown between PSQI and PGA (ρ=0.2592, p=0.0058). PSQI was correlated with STAI-State (ρ=0.5295, p<.0001), CES-D (ρ=0.5165, p<.0001), HADS-Anxiety (ρ=0.4139, p<.0001) and HADS-Depression (ρ=0.4182, p<.0001). In health status evaluating SF-36, PSQI was not correlated with PCS (ρ=-0.0370, p=0.6983), while it showed moderate correlation with MCS (ρ=-0.4186, p<.0001).

P2-242

Laugh and smile questionnaire for rheumatoid arthritis patients

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Conflict of interest: None

Object: Laughter therapy and positive thinking is important treatment for all diseases. Patients with rheumatoid arthritis (RA) answered the "Laugh and Smile questionnaire". Methods: Eighty two patients (13 men and 69 women, mean age 67 years) answered eight items at two orthopedic outpatient facilities (Sakai and Itsuki hospitals). Results: Among the all items, the highest score was (1) laughed at one time (20-50 year-olds) 43/82;(2) mild laughter 40/82;(3) recent instance of loud laughter 35/82;(4) laughter at funny situation 52/82;(5)Laughter during conversation 27/82;(6) at the medical center, laughter to family and social service 26/82; with nurses and receptionist 15/82; and doctors and patients 12/82;(7) when your doctor tickled, get smiles 35/82; did not answer to sexual harassment cases in this study, (8) smiling after answering this questionnaire, 53/82. RA patients were no different than non RA patients, regarding laughing habits. RA patients strongly desire to share laugh with their family and social service, compared with non-RA patients. Conclusion: RA patients would benefit from laughter therapy.

P2-243

Relationship between nurse's knowledge and skills and approach to management of RA

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Conflict of interest: None

【Objectives】The aim of this study was to investigate whether nurse's knowledge and skills about rheumatoid arthritis (RA) treatment and recommendations affect nurse's approach to management of RA. 【Methods】A questionnaire on EULAR recommendations, treatment and management of RA was offered to nurses between May and June 2015. 【Results】Eighty one nurses in 5 RA center (Osaka Medical Hospital, Aino Hospital, Yodogawa Christian Hospital, Takatsuki Red Cross Hospital, and Arisawa General Hospital) answered questionnaires. 76% NS recognized Remission criteria and 42.5% nurses recognized DAS 28-CRP components. However, Recognition of EULAR recommendations were poor (6.25%). Familiar to field of knowledge differ among the institution. The nurse, who had high agreement and application of EULAR recommendations, were more positive approach to management of RA. 【Conclusions】Nurse should promote knowledge and skills about treatment, management and recommendations of RA.

P2-244

Understanding of drug usage in patients with rheumatoid arthritis: from the results of questionnaire at public lectures

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Conflict of interest: None

Object: In patients with rheumatoid arthritis (RA), their powers of understanding of drug usage are varies widely. In the present study we investigated whether the patients could handle their prescribed drugs correctly in unexpected situations. **Methods:** We analyzed questionnaires collected from RA patients at public lectures held in Nara city. The questionnaires were filled out anonymously. The items contain disease duration, current treatment for RA (use biologic agents or not), and how to handle the drugs in the case of being illness. According to the last item, the answers were divided "correct" or "incorrect". The patients were divided into two groups with regard to this answer (correct or incorrect). We compared two groups. **Results:** 121 questionnaires were collected. 86 out of those questionnaires were valid and we analyzed them. There were no difference between two groups as regards disease duration. The proportion of patients using biologic agents in correctly answered group were significantly larger than incorrectly answered group. **Conclusion:** It is suggested that the patients using biologic agents have more chance to receive explanations about drugs. The methods for explanation of drug usage for the patients who do not use biologic agents is to be discussed.

P2-245

Analysis of side effect management behavior of rheumatoid arthritis outpatients on methotrexate and biologics

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Conflict of interest: None

[Object]We investigated side effect management behaviors of outpatients on MTX or Bio. [Method]The subjects were 106 female RA outpatients older than 20 years at T hospital.48 were on MTX alone (MTXG). The rest were on Bio alone or Bio and MTX (BIOG, n=58).We conducted interviews with questionnaires and collected information from medical records. Side effect items were selected from those described in package inserts of MTX and Bio. The Ethics Committee of T University Faculty of Medicine approved the study protocol. [Result]Mean Age of BIOG was 64.1±13.3 years, while MTXG was 63.9 ±13.0 years. There were significantly more BIOG subjects whose morbidity period was longer than 1 year and who had already taken their temperature on examination day. The ADL score of BIOG were significantly lower. There were significantly more BIOG subjects over the age of 65 who had received a pneumococcal vaccine. There were significantly more MTXG subjects who did not wear masks. Nearly 90% of subjects in both groups were able to visit hospitals in an emergency. [Conclusion] It is necessary for nurses to notice side effects according to package inserts in order to help patients manage these side effects and recuperate safely.

P2-246

Current state and problems of the rheumatoid arthritis patients using biological agents in our hospital

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Conflict of interest: None

(Objective) In treatment of the rheumatoid arthritis, it is extremely important to maintain patient's adherence for continuous treatment. This study is aimed to find out the opinion of the patients using biological agents (BIO) and to assess current state of our RA management in order to help our future RA care. (Methods) We performed questionnaire survey about satisfaction for the treatment, relationship to medical practitioners and patient's demands to 85 RA patients who consulted our hospital and treated with BIO between July 2015 and October 2015. (Results) 33% of patients were satisfied with treatment before using BIO while 92% of patients were satisfied after using BIO. Many patients were satisfied with current treatment because of their improvement of pain and ADL. About 90% of patients could tell their condition to doctor and nurse well however some patients who did not take self-injection practice felt few relationship to nurse. Some patients needed RA classroom, foot care, meal and exercise and drug information. (Conclusion)It became clear that our efforts in RA treatment with BIO advanced to the almost right direction however some issues were identified simultaneously. Based on this result we have to improve adherence and satisfaction of RA patients from now on.

P2-247

Approach to introduce original support device for self-injection of biologic therapy drug by RA team medical care relief patients from anxiety for injection

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Conflict of interest: None

[Purpose] Because Certolizumab Pegol (CZP) therapy has no self-injection device (SID), patients often have anxiety for injection. Thus we made SID for CZP. [Methods] 1) Extraction of necessary condition for SID, 2) Preparation of ancestor of SID by occupational therapist, 3) Review by medical care team for material of SID, 4) Hearing of opinion to patients, and 5) trial to use in medical practice. [Results] Round and heat insulating material was selected for SID. Oval 3x3 cm hole was created on the tip of SID to see removal of air easily. Three patients having anxiety for injection was selected for the trial. Procedure for SID was explained and training was carried out. The reason for anxiety was classified as follows; no confidence due to advanced age: 2, hate injection due to pain; 1, and failure of grip due to RA: 3. Review of the patients; easy to wear and use, and decrease scary emotion because of hiding of tip of injector. After 3-6 times of practice, self-injection was introduced. [Conclusions] SID enables introduction of self-injection for patient relieving patients for anxiety. We can get many good advice from staff working various job category because team medical care was carried out in outpatient service of RA. This trial clearly shows importance of team medical care.

P2-248

Reconfirming nursing-care plans and patient concerns through interviews using anInterview Sheet

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Conflict of interest: None

Purpose:We investigated the effectiveness of use of an Interview Sheet introduced by Kanzaki et al. (2013)by nurses to elucidate patient problems and concerns. **Methods**: Nine Rheumatoid Arthritis (RA) nurse specialists interviewed 21 hospitalized RA patients using the Interview Sheet. **Results**: While 19% of the patient concerns in the Interview Sheets did not differ from those in the patient history documents, 71% were new concerns. The new concerns included8for RA and3each for social backgrounds and other illnesses (total of 19 concerns). Nursing plans were designed for three of these 19 concerns (16%) (2 RA and 1other illness cases). Some of the reasons for not considering 16 of these 19 (84%) concerns included "the information was provided to the nurse-in-charge," "the problem could be solved through on-the-spot guidance," and "aconsultation and request for collaboration was made with an external specialist." **Conclusion**: The Interview Sheets elucidated 71% new patient concerns. Although new nursing-care plans were designed for only 16% of these, the ability to provide individual guidance using the Interview Sheets indicated their usefulness during interviews.Further work will be needed to educate the nurses to amend the patient history forms to include the Interview Sheets.

P2-249

Survey of living situation of rheumatoid arthritis patients; bed or futon, Japanese-style toilets or Western toilets?

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Conflict of interest: None

Purpose: The aim of this study is to investigate the situation of living of rheumatoid arthritis (RA) patients, in terms of the use of bed or futon, and Japanese-style toilets or western toilets. Method: The 200 RA patients who visited our outpatient clinic were enrolled in this survey. These patients answered the HAQ questionnaire and were asked whether they use bed or futon when they lying at night, and whether their home toilets were Japanese-style or western. Results: The bed users were 137 and futon user 63. There were only 3 cases whose house toilets were Japanese-style. Most patients answered bed was easier to get in and out than futon use. In a similar way, Western toilets were easier to use than those of Japanese-style. Conclusion: Futon and Japanese-style toilets were more difficult to use for RA patients in daily life situation.

P2-250

Disturbed body image in rheumatoid arthritis patients who requires surgical intervention

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Conflict of interest: None

【Introduction】 Body image assessment tool (BIAT) has been reported to be a reliable and valid tool. Recent development in pharmacological treatment improved the disease control of patients with rheumatoid arthritis (RA), and the change of body image of the patients might influenced the surgical indication. 【Method】120 patients with RA were divided into two groups of patients who didn't require the surgical intervention (non-operative group) and who underwent surgery (operative group). The clinical evaluation included the use of biologic agents, pain VAS, HAQ-DI, disease activity (DAS28-CRP) and body image assessed by BIAT. 【Result】In the operative group, pain VAS and HAQ-DI were significantly higher ($p<0.01$) and BIAT was significantly lower when compared with non-operative group ($p<0.01$). 【Discussion】 The result of this survey showed the disturbance of body image in the operative group. To assess the body image might be useful to understand the patients' expectation and proper indication of the surgery.

P2-251

The influence of the prevalence of the enthesophytes in the entheseal insertions of heel during the changes of foot alignment

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Conflict of interest: None

[Objectives] We aimed to examine the influence of the prevalence of the radiographic enthesophytes in the entheseal insertions of heel during the changes of foot alignment. [Methods] The subjects consisted of 424 feet in 212 patients evaluated screening or disease activity of rheumatoid arthritis (RA) or spondyloarthritis (SpA) . Independent t-tests were used to compare the non-weight bearing foot alignment angles; lateral taro first metatarsal angle (TM1A), talo-calcaneal angle (TCA) and canlcaneal pitch angle (CPA). [Result] The mean age was 58 years old, 142 female. The RA and SpA were 122 patients and 60 patients, each. The patients who had AE were significantly elderly (63.5;$P<0.01$) and had significantly low TC angle (45.4°;<0.01). The patients who had PE was significantly elderly (64.1;$P<0.01$) but didn't have statistical causation with foot alignment. Multiple regression analysis demonstrated that significant factors were age (1.05 with 95%CI 1.03~1.06 in AE group, 1.07 with 95%CI 1.03~1.12 in PE group) and TCA (0.95, 95%CI:0.91~0.99 in AE group). [Conclusion] The prevalence of AE and PE increases by advanced age and the prevalence of AE decreases by low TCA.

P2-252

The cases of gouty tophi with surgical treatment

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Conflict of interest: None

[Object] Since the medical treatment to control hyperuricaemia improved, the case of gouty tophi required surgical resection were decreased. We assessed the cases of surgical interventions. [Methods] We retrospectively reviewed the eight patients with chronic gouty tophi seen at our hospital during 2010 to 2015. There were seven men and one woman with an age ranged 56-86 years. [Results] The time of medical treatment of hyperuricaemia were ranged 0-45 years. Only two patients reported a good medical control, and others were poor control or no medical treatment. The gouty tophi deposited 4 patient in single nodule and 4 in multiple site. Clinical diagnosis of gouty tophus was defined in 6 cases without (aspiration) biopsy method. Surgical treatment was performed 5 cases, due to large tophi mass affecting skin ulcer in three cases, large mass affecting range of joint motion in one case. [Conclusions] This study represented that larger tophi correlated with the patients of poor controlled hyperuricaemia. Surgical treatment of the tophi was recommended to reduce the skin problems, functional problems of adjacent joint, differentiate to infectious disorders, and reduce the uric acid pool that would reduce the gout attack.

P2-253

Elderly onset Rheumatoid Arthritis after total knee arthroplasty

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Conflict of interest: None

Objective: Reports have increased of elderly onset rheumatoid arthritis due to the aging society (EORA). Elevations in serum inflammatory markers after total knee arthroplasty (TKA) mimicking infection, and mistaken diagnosis could lead to inappropriate debridement and antimicrobial chemotherapy. We experienced a case of EORA after TKA. We examined the frequency of EORA after TKA. Methods: A total of 112 osteoarthritis (OA) patients were enrolled from 2010 and 2014. We examined the incidence of EORA and the blood test feature of these patients around the operation. Results: Two patients (1.8%) diagnosed with RA before TKA, and 5 (4.5%) after TKA. All patients were positive for anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF) at diagnosis. The average CRP value was 0.79 mg/ml (0.12-2.65), and average ESR value was 28.6 mm/h (13-67). Two cases were positive for CRP and 4 cases for ESR before TKA. Conclusion: Correct diagnosis could reduce inappropriate debridement and antimicrobial chemotherapy. There is a case for developing RA after TKA. It is necessary to consider RA as part of the differential diagnosis in cases aggravation of inflammatory findings after TKA.

P2-254

Effectiveness of multi-vitamin on rheumatology

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Conflict of interest: None

Introduction: Previous reports showed methotrexate (MTX) induces superoxide production. Multi-vitamin possibly detoxify superoxide. We used multi-vitamin for MTX recipients to avoid adverse effects. We here report the effectiveness of multi-vitamin in our clinical practice. Methods: We extracted 72 MTX recipients who had used folic acid until switching to Panbitan (TM) during 5 years from October 2010 to September 2015. We retrospectively analyzed the indication and the effect. Results: Of all 72 patients, RA were 55 (76.4%), spondyloarthritis 8 (11.1%), and others 9 (12.5%), respectively. The mean MTX dose was 10.2mg (4-16mg), the mean folic acid dose was 7.8mg (5-15mg), and the mean amount of folic acid which Panbitan containing was 5.5mg (3-9mg). The reasons of switching the drug were liver function impairment; 36 (50.0%), stomatitis; 11 (15.3%), and malaise; 8 (11.1%). Twenty (55.6%) out of 36 showed improvement of liver function test, 8 (72.7%) out of 11 stomatitis, and 4 (50.0%) out of 8 malaise. Improvement tended to be obtained in higher MCV group. Conclusion: Multi-vitamin is potentially effective for side effects control in MTX recipients.

P2-255

An Analysis of Closed Claims of Relatively Rare Rheumatic Diseases in Japan

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Conflict of interest: None

Objective: The objective of the present study was to evaluate malpractice of relatively rare rheumatic diseases and determine contributing factors to negligence for improving patient safety **Methods**: We analyzed 57 closed claims of relatively rare rheumatic diseases extracted from 8,530 claims processed between July 2004 and July 2014 by the Tokyo headquarters office of Sompo Japan Nipponkoa Incorporated, a leading malpractice insurer in Japan. **Results**: Patient allegations were most commonly medication-related, and planning/ordering and treatment performance were vulnerable to breakdown in clinical process.Management factors were the most common contributing factors to negligent practice, with about 30% of cases accompanied by patient factors. **Conclusions**: Clinical practice carries a high litigation risk related to pharmacotherapy, and therefore, requires particular prudence when prescribing and monitoring medications. Medical facilities should promote safety cultures in order to prevent malpractice, and clinicians need to exercise prudence in treating patients presenting with atypical or complex clinical findings.

P2-257

A case of severe aortic stenosis developed in a patient with spondyloarthritis

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Conflict of interest: None

Spondyloarthritis (SpA) is characterized by chronic low back pain (referred to as inflammatory back pain), enthesitis and arthritis, but it also shows uveitis and valvular diseases. We here report a case of severe aortic stenosis (AS) whose underlying disease is SpA. A 33 year-old woman who had bronchial asthma and atopic dermatitis was referred to our department for the treatment of asthma. Loud systolic and diastolic murmur was audible at 2LSB. Echocardiogram revealed that her aortic valve was tricuspid with the blood flow velocity of 3.53 m/sec and valve area of 0.76 cm^2. The AS was severe and aortic regurgitation was grade 3. She noticed chronic lumber pain in 2013 suggestive of inflammatory back pain. On examination, chest expansion test was 1.5 cm, which were lower than the normal limit. Cervical rotation was normal, and Schober test was negative. CT scan revealed sclerotic change and joint surface irregularity of sacroiliac joint, which was predominant on iliac side (NY criteria grade 2 both sides). According to cardiologists, the severity of As is incompatible with her age, therefore we thought that her AS developed as a part of organ involvement. We suggest that when severe valvular diseases were seen, presence of SpA should be taken into consideration.

P2-258

A case of radiation osteitis mimicing spondyloarthritis

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Conflict of interest: None

Spondyloarthritis (SpA) is a disease characterized by inflammatory low back pain and sacroiliac arthritis. SpA usually occurs in young, and its prevalence is 0.1-15% in age between 8 and 45. Here we report a case referred as SpA, which was finally diagnosed as radiation osteitis. A 62 year-old woman was diagnosed as uterine stageIIIb cervical cancer in 2003. Radiation therapy was selected. She totally received 30Gy on intra-pelvis lesion and 50Gy on extra-pelvis lesion, respectively. She noticed right shoulder and low back pain in 2011 and visited a spinal surgery clinic. Lumber spine MRI revealed 5th lumber compression fracture. Low back pain gradually expanded to right hip and right thigh back on March 2015. Pain was strong upon waking, and improved in the daytime. Pelvis MRI revealed high STIR signal on iliac side of sacroiliac joint. SpA was suspected and referred to rheumatology department. Although symptoms and imaging findings was consistent to SpA, age did not match. We diagnosed her as osteitis related to radiation on her pelvis. If there is a history of radiation to the pelvis, it is necessary to consider the radiation osteitis in the differential of SpA.

P2-259

A case of intestinal abscess while treating giant cell arteritis

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Conflict of interest: None

[Case] Fifty-nine year old, male. He entered our hospital due to fatigue, headache, and transient dimmed vision. He showed fatigue and fever 2 month before first presentation, and was aware of pain in his forehead a month before visiting. In first visit at our hospital, he also complained jaw caudation and transient dimmed vision. Leukocytosis

and elevation of CRP were seen in laboratory data. Thickening of vessel wall and stenosis in bilateral internal carotid artery were detected by enhanced computed tomography (CT). He was diagnosed as giant cell arteritis, and treated with prednisolone. A month after inducting prednisolone, he suddenly showed melena, and tumor lesion, which was suspected of abscess were observed in ascending colon by enhanced CT. Though antibiotics were started, the tumor was rapidly got larger and made fistula to other site of intestine. As the abscess were not diminished, though several tube for drainage were made in abscess, subtotal resection of colon was performed. After the operation, intestinal perforation was made, and died due to sepsis. [Conclusions] The abscess is thought to be made by intestinal infection, such as diverticulitis. The intestinal infection in steroid dosing should be warranted.

P2-260

A case of TINU syndrome diagnosed by renal biopsy after presenting uveitis prior to proteinuria

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Conflict of interest: None

Forty-year-old woman has had general fatigue and bilateral blurred vision since 2015 July. She saw her primary doctor and been diagnosed as uveitis and prescribed 10 mg/day of prednisolone. Two month later, she had been having high fever everyday. Because of ANA positivity in her serum, she was consulted our hospital. Her laboratory data showed MPO-ANCA positivity and proteinuria. A percutaneous renal biopsy revealed a diffuse interstitial nephritis with infiltration of neutrophil and eosinophil granulocytes, many lymphocytes and plasma cells without granuloma. On this basis, we diagnosed her as Tublo-Interstitial Nephritis and Uveitis Syndrome (TINU). It was suggested that TINU was related some antibodies, which might react both uvea and interstitium of kidney. Tan Y et al. reported that modified C-reactive protein would be auto antigen localized at both uvea and interstitum of kidney. TINU is caused by drug, infection and autoimmune-disease and so on. However, our case was not diagnosed as any those diseases. She has many auto-antibodies (anti-dsDNA Ab, MPO-ANCA, PR3-ANCA) leukocytopenia and hypocomplementemia. We considered that she had some autoimmune problems and this caused her TINU via some autoantibodies for uvea and interstitum of kidney.

P2-261

A case report of an adult patient with fever of unknown origin and characteristics of Kawasaki disease

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Conflict of interest: None

(background) Kawasaki disease (KD) is characterized by persistent fever, mucous membrane hyperemia, cervical lymph node enlargement, exanthema and desquamation. Though KD is almost exclusively an illness of children, with about 80% of the patients under the age of 4 year, a few cases of adult KD have been reported in the world. We report an adult patient with fever of unknown origin and characteristics of KD. (Case) A 39 year-old male developed fever and polyarthritis 25 days before visiting our hospital. He also presented hyperemia in his conjunctivas and pharynx, and his palm and plantar went red firstly and showed desquamation then. All blood cultures and Streptococcus rapid tests were negative and antibiotics didn't improve fever. After screening of infection, collagen disease and malignancy, aspirin (0.4g/kg/day) was prescribed at 4th day and decreased fever and elevated CRP. At 15th day, IVIG (0.8g/kg) was prescribed to completely suppress persisting low grade fever and slightly elevated CRP and the treatment succeeded. Complete suppression of inflammation by aspirin and IVIG indicate that FUO might be KD although absence of coronary artery aneurysm conflicts with it. Antibody for Yersinia pseudotuberculosis is known as a mimic of KD was negative.

P2-262

Colchicine was effective in 6 -year-old boy with acute acute pericarditis

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Conflict of interest: None

«Case» A 6 year-old boy was admitted to a general hospital with prolonged fever for five days. First, cellulitis was suspected in the right hip and treated with ABPC / SBT. At day 7, he began to suffered from a chest pain, abdominal pain, orthopnea and eyelid edema and was treated with MEPM and VCM. At day 8, a Xray, contrast CT, heart echocardiography were taken and pulmonary hypertension and right heart failure were found. Furosemide, heparin and oxygen were started and the symptoms were improved. But at day 20, eyelid edema and cardiac effusion was found again. He was diagnosed with acute pericarditis and began to be treated with aspirin. Because there was no improvement, he was referred to our hospital. Although he had cardiac effusion, he was generally in good condition and aspirin was decreased. But again he started to have high fever and CRP increased. Aspirin was switched to ibuprofen (20mg/kg/day) with little effect. At day 43, colchicine was started and ibuprofen was increased. Then cardiac effusion disappeared gradually. Currently there is no relapse of pericarditis. «Clinical significance» Acute pericarditis is rare in children. Combination therapy of NSAIDs and colchicine is effective not only in adult but also in children with acute pericarditis.

P3-001

Orthopedic surgeries for RA using NinJa in 2014

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Conflict of interest: None

Aim Analyze/report RA-related orthopedic surgeries performed in '14 using NinJa. **Method** Presence or absence, type, frequency, etc. of surgeries examined in 15023 patients registered in '14 (1,2078 women, 2945 men) & compared with '03 to '14. **Results/Discussion** Of 15023 patients in '14, 513 patients/645events (3.4%/4.3%) underwent RA surgeries. The number of RA surgery cases decreased from 8.5% in '03 to 3.4% in '14. In '14, RA surgeries to total patient number ratios were (per type) 2.09%(TJA), 0.23%(synovectomy), 1.01%(arthroplasty), 0.28%(arthrodesis), 0.11%(tendon repair) & 0.23%(revision TJA). Medication: 63.8%, 27.0% and 0.29% of patients received total MTXs, total biologicals & total JAK inhibitors, respectively: an increase. In the main-Bio group, the rate of RA surgery peaked at 15% in '06 and decreased thereafter to 6.4% in '14. In the main-MTX group, the rate of surgery also decreased from 9.5% in '03 to 3.2% in '14. Among patients receiving JAK inhibitors, eight surgeries had been performed. Although the number of surgeries decreased with increasing use of drugs in the Bio and MTX groups, the rate of decrease was decreasing. We plan to continue to follow up on changes in surgery rates with the emergence of new drugs such as JAK. Follow up planned.

P3-002

Advanced chronic kidney disease might make disease control difficult in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify the correlation of basal estimated glomerular filtration rate (eGFR) with chronological change of disease activity of rheumatoid arthritis (RA). [Methods] Using data from 3909 RA patients with eGFR<100 mL/min./1.73m2 in the year 2012, registered in the large cohort database (NinJa: National Database of Rheumatic Diseases by iRnet in Japan) sequentially all in 2012, 2013 and 2014, DAS28-ESR, DAS-CRP, CDAI, and SDAI were compared between 2012, 2013 and 2014 in group A (60≦eGFR<100), group B (30≦eGFR<60), and group C (eGFR<30). Friedman test was employed to test the significance of difference. [Results] All of DAS28-ESR, DAS28-CRP, CDAI and SDAI were significantly improved in group A (all p<0.0001) and B (DAS28-ESR p=0.0037, DAS28-CRP p<0.0001, SDAI p=0.0031, and CDAI p=0.0075). Meanwhile, all of RA disease activity score and index as above were not significantly improved in group C. [Conclusion] Advanced chronic kidney diseases (stage G4 and G5) might make disease activity control difficult in RA.

P3-003

Changes in clinical conditions of patients with rheumatoid arthritis in our University Hospital during recent 11 years

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Conflict of interest: None

[Objectives] Since Treat to Target (T2T) is a major strategy for management of rheumatoid arthritis (RA), we intended to clarify the actual treatment conditions of RA patients during recent 11 years in our hospital. [Method] We have registered clinical data of patients with RA in a database of our hospital. 4862 of cumulative total number of RA patients during 11 years were included. This study was approved by Ethics Committee of Toho University Medical Center Omori Hospital. [Result] 136 RA patients (mean age, 57.9 year-old; disease duration, 9.3 years) were registered in 2005. The patient number was increased every year to 860 patients (61.7; 9.6) in 2015. The mean values of the clinical indexes in 2004 and 2015 were as follows: DAS28-ESR, 3.66 to 2.68; patients with remission by DAS28-ESR, 21.3% to 48.7%; HAQ-DI, 0.77 to 0.39; patients undergoing methotrexate (MTX) therapy, 46.3% to 59.9%; MTX dose, 6.9 to 8.9 mg/week; patients undergoing biological agents, 11.8% to 29.9%; patients undergoing glucocorticoid (GC) therapy, 52.2% to 32.0%; mean GC dose, 5.0 to 4.2 mg/day. [Conclusion] Clinical conditions including not only inflammation measures but also outcome measures of patients with RA have considerably improved during recent 11 years in our University Hospital.

P3-004

Medical treatment of rheumatoid arthritis for elderly in the latter stage of life

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Conflict of interest: None

Object: Recently, patients of rheumatoid arthritis (RA) are aggressively treated by methotrexate (MTX) and biological drugs. However,it is often difficult for advanced elderly patients to treat ideally for RA. So, we investigate situation of RA treatment for advanced elderly patients. Method: We investigate advanced elderly outpatient of RA in our hospital at October 31th 2015. Then, we classified them by age; 75-79, 80-84, over 85 years old and investigate their clinical data, treatment, and so on. In addition, we compared them with patient who were under 65 years old.Result: When we compared advanced elderly patients who were 75 years or older with other patients, Serum Cr, eGFR, and dose of MTX were significantly low and little. However, there were no significant difference about disease activity. When we compared the super elderly patients who were 85 years or older with other patients, disease duration were significantly long and dose of MTX were little. Conclusion: Dose of MTX tended to decrease in advanced elderly patients because of decreased renal function and risk of infection.

P3-005

The association of clinical features and HLA-B27 in Japanese ankylosing spondylitis patinents in Juntendo hospital

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Conflict of interest: None

(Object) Ankylosing spondylitis is highly associated to HLA-B27,but HLA-B27 positivity is extremely low in japanese. therefor many physician has low clinical experiment and some patients was overlooked or misdiagnosed. We had questionnaire survey to AS patients and analyzed the association of the clinical features and HLA-B27. (Method) We had questionaire survey to AS patients who met the modified New York criteria in our hospital. The clinical characteristics, laboratory data, imaging and HLA-B27 positivity were collected. (Result) AS patients who met the modified New York criteria were 61 cases in November 11. Fifty were male (82.0%) and 11 were female. Forty-nine were Japanese, 7 were Chinese and 5 were Korian. Forty-one cases (93.2%) were HLA-B27 positive in all examined patients (n=43). With limited in Japanese, 30 cases (93.8%) were positive (n=32). Inflammatory back pain was seen in 50 cases (82.0%), enthesitis was seen in 25 (41.7%). Thirty-two cases (52.4%) has bamboo spine, and in these cases 20 were HLA-B27 positive. Twenty-three (37.7%) has uveitis, and in these cases 17 were HLA-B27 positive. (Conclusion) In Japnese AS patients, HLA-B27 was positive in about 90%, and B27 positivity was associated with bamboo spine and uveitis co-mobidity.

P3-006

Long-term prognosis of patients who have vistied our hospital due to connective tissue diseases

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Conflict of interest: None

【Background】In recent years, larger number of drugs can be used for the treatment of connective tissue disease. Treatment options have increased. It is believed that the improvement of life prognosis is seen along with the improvement of technology, but in clinical practice, cases of death can be found in time. It is necessary to verify whether the progression can be seen in the life prognosis with additioning treatment options. 【Objective】To reveal the long-term prognosis of connective tissue disease in our hospital. 【Methods】From all patients who visited our office since 2008, we extract the patients who have registered in specific disease name (SLE, polymyositis / dermatomyositis, vasculitis syndrome). Then we brought out the rates of survival and the causes of death in these patients, 【results】. The number of patients who have been diagnosed specific disease in our hospital / the numbers of patients who died the number of patients within this period are 393 / 27 in SLE, 63/9 in myositis, 103/15, 48/1 in ANCA-associated vasculitis. The causes of deaths in these people were of malignancy, original illness and infection in most

part.

P3-007

Oxidative stress and arteriosclerosis in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the oxidative stress in patients with rheumatoid arthritis (RA) and to investigate the association with disease activity and risk factors for atherosclerosis. [Methods] Twenty-two patients with RA (age 59.6±8.9 year old) who had not been changed their treatment for more than three months and whose disease activity was moderate to low. The derivatives of reactive oxygen metabolites (dROMs) and the biological antioxidant potential (BAP) were measured by portable spectrophotometer. And oxidative stress index (OSI) was calculated (dROMs / BAP × 8.85). [Results] dROMs were high (827.0±237.2 U.CARR, range 482-1431) and BAP was not decreased (3125.5±571.3 μmol/L, 2381-4672). OSI was also high 2.43±0.87 (0.94-5.0). OSI and dROMs were positively related to CRP, HbA1c and cardio-ankle vascular index. BAP was positively related to DAS28. [Conclusion] Oxidative stress was high in patients with RA even if disease activity was controlled within moderate to low. Stronger control of disease activity and diabetes mellitus might reduce the oxidative stress in patients with RA.

P3-008

The significance of measuring Anti-galactose-deficient IgG antibody (CARF) in rheumatoid arthritis

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Conflict of interest: None

Purpose: CARF is one of the serological markers for RA, listed in Japanese national insurance and has been accepted as more sensitive for diagnosis in early RA than RF. However, its significance decreased because ACR/EULAR criteria does not include CARF. In this study we assess the utility of CARF as compared with RF and ACPA. Methods: The data was collected from a part of our prospective cohort study (TOMORROW study). We examined correlation, concordance rate and association with disease activity (DA) of RF, ACPA and CARF. Result: The number of patients is 90 (87% female) and their average age was 56 years, disease duration 11 years. Correlation coefficient of RF-CARF was r=0.96, p=0; RF-ACPA r=0.12, p=0.086; CARF-ACPA r=0.08, p=0.431. This indicates RF and CARF could be regarded as same. In early RA patient Kappa coefficients of ACPA-RF, ACPA-CARF, RF-ACPA was 0.733, 0.862, 0.862, respectively. Each baseline antibody titer showed no significant relation among those with good/moderate DA improvement and those with no improvement/worsening (ACPA, RF, CARF: p=0.773, 0.536, 0.319 respectively). Discussion: In this study CARF and RF could be taken as the same test and no advantage for CARF is observed even in early RA patients.

P3-009

Analysis of rheumatoid factor positive cases revealed in the routine medical checkup

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Conflict of interest: Yes

Purpose: In routine medical checkup, rheumatoid factor (RF) is often checked up. RF positive cases visited to the clinic for further tests or examinations. The aim of this study was to evaluate the usefulness of the RF test in the routine medical checkup. Methods: RF positive 65 cases visited our clinic were analyzed. Results: There were 33 men and 32 women. Age ranges from 31 to 84, with average 50.8 years old. All 65 cases were anti-CCP negative. Only one case had the symptom of morning stiffness and fingers pain at movement. We prescribed the DMARD to her. Conclusion: The necessity of RF test in routine medical checkup was doubtful. RF test should be done when the patients has the symptoms of rheumatoid arthritis.

P3-010

How do the high titer of ACPA affect the diagnosis of rheumatoid arthritis?

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Conflict of interest: None

Anti-CCP antibody (ACPA) is very important factor in the diagnosis of rheumatoid arthritis (RA), when we apply 2010 ACR-EULAR classification criteria for RA. The patients having paersistent polyarthropathy including active synovitis and positive ACPA, is basically, simply, diagnosed as definite RA. In other hands urgent tight-planned treatments againt RA are recommended to avoid the pesmistic prognosis such as bone erosions and severe deformity of joints. However we also meet non-RA cases having high titers of ACPA, and such patiets are treated as RA, with expensive medication like methotrexate and biologics. We checked the ACPA in the refered patients suspected RA with arthopathy and many of them showed high units of anti-CCP, more than tripled number of standard value. The ACPA untit in seven cases existed over five handred units whereas normal range of ACPA was below 4.4U/ml. Those patietns included such as no arthritis case, and anti-Ro antibody posive case. ACPA is very useful serological test in the diagnosis of RA, but especially in the highly-positive patients we should pay much attention to check the other genesis and complications.

P3-011

Comparison of tests results between RNA Immunoprecipitation, Myositis profile 3, and anti-ARS test to detect anti-synthetase antibodies in connective tissue disease patients

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Conflict of interest: None

[Objectives] Anti-synthetase antibodies (ASAs) are useful in the diagnosis of inflammatory myopathy. We compared the test results between RNA-IP, Myositis profile 3, and anti-ARS test. [Methods] We performed Myositis profile 3, and anti-ARS test in CTD and interstitial pneumonitis (IP) patients. 47 cases had positive results in either Myositis profile 3 and/ or anti-ARS test. They include PM (10 cases), DM (9), ADM (3), IIP (14), RA (2), MCTD (2), and SJS (6). Each sera was measured by RNA-IP to detect ASA. [Results] ASAs were detected in 38/37/29 cases by Myositis profile 3, anti-ARS test, and RNA-IP. Although the results of 16 +++ cases and 11 ++ cases in Myositis profile 3 was almost consistent with anti-ARS test and RNA-IP, the result of 11 + cases had negative results in other two methods except a case. Out of 9 cases (positive anti-ARS test and negative Myositis profile 3), which predict anti-KS antibody, a case showed anti-KS antibody. [Conclusion] Tests results of ASAs was different in different assays. Although, RNA-IP was golden standard method to detect ASAs, Myositis profile 3, and anti-ARS test might have high sensitivity to detect ASAs.

P3-012

Sex hormone and women's joint pain

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Conflict of interest: None

(Object) Peri-/post- menopausal women complaining of MS and joint pain visited the hospital on division of Rheumatology. Most cases showed no evidence of abnormality in blood test except for joint pain. We present clinical practice for these patients. (Methods) 218 patients visiting clinic from 2013/1 to 2015/6 with the average age 48 (26~74) were enrolled. Blood exam included serum CRP, RA, ANA, anti-SS-A, E2 and FSH. The score of simplified menopausal index (SMI), SDS, and J-FIQ were obtained on the first visit. Assessment of joint pain was recorded by patient VAS. The treatment for these patients included Lunabell ULD, Tocopherol 600mg/day, and HRT in postmenopausal women. (Results) Twenty three with Sjogren's syndrome (SjS) or SLE and 24 with RA was diagnosed on the second visit and 132 peri/post-menopausal arthralgia including premenstral syndrome were diagnosed by following efficacy of lunabell ULD or HRT for 6 months. MS and joint pains were disappeared within 2 months. In case of presenting RF or ANA, they have continue taking them to prevent RA or SjS. (Conclusions) We came across many female patients with peri-/post- menopausal arthralgia, in contrast to Europe or other developed country. HRT is very effective in such disease condition and recommended more.

P3-013

Screening of rheumatoid arthritis by using Ultrasound Score(US)-7

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Conflict of interest: None

Inroduction The ultrasonographic examinations (US) are useful for early diagnosis of rheumatoid arthritis (RA).However,it is difficult to examine all joints by US in clinical setting.To screen RA,the joints to evaluate in DAS28 or 44 were used.In this study,we screened RA by using the joints to evaluate in US7. Objectives We exmined usefulness of US-7 as screening of rheumatoid arthritis. Methods Thirty seven patients (12 men and 25 women),with median age of 54.2years, who are suspected RA and want to examination of RA from June 2014 through May 2015. We devided into two groups,one is RA group the other is non RA group. The diagnosis obeyed EULAR score. We evaluated synovitis each groups with Power Doppler US (PDUS) of US-7.The evaluation assumed 13 sites (wirst is dorsal,palmar and ulnar.PIP2 and PIP3 are dorsal and palmar.MCP2 and MCP3 are dorsal and palmar.MTP2 and MTP5 are dorsal.).We scored by power Doppler US grade0-3.The scoring range is 0-78 (left and right) for PDUS.We excluded polymyalgia rheumatica,gout and infection. Results RA group is 15.9,non RA group is 3.2 points ($p<0.01$).Cut off value is 9.00.Specificity is 96.4%.Sensitivity is 88.9%. Conclusions We suggested that US-7 was useful for screening of RA.

P3-014

A case of systemic lupus erythematosus that exhibits pseudo-high concentration of cyclosporine

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Conflict of interest: None

[Case report] We report systemic lupus erythematosus (SLE) patient who exhibits pseudo-high concentration of cyclosporine. A 46-year-old woman was diagnosed as SLE twenty years ago. Because she developed pancytopenia despite treatment of glucocorticoid, we administrated cyclosporine in addition to glucocorticoid. We monitored the blood concentration of cyclosporine within trough level 100-150 ng/ml using ACMIA method. Because the trough level exhibited 396.0 ng/ml when she was administrated 125 mg/day of cyclosporine, we stopped the administration of cyclosporine. However, the blood concentration of cyclosporine continued to increase to 459.6 ng/ml without any drug interactions. When we estimated the blood concentration of cyclosporine using CLIA method, the concentration of cyclosporine was not detectable. Moreover, when we performed immunoglobulin adsorption the blood concentration of cyclosporine decreased from 361.1 to 8.5 ng/ml. This is the first report of pseudo-high concentration of cyclosporine in patient with SLE.

P3-015

The difference of the Ultrasonographic grade decision among JCR registered sonographers

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Conflict of interest: None

[Objectives] To calculate the concordance rate of grade decision and review the identity between the sonographer for patients with rheumatoid arthritis (RA) receiving DMARD therapy using ultrasonography (US). [Methods] Each 10 cases underwent US by four sonographers (after experience their 200 or more cases) were extracted. three sonographers other than charge went the grade judgment of the gray scale (GS) and power doppler (PD), 26 synovial sites in 22 joints: bilateral first to fifth metacarpophalangeal (MCP) joints, first interphalangeal (IP) joint and second to fifth proximal-interphalangeal (PIP) joints and the wrists (radial, median and ulnar). [Results] The average GS concordance rate was each MCP: 85.1%, PIP: 90.3%, wrist: 74.1%, in the whole was 84.6%. Also the average PD concordance rate was each MCP: 96.5%, PIP: 99.0%, wrist: 91.9%, in the whole was 96.3%. [Conclusion] The concordance rate of GS and PD among the sonographers was in the order of PIP · MCP · wrist. The concordance rate of the wrist joint was low. We seemed to be due to the difference increases for individual subjectivity enters because of there is no guidelines for grade determination.

P3-016

Second report on the benefits of Filemaker database (FMDB) for ultrasonography

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Conflict of interest: None

[Objectives] We have introduced Filemaker database (FMDB) for ultrasonography (US) in RA, and evaluate the effect of input proficiency and the benefits of FMDB after one and a half years. [Methods] We compared the actual US examination time before the introduction of FMDB, immediately after, and one and a half years later. [Results] We expected the input proficiency effect initially, because FMDB includes free comments area requiring complicated keyboard operations. Before the introduction of FMDB, it took a total of about three minutes in searching US history, calculation, and writing reports. After that, it takes only few seconds in inputting the patient identification and printing reports. Examination time for US was average of 21 minutes 3 seconds before the introduction of FMDB, 20 minutes 1 second immediately after that, and 18 minutes 49 seconds one and a half years later (There was no significant difference between them). On the other hand, the viewpoints were unified among the US examiners and increased after the introduction of FMDB. Despite the increase in the viewpoints, examination time was not extended. [Conclusion] FMDB was well received in the US examiners. We have about 1,700 cases per year of fingers and hands US, and FMDB introduce great effect.

P3-017

Ultrasonography of joimts in patients with arthritis before diagnosis - GS score and PD score-

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Conflict of interest: None

【Objectives】Ultrasonography of joints (US) is important in diagnosis of rheumatic diseases such as rheumatoid arthritis (RA). US are utilized in our institute and scoring according to JCR guideline is performed as the results of US. In this study, we investigated the relationship between the score and the diagnosis. 【Methods】255 patients with arthritis were used. US were performed before diagnosis. The sum of grading of B-mode and power Doppler (PD) was called total GS (T-GS) and total PD (T-PD), respectively. Average scores were calculated in distinct diagnosis, such as RA, undiagnosed arthritis, polymyalgia rheumatica (PMR) and RS3PE syndrome. 【Results】Average T-GS and T-PD in 99 RA were 6.1 and 3.3. PD of wrist in RA was seen in 76%. Average T-GS and T-PD in 99 cases with undiagnosed arthritis were 1.7 and 0.4. Average T-GS and T-PD in 30 PMR were 3.3 and 1.5. PD of shoulder was seen in 83%. Average T-GS and T-PD in 7 RS3PE were 19.0 and 9.3 that was higher than that in RA. PD of wrist in RS3PE was seen in 86%. 【Conclusions】US of joints is effective as imaging tool which can visualize arthritis objectively. We can know the tendency of scoring in different rheumatic diseases. It is important to know that scoring of finger joints and wrists were elevated in PMR or RS3PE.

P3-018

The peak grade level of the power Doppler sonography in joints correlates with serum MMP-3 level

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Conflict of interest: None

Purpose: The blood flow signal using the power Doppler method of the joint ultrasound means neovascularity and is thought to reflect synovial growth. Serum MMP-3 is an enzyme produced with a synovial superficial cell with synovial growth. As a result of matrix resolution effects of MMP-3, the patients are thought to cause joint destruction. Patients & Methods: The study enrolled 140 patients in Rheumatoid Arthritis (RA) We examined the correlation of value of highest grade at testing (peak-grade; PG) and serum MMP-3 level. The evaluation of the blood flow signal using the power Doppler method conformed to grade classification by OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trial) recommended in "joint echo imaging law guidelines" in JCR. We examined a correlation of PG and MMP-3. Results: Coefficient of correlation (r) (Welch test) of PG and MMP-3 was r = 0.266. Conclusion: It is important that we hit the swelling and remarkable painful site with a probe preferentially and examine it. Because we recognized a positive correlative tendency between PG and MMP-3 level, it seemed that PG could predict future bone destruction.

P3-019

Usefulness of joint ultrasonography (US) in the early diagnosis of rheumatoid arthritis

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Conflict of interest: None

【Objective】It is difficult for some patients to be diagnosed with early rheumatoid arthritis (RA). Therefore we examined it whether we could significantly perform differentiation with early diagnosis by performing US.【Method】From February 2014-October 2015, among the 163 patients who underwent the US, we intended for 74 undiagnosed patients who assumed the finger joints swelling and tenderness that occurred within one year. Synovitis evaluation was evaluated both hands 22 joints.【Result】32 people were admitted US positive joint findings. There was the case that the estrangement with the clinical examination was, so to speak, seen in that power doppler (PD) was observed in the joint except the swelling tenderness joint. We were able to distinguish inflammatory synovial hyperplasia or the synovial hyperplasia as the fibrous scar without the blood flow from gray scale (GS) by PD.【Result】We were able to diagnose it in the case that it was hard to conclude to be it only in clinical information early with RA by utilizing US by pointing out latent synovitis. By presence or absence of PD, we proved inflammatory clinical condition and the likelihood that could perform the differentiation of the aging-related change more exactly than a medical examination if degenerative.

P3-020

Active synovitis is detected by ultrasound sonography in established rheumatoid arthritis patients even when they fulfilled three components except patient global assessment of Boolean remission criteria: analysis by KURAMA cohort

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Conflict of interest: None

[Background and objective] Boolean remission criteria (BR) is difficult to be met in established rheumatoid arthritis (eRA) because of high patient global assessment (PGA). It is accepted to permit such high PGA. Ultrasound sonography (US) can detect subclinical synovitis (SS). The objective of our study is to evaluate whether it is relevant to permit high PGA in eRA using SS. [Method] 253 RA patients who visited our clinic from May to August in 2015 were evaluated. Bilateral 2-5 MCP, wrist, ankle, and 2-5MTP were scanned by 5 sonographers using Aplio300 (TOSHIBA) and 12MHz probe. Power Doppler (PD) signal was obtained by SMI. PD score were decided by the discussion between 2 of the sonographers. Clinical assessment was done by physicians being blind to US result. Semi-BR (SBR) was defined as the status that 3 components except patient global assessment of BR were met. [Result] 197 patients were enrolled. 49 and 82 met SBR and SBR, respectively. There was no significant difference in total PD score (PDS). Significantly higher PDS was seen in eRA even when BR or SBR was met. PDA and PGA showed no correlation. [Conclusion] Our results imply that synovitis in eRA is difficult to be assessed both by patients and physicians. US should be used for accurate evaluation of eRA.

P3-021

[methyl-(11)C]4'-thiothymidine-PET/CT as a novel tool for the evaluation of disease activity of rheumatoid arthritis

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Conflict of interest: None

[Objectives] [methyl-(11)C]4'-thiothymidine (4DST) is incorporated into DNA and was developed as novel tracer for imaging cell prolifera-

tion.The purpose of our study is to examine the usefulness of 4DST and 18F-fluorodeoxyglucose (FDG)-PET/CT for evaluation of synovitis of proximal interphalangeal (PIP), metacarpophalangeal (MCP), and wrist in RA. [Method] We assessed synovitis of the 176 joints from 8 patients (mean age: 70.5 years old, stage I,II: 5 patients, anti-CCP positivity: 75%) by physical examination, ultrasonography (US), 4DST-PET/CT, and FDG-PET/CT. [Results] Five patients had high disease activity, and 3 moderate disease activity. Synovitis was detected in 25% of 80 PIP joints by visual score of 4DST-PET/CT based on uptake of bone marrow, and 35% by FDG-PET/CT, compared to 20 % and 11.3% by US based on gray scale (GS) imaging score≧1 and power doppler (PD) signal score≧2. The frequency of synovitis was same in the evaluation of MCP and wrist joints. One-way analysis of variance showed standardized uptake values (SUV) max of 4DST-PET/CT and FDG-PET/CT of each joint was significantly associated with grade of GS and PD in US. [Conclusion] 4DST-PET/CT as well as FDG PET/CT is a powerful tool to detect synovitis and evaluate the severity of synovitis in patients with RA.

P3-022

2-[18F]fluoro-2-deoxy-D-glucose (FDG)-PET/CT for diagnosis of the inflammation of unknown origin

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Conflict of interest: None

[Object]The usability of 2 - [18 F] fluoro-2-deoxy-D-glucose (FDG) - positron emission tomography (PET) / computed tomography (CT) is being recognized in the area of the treatment of rheumatic diseases. But its limit has not been clarified. [Methods]This is a single-centered retrospective cohort study, which includes all patients who received FDG-PET/CT to identify the origin of inflammation, in the department of Immune Medicine, Kinki Central Hospital since January 2011 to May 2015. FDG-PET/CT was done in the department of PET Center, Osaka Saiseikai Nakatsu Hospital. Diagnosis indicated from FDG-PET/CT, final diagnosis, age, gender, points of FDG accumulation were collected. [Results] 27 patients were included. Diagnoses indicated from FDG-PET/CT were arthritis (7 patients), vasculitis (4), lymphoma (7), lymphadenitis (3), myositis, Carcinoma, and unidentified (2). “Arthritis” and “vasculitis” indicated from FDG-PET/CT were almost perfectly consistent with final diagnoses, but only 50% of “lymphoma” and “lymphadenitis” indicated from FDG-PET/CT were consistent with final diagnoses. [Conclusions] FDG-PET/CT is a very powerful method to identify the origin of inflammation. But some patients with rheumatic diseases may mimic lymphoma.

P3-023

A study of the imaging evaliation method of cartilage in patients of rheumatoid arthritis with an X-ray Talbot-Lau interferometry

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Conflict of interest: None

Purpose:An x-ray Talbot-Lau interferometry has high sensivity to soft tisuues.We focused on the depiction of cartilage with it and evaluated the possibility of applying it to RA patients. Method:We acquired an image of two MP joint with 55 healthy volunteers (Averaged age 42.5,Male /Female:15/40)and 42 RA patients (Averaged age 63.2,Male / Female:8/34, Steinbrocker classificasion Stage 1/2/3/4:19/12/6/5).We evaluated the thickness of the cartilage was 632μm with healthy voluteers and 553μm with RA patients, in which 572μm with Grade 0 and 557μm with Grade1 by Larsen grading scale. There was no correlation of the thickness with the age and sex. The difference of it between the healthy volunteer and the patints were signficant,even though the joints were in early stage RA. This result suggested that the system would detect the status of the joints in early stages. connclusion: An x-ray Talbot-Lau Interferometry has a possibility to diagose RA patients by imaging cartilage.

P3-024

Changes in forefoot MRI findings during treatment with biologics in patients with rheumatoid arthritis

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Conflict of interest: None

[Subjects]Subjects were one male and four female RA patients (mean age, 34.8 years) who underwent forefoot MRI before and after treatment with biologics. **[Methods]**The modified RAMRIS scoring system was used to assess forefoot MRI findings during treatment with biologics and one year after initiation of treatment. I also measured MMP3 levels before and after treatment with biologics, as well as the disease activity score for 44 joints including the feet (modified DAS44CRP). **[Results]**The mean modified DAS44CRP score before treatment with biologics was 3.57, which decreased to a mean of 2.30 one year after treatment. MMP3 levels decreased from a mean of 61.2 before treatment to 41.9 one year after treatment. Mean MRI scores for bone erosion, bone marrow edema, and synovitis before treatment were 7.6, 9.6, and 8.0, respectively, and these decreased one year after treatment to 7.2, 6.2, and 2.6, respectively, with marked improvements in synovitis and bone marrow edema scores. **[Conclusions]**Treatment with biologics improved disease activity and forefoot MRI findings, including synovitis and bone marrow edema scores.

P3-025

The three cases in whom US was useful for differential diagnosis of seronegative arthritis

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Conflict of interest: None

Case 1:80-year-old woman had polyarthralgia and pitting edema in bilateral foot and hands. Both RF and anti-CCP antibody (ACPA) were negative. Tenosynovitis and subcutaneous edema were detected by US. She was diagnosed as RS3PE syndrome. She was treated with PSL 15mg/day and her symptoms improved promptly. Case2:73-year-old woman had arthralgia of right wrist and pitting edema in bilateral foot and hands. Both RF and ACPA were negative. Subcutaneous edema and mild synovitis of bilateral wrist and MCP joints were detected by US. She was diagnosed as RS3PE syndrome. She was treated with PSL 15mg/day and her symptoms improved promptly. Case3: 68-year-old woman had polyarthralgia of bilateral shoulders, knee, and wrist joints. CRP was elevated to 11.46mg/dl. Both RF and ACPA were negative. US showed synovitis of bilateral wrist, MCP, and PIP joints. She satisfied the diagnostic criteria of PMR and treated with PSL15mg/day. However CRP was persistently high. She was diagnosed as RA based on refractory to corticosteroid and US-proven synovitis of peripheral joints. Methotrexate was additionaly induced. It is sometimes difficult to distinguish seronegative RA from PMR and RS3PE syndrome. We report 3 cases in whom US was useful for differential diagnosis of seronegative arthritis.

P3-026

Patients with spondylarthritis showed microgeodic phalageal disease-like bone edema - Case report

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Conflict of interest: None

Microgeodic phalangeal syndrome is a rare condition affecting the fingers in children. Radiographically, the affected phalanges show sclerosis with multiple small areas of osteolysis. The pathogenesis of microgeodic phalangeal syndrome is considered to be a transient disturbance of the peripheral circulation caused by cold temperatures. We experienced two undifferentiated spondylarthritis patients with dactilytis whose hand enhanced MRI showed the clear bone edema like microgeodic phalangeal syndrome. It is considered that bone edema is one of the major pathological condition of dactilytis.

P3-027

Morning Stiffness in Rheumatoid Arthritis; Investigating Relationship to Ultrasonography

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Conflict of interest: None

Objective: Purpose of our study was investigation of association between morning stiffness (MS) and assessment of ultrasonography (US) in rheumatoid arthritis (RA). Patients and Methods: We conducted a retrospective analysis of 22 consecutive patients with RA (6 males, 16 females; mean age, 48.6±10.7 years; range, 39-65 years; mean disease duration, 7.1 ± 5.4 years; range, 0-17 years). Patients were assessed by US of the wrists, MCP and PIP joints. US, estimation of the duration of MS (min) of all patients were performed on the same day. Patients were divided into the following two groups: 'MS positive group (n=9)' and 'MS negative group (n=13)', and the US findings were compared. Results: The number of joint synovitis was not significant. The number of patients who has tenosynovitis detected by power Doppler was significantly higher in the MS-positive group ($p<0.01$). There were also significant correlations between MS duration and numbers of tenosynovitis detected by power Doppler ($r=0.5884$ $p<0.01$). Conclusion: We found that MS duration was associated tenosynovitis.

P3-028

Efficacy of abatacept in patients with rheumatoid arthritis evaluated by ultrasound examination

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Conflict of interest: None

[Objective] The aim of this study was to evaluate effectiveness of abatacept (ABT) for rheumatoid arthritis (RA) using ultrasound examination. [Methods] Thirty three patients with RA who had received ABT were enrolled. Patients underwent clinical, laboratory assessment and ultrasound examination at baseline and 24 weeks. Twenty-eight joints (bilateral wrists, 1st-5th metacarpophalangeal joints, and 1st-5th proximal interphalangeal joints) were evaluated by a systematic multiplanar greyscale (GS) and power Doppler (PD) examination. [Results] Mean age was 68.2 years old. Mean disease duration was 8.3 years. Disease activity score 28-CRP was significantly decreased from 3.75 at baseline to 2.44 at 24 weeks. Total PD score was significantly decreased from 13.0 at baseline to 5.7 at 24 weeks. The patients who were total PD score ≤ 2 at 24 weeks were shorter disease duration than the patients who total PD score > 3 at 24 weeks (4.0 vs 10.3 years $p=0.048$). [Conclusion] ABT therapy improved Total PD score at 24 weeks, particularly early RA.

P3-029

Clinical analysis of arthralgia patients showing synovial membrane thickness by joint ultrasonography

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Conflict of interest: None

Object: We studied usefulness of joint ultrasonography (JUS) for the patients with arthralgia. Subjects: JUS was performed for the patients suffering arthralgia. The 39 cases showed synovial membrane thickness by JUS at bilateral wrists, 1 to 5 MCP, 1IP, and 2 to 5 PIP joints. Methods: Painful and/or swollen joints and the levels of CRP, ESR, RF, antiCCP-Ab and MMP-3 were examined. Sites showing synovial membrane thickness, grading of B-mode and power Doppler, number and sites of bone erosion were evaluated. Results: 6 males / 33 females aged 67.2 y included 33 RA, 2 PMR, 1 scleroderma, 1 osteomyelitis, and 2 undifferentiated arthritis. Painful (3.5) and swollen (1.9) joints were counted in PIP, MCP, wrist, elbow, MTP, ankle, knee joints. CRP 0.64 mg/dl, ESR 22 mm/h, RF: 44.4 IU/l, antiCCP-Ab 126.9 U/ml, and MMP-3 165.1 ng/ml. Synovial membrane thickness count was 1.7, graded as 1.3 by B-mode and 0.6 by power Doppler. The site of bone erosion was seen in PIP and the erosion counts were 1/2 cases and 2/1 case among 39 cases. Conclusion: JUS was useful for motivating the patients to receive appropriate therapy. Synovial membrane thickness was correlated with the count of swollen joints rather than that of painful joints.

P3-030

A case of rheumatoid arthritis of chronic monoarthritis diagnosed using contrast-enhanced magnetic resonance image

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Conflict of interest: None

Case report: A 63 year-old woman was referred with arthritis in the right knee lasting for 2 months. Despite presenting with monoarthritis, refractory hydrarthrosis, positive of anti-CCP antibody (21.5 U/ml, cutoff < 4.5 U/ml), and elevation of CRP (1.19 mg/dl) were noted. Because the contrast-enhanced MRI revealed synovitis in the right knee, she was diagnosed as rheumatoid arthritis (RA). Methotrexate 6 mg/week and bucillamine 200 mg/day were started with satisfactory improvement of arthritis. **Summary:** Because chronic monoarthritis can occasionally be an early manifestation of several systemic rheumatic disorders, the differential diagnosis poses clinical challenge for rheumatologists. We report this case with literature review for the role of contrast-enhanced magnetic resonance image in patients presented with chronic monoarthritis.

P3-031

Clinical features of seronegative rheumatoid arthritis evaluated with musculoskeletal ultrasound sonography

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Conflict of interest: None

(Objective) We assessed the clinical characteristic in seronegative rheumatoid arthritis (SNRA) evaluated with musculoskeletal ultrasound sonography (MSUS). (Method) This study included 66 RA patients, who were newly visited our department since 2010 to 2015. We have defined RF negative and ACPA negative RA as SNRA, whereas RF positive and/or ACPA positive RA as Seropositive RA (SPRA). And their clinical features, laboratory data and MSUS findings were statistically compared. (Results) There were 28 cases of SNRA (MSUS was performed for 23 cases), and 38 cases of SPRA (MSUS was performed for 20 cases). In

patients who were underwent MSUS at the time of diagnosis, it seemed that SNRA group has longer tendency of disease duration than that of SPRA group. Loboratory data revealed that CRP levels of SNRA were significantly higher than that of SPRA, 2.94 and 0.34 mg/dl (median, p = 0.011), respectively. In contrast, there was no difference of clinical features between two groups that MSUS was not performed. (Conclusion) We suggest that MSUS might be useful tool to capture disease activity of long disease duration of SNRA patients.

P3-032

Ultrasonographic assessment of the midfoot and hindfoot joints in RA patients

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Conflict of interest: None

[Background] Patients with rheumatoid arthritis (RA) experience various foot lesions; however, disease activity indices such as DAS do not consider the foot or the ankle. Recently, joint ultrasonography has been widely used in the treatment of RA. However, ultrasonography of the foot joints has only been analyzed in a few cases. [Objectives] We analyzed ultrasonographic assessment of the midfoot and hindfoot joints in RA patients and the symptoms. [Methods] We studied 44 RA patients (51 feet). After complaints about the foot were examined, joint ultrasonography was performed. The calcaneocuboid and talonavicular joints were scanned to assess the midfoot; and tarocruel and subtalar joint were scanned to assess the hindfoot. [Results] From the total of 51 feet, 12 feet showed subjective symptoms in the midfoot and hindfoot (5 midfoot, 7 ankles, 23.5%). Synovitis was detected in the ankles and the calcaneocuboid and talonavicular joints of 10 feet (19.6%). The detection rates of synovitis in patients with symptoms were 42.9% in the hindfoot and 80.0% in the midfoot. [Conclusions] The results of this study showed that synovitis was detected in both the hindfoot and the midfoot. This suggested that assessment of the entire foot would be required in the future.

P3-033

Importance of the joint echo in the toe joint

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Conflict of interest: None

«Objective» In rheumatic patients toe joint clause, by comparing the positive findings of the joint echo inspection by the inspection engineer and physical findings of doctors, was examined the importance of joint echo in the toe joint. «Methods» The power Doppler and gray scale to each 0-III, it was evaluated by using a semi quantitative method. Of the RA patients 157 cases who underwent an echo, moderate or more of echo positive findings on toe joint clause 56 cases that were observed target. «Results» 56 cases in the joint echo, a total of 560 in the joint, PD positive 58 joint, GS-positive joint was 156 joint. Concordance rateκ0.35 of PD and physical findings (pain), positive predictive value is 56%, and the concordance rateκof GS and physical findings (swelling) 0.39, positive predictive value was 68%. «Conclusions» It is thought that Concordance rate and the positive predictive value vary with the palpation sensitivity of the doctor. Since joint echo also introduced in our hospital. In addition, physical assessment or by multiple physicians in assessing disease activity in one patient, it should be multifaceted approach by adding evaluation by echo.

P3-034

Usefulness of power Doppler sonography in the sacroiliac joint

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Conflict of interest: None

Objective: The aim of this study was to investigate the usefulness of the sonographic evaluation in the sacroiliac joint. ***Methods:*** Sacroiliac joints in 22 patients who visited the outpatints clinic for reporting sacroiliac joints pain, were examined by gray scale and power Doppler ultrasonography (PDUS). ***Results:*** There were 10 patients with rheumatoid arthritis (RA), 3 patients with fibromyalgia (FM), 3 patients with ankylosing spondylitis (AS), 3 patients with lumbar spinal canal stenosis, 2 patients with spandyloarthropathies (SpA), and 1 patient with psoriatic arthritis. The synovial blood flow was detected in 5 patients (23 %). C-reactive protein (CRP) values were positive in these 5 patients when PDUS was performed. Concerning the patients with AS, PDUS signals decreased in all cases after biological agent therapy. ***Conclusion:*** Although the sensitivity of PDUS in sacroiliac joints was inferior to joints of limbs, PDUS may be a valuable tool for the confirmation of the sacroiliitis and determination of the therapeutic effect.

P3-035

Clinical features and course of undiagnosed rheumatoid arthritis(RA)

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Conflict of interest: None

[Purpose] The significance of early diagnosis in RA has increased with advances in RA treatment. The state of "self-proclaimed rheumatism" patients who presented with undifferentiated arthritis (UA),RF positivity, or joint symptoms was investigated as undiagnosed RA. [Methods]The clinical features and follow-up observations of 763 patients with undiagnosed RA, who had been examined between April 2005 and July 2011, were investigated. [Results] Three groups of patient were treated: Group 1 included 232 RF-positive patients; group 2 included 314 RF-negative patients; group 3 included 217 patients who had "self-proclaimed rheumatism." RA was diagnosed on the basis of clinical features after follow-up observation in 31 patients in group 1, 7 patients in group 2, and 6 patients in group 3. Treatments with conventional antirheumatic drugs were initiated in these patients, whose prognoses were relatively good. There were also increased number of patients diagnosed with SpA for their joint symptoms accompanying RF-negative arthritis or fibromyalgia.[Conclusions] Undiagnosed RA is common. It is of importance to begin relevant treatment on the basis of early diagnosis and differential diagnosis using MRI, joint ultrasound, and such, according to diagnosis criteria for RA and SpA.

P3-036

Ultrasound finding of eosinophilic fasciitis: two case repots

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Conflict of interest: None

Case 1, A 67 year-old woman was referred to our hospital for muscle weakness, swelling, pain, redness and fever in both forearm. Blood tests revealed normal levels of WBC and eosinophil, and elevated level of CRP. Contract enhanced MRI showed high intensity in muscle and fascia. Ultrasound demonstrated abnormal Doppler signals in fascia. The biopsy specimen of fascia revealed infiltration of eosinophils and the patient was

diagnosed with eosinophilic fasciitis. This patient was getting better with 40 mg/day of prednisolone. Case 2, A 25 year-old man had swelling and pain in right finger and was diagnosed with rheumatoid arthritis in another clinic. He was referred to our hospital eight months later since his symptom turned worse. The patient had marked hardening of the skin in upper and lower limbs. Blood tests revealed increase of eosinophil, and elevated level of CRP. Contract enhanced MRI showed high intensity in the muscle and fascia, but ultrasound did not demonstrate abnormal Doppler signals in fascia. The biopsy specimen of fascia revealed fibrosis of fascia and infiltration of lymphocyte and plasmacyte. The symptoms was slightly improved with 40 mg/day of prednisolone. We could confirmed the finding of eosinophilic fasciitis in acute and chronic phase by ultrasound.

P3-037

Comparative study on distribution of the arterial lesions among large vessel vasculitides. Large vessel vasculitis: Clinical features of 27 patients

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Conflict of interest: None

Purpose: There is an argument about the difference of Takayasu arteritis (TAK) and giant cell arteritis (GCA). We compared the difference of the distribution of arterial lesions. Method: The medical records of 27 (10 male, 17 female) patients who diagnosed TAK or GCA from 2008 to 2013 were reviewed retrospectively. We divided these cases, according to the ACR classification criteria in 1990, into TAK group, GCA group and unclassified group. The unclassified group were divided into two groups with aged 40 or below and aged 41 or older. The distribution of the arterial lesions was investigated using MRA and CT. Result: Among 27 cases diagnosed as TKA or GCA by the clinician, nine cases were unclassified with the ACR classification criteria. TAK group, as compared with a GCA group, had a higher incidence of descending aorta and pulmonary arterial lesions, and this difference was reflected also in the difference among the unclassified group with under 40 and over 40. In the unclassifiable group, as compared with the TAK group or the GCA group, an arterial stenotic lesions and an aneurysm were hardly seen. Conclusion: It was suggested that there is a difference of the main arterial lesions between TAK and GCA. The unclassified group seems to be an early phase of the diseases.

P3-038

Examination of Capillary Disorder in Patients with Rheumatic Disease by using Nailfold capillaroscopy(Second report)

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Conflict of interest: None

(Introduction) Rheumatic disease is caused by impaired blood flow in microvessels, which leads to various disorders. We have been reporting capillaroscopy studies from Japan. (Methods) The subjects were patients with connective tissue disease who visited Kyoundo Hospital and provided consent between October 2012 and January 2013. We observed capillaries of the nail epithelium by capillaroscopy. Since we have previously reported the relation with disease types and duration, in the present study, we analyzed the relation with autoantibodies, the relation between cytokines involved in microvascular dysfunction and treatment, as well as visceral complications. (Results) Capillary dysfunction progressed faster in anti-centromere-positive patients than in anti-Scl-70-positive patients, and most anti-centromere-positive patients had visceral complications, including interstitial pneumonia and pulmonary hypertension. Serum endothelin-1 levels were significantly elevated in patients with rheumatic disease. (Conclusion) Findings of specific abnormal capillary patterns in rheumatic disease allow not only early diagnosis but also the potential prediction and prevention of complications.

P3-039

Inverse correlation of IFNg$^+$Th17 and ACPA in early RA

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic autoimmune disease with chronic joint inflammation characterized by activated T cells. IL-17 and Th17 cells play important roles in the pathogenesis of RA. Recently, plasticity in helper T cells has been demonstrated; Th17 cells can convert to Th1 cells. However, it remains to be elucidated whether this conversion occurs in the early phase of RA. Here, we validated the methods of the Human Immunology Project (HIP) using only the cell-surface marker through measuring the actual expression of IL-17 and IFNg. We then tried to identify Th17 cells, IL-17$^+$ Th17 cells and IFNg$^+$ Th17 cells in the peripheral blood of early-onset RA patients using the standardized method of the Human Immunology Project. Our findings validated the method of HIP. The ratio of IFNg$^+$Th17 cells in memory T cells was inversely correlated to the titers of anti-CCP antibodies in the early-onset RA patients. These findings suggest that Th17 cells play important roles in the early phase of RA and that anti-IL-17 antibodies should be administered to patients with early phase RA, especially those with high titers of CCP antibodies.

P3-040

Decoy receptor 3 down regulates the expression of centrosomal protein 70kDa in rheumatoid synovial fibroblasts

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Conflict of interest: None

[Objectives] We newly reported that the microarray assay revealed decoy receptor 3 (DcR3), a secreted tumor necrosis factor receptor, regulates gene expression in rheumatoid synovial fibroblasts (RA-FLS). The profiles indicated that centrosomal protein 70kDa (Cep70) was down-regulated by DcR3. CEP family is the active component of centrosome and plays a vital role in cell cycle progression. In this study, we studied Cep70 as one of the key molecules in DcR3-TL1A signalling in RA-FLS. [Methods] RA and osteoarthritis (OA)-FLS were stimulated with inflammatory cytokines or DcR3. RA-FLS were treated with DcR3 after pretreatment with anti-TL1A Ab. Cep70 mRNA were quantified by real-time PCR. The expression of Cep70 protein in RA and OA synovium were evaluated with immunohistochemistry and Western blotting. [Results] Real-time PCR revealed Cep70 in RA-FLS was higher than that in OA-FLS. Immunohistochemistry revealed that Cep70 protein was expressed more in superficial lining layer of RA synovium than that of OA synovium. DcR3 decreased Cep70 mRNA and protein in RA-FLS. Anti-TL1A Ab inhibited the down-regulation of Cep70 in RA-FLS induced by DcR3. [Conclusions] Cep70 was increased in RA-FLS and Cep70 expression in RA-FLS was decreased by DcR3 by binding to TL1A in a disease-specific fashion.

P3-041

The analysis of stimuli-response mechanisms of fibroblast-like synoviocytes from rheumatoid arthritis patients

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Conflict of interest: Yes

[Object] Fibroblast like synoviocytes (FLS) play a major role in the pathogenesis of rheumatoid arthritis (RA) through the expression of matrix metalloproteinase, cytokines and chemokines in response to various stimulations in the joints. In the present study, we analysed the mechanisms of stimuli-responses specific for RA-FLS. [Methods] RA/Osteoarthritis (OA)-FLS (n=3) were stimulated with each cytokine (TNF-α, IL-1β, IL-6/sIL-6R, IL-17A, IL-18, IFN-γ, IFN-α, TGF-β1) and combination of all cytokines as a simulated intraarticular environment. The expression of mRNA at 10 and 24 hours were analysed using semi-quantitative RT-PCR for selected genes important for RA pathogenesis and RNA-seq. [Results] The mRNA expression responses were different depending on cytokines and time courses. (i.e, MMP3:TNF-α·IL-1β·IL-17, RANKL:TNF-α·IL-1β·IL-6/sIL-6R, HLADR:IFN-γ·IFN-α) The synergistic influence for mRNA expressions with the exception of HLADR was observed in the combination of all cytokines. The genome-wide analysis by RNA-seq is going on. [Conclusions] The comprehensive analysis of transcriptomes of RA-FLS could reveal the mechanisms of stimuli responses with a focus on transcription factors.

P3-042

No cellular influx is responsible for synovial fibroblast accumulation in collagen-induced arthritis

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Conflict of interest: None

Object: How synovial fibroblasts (SFs) accumulate could be new therapeutic targets in rheumatoid arthritis (RA) while current therapies that suppress inflammation have problems in efficacy and safety. Recent studies reported that fibroblasts accumulate via influx of bone-marrow-derived cells in murine models of kidney fibrosis and wound healing. We demonstrated that local cellular proliferation but not influx is responsible for SF accumulation in collagen antibody-induced arthritis (CAIA). The aim of this study is to clarify whether cellular influx is responsible for the SF accumulation in collagen-induced arthritis (CIA) which is a relatively chronic model of RA compared to CAIA. Methods: SFs were identified using collagen type I (Col1)-GFP mice. Wild-type (WT) mice were transplanted with the bone marrow from Col1-GFP mice. Col1-GFP and WT mice were conjoined for parabiosis. Mice were subjected to CIA. The synovial tissues were examined for histological changes. Results: No GFP+ cells were found in the CIA synovial tissues from the bone-marrow-transplanted mice. GFP+ cells were also absent in the CIA synovial tissues from the WT parabionts in contrast with those from Col1-GFP parabionts. Conclusion: No cellular influx is responsible for the SF accumulation in CIA.

P3-043

Variant death receptor 3 (*DR3*) contributes to the pathogenesis of rheumatoid arthritis (RA) by inhibiting apoptosis-induction

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Conflict of interest: None

Variant death receptor 3 (*DR3)* gene, a *Fas* gene family, contains 4 single nucleotide polymorphisms (SNPs) and a 14-nucleotide deletion, i.e., nt564 (A>G); Asp159>Gly, nt 630+622 (del 14), nt631-538 (C>T), nt631-391 (A>T), nt631-243 (A>G), within exon 5 and intron 5. The deletion results from the binding of splicing regulatory proteins to *DR3* pre-mRNA intron 5, causing the insertion of a portion of intron 5 into the coding sequence, and generating a premature stop codon. This truncated DR3 product lacks the death domain, acts as a dominant-negative factor associating with wild-type DR3, and inhibiting ligand-induced apoptosis in the lymphocytes of patients. The truncated DR3 also acts as a soluble factor to enhance arthritis, thereby predisposing to human RA. We here studied the frequency of *DR3* variant among anti-citrullinated protein antibody (ACPA)-positive patients with RA to show that variant *DR3* was detected in 15/ 571 (2.62%) ACPA-positive (odds ratio 7.4) and 15/ 516 (2.92%) ACPA and RF-positive (odds ratio 9.14) patients, the frequency of which were significantly high as compared to healthy control (2/ 547: 0.36%): p=0.0029 and p=0.00095, respectively.

P3-044

Expression of mRNA for signaling lymphocytic activation molecule associated protein in CD34+ cells of the bone marrow in rheumatoid arthritis

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Conflict of interest: None

[Object] Signaling lymphocytic activation molecule associated protein (SAP) was identified as the causative gene product of X-linked lymphoproliferative syndrome. A previous study disclosed that the SAP transcripts level in peripheral leukocytes of RA patients was significantly lower than that of normal individuals. The current study therefore examined the mRNA expression of SAP in bone marrow (BM) CD34+ cells from RA patients. [Methods] CD34+ cells were purified from BM samples from 47 RA patients and 30 OA patients during joint operations via aspiration from iliac crest. The expression of mRNA for SAP was examined by quantitative RT-PCR. [Results] There was a tendency that the expression of mRNA for SAP was higher in RA BM CD34+ cells than OA BM CD34+ cells (p=0.0888). The SAP mRNA expression level was not correlated with serum CRP or medication. [Conclusion] These results suggest that the reduced expression of SAP in RA leukocytes was not due to the intrinsic abnormalities of RA BM CD34+ cells.

P3-045

Resistin enhances production chemokines by rheumatoid synovial fibroblast

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Conflict of interest: None

【Objectives】 We have previously reported that serum resistin level was significantly higher in rheumatoid arthritis (RA) patients. Accordingly, the aim of this study is to elucidate the direct effects of resistin on rheumatoid synovial fibroblasts (RSFs). 【Methods】 RSFs were established from synovial tissues of RA patients. RSFs were treated with various concentrations of resistin for 18 hours. Then, total RNA was extracted from the cells and the gene expression profile of RSFs was analyzed by DNA microarray. The gene expression of several chemokines was also examined by semi-quantitative RT-PCR. Concentration of CXCL8 in the culture supernatant was determined by ELISA. 【Results】 Microarray analysis revealed that expression of 45 genes, including 13 chemokines, were up-regulated in RSFs by stimulation with resistin when we applied

equal to or more than a 3-fold increase to cut-off value for gene expression. Increased expression of CXCL1, CXCL6, CXCL8, CCL2 and CCL7 was confirmed by semi-quantitative RT-PCR. Production of CXCL8 in the culture supernatant was increased by the incubation with resistin. 【Conclusion】 Resistin might play an important role in pathogenesis of RA via up-regulation of chemokine expression in the synovial tissue.

P3-046

IL-29 is expressed in rheumatoid arthritis serum and synovial tissues

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Conflict of interest: None

Objective: Cytokines play a critical role in modulating the innate and adaptive immune systems. Interleukine (IL)-29 is distantly related to IL-10. IL-10 is elevated in patients with rheumatoid arthritis (RA). In this study, we examine the expression of IL-29 in RA serum and synovial tissues. **Methods**: IL-29 expression was determined in serum from normal (NL) subjects (n=47) and RA patients (n=22) using enzyme linked immunosorbent assay (ELISA).To determine expression of IL-29 on RA synovial tissues, immunohistchemistry was performed. Finally, examine the correlation of IL-29 which was measured by ELISA at 0, 12 and 24 weeks and DAS28. **Results**: The expression of IL-29 in RA serum was significantly higher compared to NL serum [mean ± SE; 570 ± 173 pg/ml and 39 ± 13 pg/ml, respectively]. IL-29 was expressed on RA synovial tissue lining cells, endothelial cells, and synovial fibroblasts. In TCZ group,serum IL-29 levels were decreased (baseline 602 ± 184 pg/ml, 12 weeks 432 ± 144 pg/ml and 24 weeks 276 ± 118 pg/ml), which showed highly significant improvement of DAS28 baseline was 5.2 ± 0.2 (2.6-6.7), after 12 weeks (2.6 ± 0.4), and 24 weeks (1.9 ± 0.3). **Conclusion**: In this study, IL-29 is expressed in RA serum and synovial tissues and is decreased with TCZ treatment.

P3-047

Enhanced expression of mRNA for S100A12 in CD34+ cells of the bone marrow in rheumatoid arthritis

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Conflict of interest: None

[Object]: The calcium-binding protein S100A12 is expressed in neutrophils and monocytes. Recent studies have disclosed that S100A12 was increased in serum and synovial fluid of patients with rheumatoid arthritis (RA). Furthermore, S100A12 correlated with measures of disease activity in RA patients. The current study therefore examined the mRNA expression of S100A12 in bone marrow (BM) CD34+ cells from RA patients. **[Methods]:** CD34+ cells were purified from BM samples from 45 RA patients and 28 OA patients during joint operations via aspiration from iliac crest. The expression of mRNA for S100A12 was examined by quantitative RT-PCR. **[Results]:** The expression of mRNA for S100A12 was significantly higher in RA BM CD34+ cells than OA BM CD34+ cells. The S100A12 mRNA expression level was not correlated with the administration of MTX or oral steroid. S100A12 mRNA expression was significantly correlated with S100A8 and S100A9 mRNA expression in RA BM CD34+ cells. **[Conclusions]:** These results indicate that the enhanced expression of S100A12 mRNA in BM CD34+ cells plays a pivotal role in the pathogenesis of RA, and might be closely associated with the enhanced mRNA expression of S100A8 or S100A9.

P3-048

Immunohistochemistry of Heme oxygenase-1 expression in synoviocytes in rheumatoid arthritis

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Conflict of interest: None

Heme oxygenase (HO)-1 is a stress-induced enzyme that caralyzes heme degradation. HO-1 expression increased in rheumatoid arthritis (RA), it contribute to anti-inflammatory effects. Objects: To investigate HO-1 expression in RA synovial lining layer. Methods: Synovial samples (51 RA, 14 OA). Synovium were obtained at total knee arthroplasty. The formalin-fixed paraffin-embedded tissue were stained by using mouse monoclonal antibodies directed toward HO-1 (D-8, Santa Cruz). The number of positively stained cells was counted of 10 fields. Double-staining immunohistochemistry to reveal relation to antigen-presenting cell. Results: HO-1+ cells were 50-70% in RA, 30-60% in OA. HO-1 expression increased with the progress of inflammation. There was HO-1+/CD68+, HO-1+/CD163+, HO-1+/CD206+, was not HO-1+/5B5+. Conclusions: HO-1 expression was increased in high-level inflammation. HO-1+ cell was characterized by macrophage phenotype.

P3-049

Inflammation mechanism of rheumatoid arthritis (RA) is supposed by the relation between MMP-3 and some inflammatory markers

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Conflict of interest: None

[Purpose] MMP-3 is specific for a synovitis of RA. The relation between MMP-3 and some inflammatory markers are analyzed statistically and an inflammation mechanism of RA is supposed.[Method] 1175 patients with RA are divided into 4 groups < 0.1, 0.1-0.3, 0.3-3, 3< by CRP. A relation between CRP and 1/Fe, MMP-3, Granulocyte, Gamma globulin (γ-glb) and in each group, a relation between MMP-3 and 1/Fe, CRP, Granulocyte, γ-glb are examined for a rank correlation coefficient and a multiple regression analysis.[Result] CRP was related to 1/Fe (equivalent to Proinflammatory cytokine, following Cytokine) in particular, MMP-3, Granulocyte, γ-glb, respectively.MMP-3 was related only to Granulocyte in CRP<0.1,and in 0.1-0.3 to Granulocyte mainly and 1/ Fe weakly, and in 0.3-3 to CRP and 1/ Fe mainly and Granulocyte weakly and in 3<CRP only to γ-glb.[Conclusion]In low Cytokine, the inflammation related to Granulocyte predominates in the synovitis of RA, and Cytokine predominates in the rise substitute for Granulocyte, in rising more, γ-glb predominates. We suppose that the synovitis of RA occurs in an inflammation due to the innate immunity in low to middle activity and an acquired immunity in high activity and that the innate immunity is related to the onset of RA as well as early RA.

P3-050

Gender difference in forefoot deformity in the patient with rheumatoid arthritis

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Conflict of interest: None

Purpose: Rheumatoid arthritis (RA) patients undergoing surgical treatment for their forefoot deformity are mostly women. This high rate of surgical treatment in female seems much higher than the prevalence of forefoot involvement by arthritis condition. Therefore, in this study we evaluate the factors contributing to forefoot deformity, and investigate the significance of gender difference in the forefoot deformity. Method: In this cross sectional study, 165 women and 100 men were enrolled. The difference between men and women in forefoot deformity was assessed by patient characteristics, radiographic and blood examination. Result: Statistical analysis revealed that age, sex, BMI, disease duration, Steinbrocker staging, angle of M1/M2, M1/M5 and calcaneal pitch, ESR, CRP, MMP-3, ACPA were correlated with hallux valgus angle by a single regression analysis. By a multiple regression analysis age, BMI, stage,

M1/M2 and M1/M5, as well as female gender were correlated independently with hallux valgus angle. Conclusion: Hallux valgus deformity observed in the patients with RA was predominant in female gender, which was independent with Steinbrocker Staging. This finding emphasizes that female gender is one of the factors to deteriorate for progress of rheumatoid forefoot deformity.

P3-051

Fractures lead to worsening of disease activity in rheumatoid arthritis

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Conflict of interest: None

Objective: The cause of RA flares is multifactorial and little known. The purpose of this study was to determine whether fractures influence disease activity in RA patients. Methods: A total of 189 patients who had achieved the minimum value of the DAS28-ESR (min DAS28-ESR) in the course of treatment and could be observation least six months were enrolled from 2011 and 2014 for the multiple liner regression analysis. The explanatory variable was set to age, sex, disease duration, stage, class, RF, ACPA, min DAS28-ESR, follow-up period and an incidence of fracture, and the objective variable DAS28-ESR at the last observational period (last DAS28-ESR). We examined the incidence of flare using DAS28-ESR, DAS28-CRP and drug changes before bone fracture until bone union. Results: The analysis showed that female ($p<0.001$), bottom DAS28-ESR ($p<0.001$) and fracture ($p=0.041$) were the independent risk factors for last DAS28-ESR. The average DAS28-ESR value was significantly increased from 3.19 (pre-fracture) to 3.58 (bone union). The average DAS28-CRP value was also significantly increased from 2.45 (pre-fracture) to 2.79 (bone union). Conclusion: We have demonstrated that fractures influence disease activity in RA patients. Prevention of fracture is clearly necessary for RA patients.

P3-052

Monoclonal ACPA derived from rheumatoid arthritis patients reacts with numerous citrullinated microbial and food proteins

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Conflict of interest: None

We obtained a human monoclonal ACPA (cyclic citrullinated peptide antibody 1 [CCP-Ab1]) from peripheral blood lymphocytes from patients with RA using a novel monoclonal antibody-secreting cell (ASC) screening system, the immunospot-array assay on a chip (ISAAC). The essential epitope for CCP-Ab1 was determined using epitope mapping. Then, human, microbial, and plant proteins that share the essential epitope identified were searched using BLAST. Finally, representative proteins identified by the search were produced in vitro, and their reactivity with CCP-Ab1 was examined. CCP-Ab1 bound CCP in a citrulline-indispensable manner. In CCP, the 6 amino acid residues required for CCP-Ab1 binding were identified. In the BLAST search, 38 human, 56 viral, 1,383 fungal, 547 bacterial, and 1,072 plant proteins were found to share the essential epitope, and CCP-Ab1 reacted with all of the recombinant citrullinated proteins tested, which included the various environmental factors. These results indicate that the CCP-Ab1 is cross-reactive to citrullinated proteins of not only human but also other organism. We propose that infection of many bacteria or virus and citrullination of these microorganisms proteins induce ACPA as a result of molecular mimicry.

P3-053

Effects of the HDAC inhibitor on rheumatoid arthritis synovial fibroblasts

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Conflict of interest: None

Plasma IL-6 concentration is known to be elevated in patients with rheumatoid arthritis (RA) as compared from healthy individuals. Since actions of IL-6 represent most of RA pathophysiology, we have focused on the production of IL-6 from the synovial fibroblasts obtained from RA patients during surgical operations. Under non-inflammatory environments the synoviocytes from RA exhibited elevated production of IL-6, suggesting aberration in the regulation of IL-6 gene expression. In addition, the IL-6 protein levels varied even among RA patients. These results lead us to examine the efficacy of inhibitors of histone deacetylase (HDAC). We observed significant repression of IL-6 protein expression in all RA cells examined. Moreover, we measured the mRNA levels of cytokines including IL-6 by real time RT-PCR. These results suggest a possibility that inhibitory mechanism might be involved in the RA pathophysiology through epigenetic regulation.

P3-054

Four cases of methotrexate-associated lymphoproliferative disorders

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Conflict of interest: None

Methotrexate (MTX) has been reported to increase the risk of lymphoproliferative disorders (LPD). We have reported four cases of MTX-associated LPD. Case 1: A 78-year-old man with active rheumatoid arthritis (RA) had been treated with MTX (4-8 mg/week) for 7 years, and CT imaging revealed the right inguinal lymphadenopathy. Case 2: A 73-year-old woman with active RA had been treated with MTX (6mg/week) with infliximab for 7.5 years and tocilizumab for 0.5 year and CT imaging revealed tumor in the right greater pectoral muscle and left inguinal tumor. Case 3: A 57-year-old man with active RA had been treated with MTX (6-12 mg/week) and etanercept for 5 years, and CT imaging revealed both axillar lymphadenopathies. Case 4: A 71-year-old woman with active RA had been treated with MTX and etanercept for 3 years, and CT imagind revealed a multiple pulmonary tumor and occipital and cervical lymphoadenopathy. Only one case was MTX alone treatment. A Lymph node biopsy was performed in two cases. Histological finding revealed that lymph node had necrotic portion in a case, and a positibe immunological staining of CD30 and EBER in a case and positive CD30 and negative EBER stainings in other case.Withdrawal of MTX treatment has led complete remission in four cases.

P3-055

Large pericardial effusion in a patient with rheumatoid arthritis

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Conflict of interest: None

A 38-year-old woman was admitted to our hospital complaining of dyspnea. She was diagnosed with rheumatoid arthritis at 22-year-old, and was treated with DMARDs. For the past 10 years, she has been treated with MTX, PSL, and BUC. Moderate to high disease activity persisted and joint destructions gradually progressed. She acquired MAC lung disease at 31-year-old, and she had been suffered from chronic respiratory symptoms. A day before admission, she experienced nausea and vomiting with exacerbation of cough and dyspnea. On admission, her blood pressure was 130/80 mmHg then dropped to 80 mmHg in few hours, and pulse rate was 120-150 bpm. Chest X-ray showed cardiomegaly, CT demonstrated a large pericardial effusion. Echocardiogram showed signs of restriction of cardiac filling by the effusion. Cardiac tamponade was diagnosed and pericardiocentesis performed, yielding 100 ml of serum fluid. Laboratory data of the fluid indicated normal ADA, high rheuma-

toid factor and low complements level. Bacterial cultures showed no organisms and mycobacterium. These findings suggest that rheumatoid pericarditis was considered to be the cause of pericardial fluid. She was treated with loxoprofen, resulted in a marked reduction of pericardial effusion and no recurrence up to now.

P3-056

Assessment of activity with rheumatoid arthritis by Onomatopoeia

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Conflict of interest: None

Objective: To identify the relationship with rheumatoid activity and Onomatopoeia Methods: Onomatopoeia questionnaires in rheumatoid arthritis (RA) was conducted in 147 patients whose average age was 64 years and average duration was 14 years. 9 items of Onomatopoeia expression in the time of onset whose group 1 was (jinnjinn, piripiri, chikuchikuk), group 2 was (zukizuki, zukinzukin, zuki-nzuki-n) and group 3 was (gangan, gishigishi, gorigori) were chosen by each 147 RA patient. Results: The cases that selected only one item of Onomatopoeia were 107 cases. These 107 cases were divided into three groups. 25 cases were group 1, 80 cases were group 2, and 2 cases were group 3. Furthermore 34 cases selected two or more items. The positive rate of rheumatoid factor and anti-CCP antibody were relatively higher in group 1 compared with group 2 although the activity of RA were not differentiated with three groups. Conclusion: Whether the rheumatoid activity was not evaluated by Onomatopoeia expression, henceforward pain assessment of RA patients by Onomatopoeia will be useful to more fine treatment against arthritis related pain.

P3-058

Joint prognostic factors on CRP negative ultrasound power doppler positive RA patients

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Conflict of interest: None

(objective)We sometimes see difficult cases in diagnosing and evaluating prognosis of CRP negative RA patients. In this study we studied joint prognosis of CRP negative and ultrasound power doppler (USPD) positive RA patients followed in our hospital. (material & method) From Jan.2013 to Oct. 2014, among DMARD naive CRP negative RA patients, diagnosed and followed in our hospital, USPD positive patients were extracted and their hand and foot were evaluated with modified sharp score at 0 and 52 week. We set up two groups, more than one sharp score increase was found in P group (PG), no progression was found in N group (NG) 52 weeks later. We compared two groups about RA disease activity factors. (result) NG was included in 8 cases (2male, 6 female), PG 6 cases (1 male 5 female). Mean age was 55.9 years old, disease duration 6.2 month, serum CRP 0.15 mg/dl, MMP-3 84.3 ng/mL, RF 72.7mg/dl, ACPA 130U/mL, DAS 28 3.28, SDAI 10.9, while only ACPA (NG 100:PG 169.6)U/mL was significantly high in PG ($P<0.05$). Among USPD positive joints, one joint of 20 in grade 1, 3 joints of 9 in grade 2, 2 joints in 2 in grade 3 were progressively destructed one year later. (conclusion) ACPA and serum USPD are important prognostic factors on serum CRP negative RA patients.

P3-059

Swollen to tender joint count ratio is a feasible predictive marker of joint destruction, but is not a response marker of tocilizumab in rheumatoid arthritis patients

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Conflict of interest: None

Objective: The swollen to tender joint count ratio (STR) has been newly suggested as a new response predictor of anti-tumor necrosis factor (TNF) treatment in rheumatoid arthritis (RA) patients. However, the relationship between STR and response to tocilizumab (TCZ) therapies is unclear. The aim of this study is to clarify the impact of STR on treatment response to TCZ therapy in RA patients. Methods: A total of 87 RA patients were included in this study (average age 61 years, 18 male, 69 female). All patients were treated with TCZ for 24 weeks or longer. Patients were categorized as having low (STR < 0.5), moderate ($0.5\leq$ STR ≤ 1.0), or high (STR > 1.0) joint count ration. Results. 9 patients had a low STR, 27 patients had a moderate STR, and 51 patients had a high STR. The Δ DAS28-ESR, Δ CDAI and ΔmTSS (Δ; post-treatment? baseline) is not significantly linked to STR. However, Δ MMP-3 is significantly related to STR (High STR MMP-3 vs. Low + Moderate MMP-3: 194.6 vs. 44.2 ng/ml; $p = 0.03$). Conclusion: STR is a feasible predictive marker of joint destruction, but is not a response marker of TCZ.

P3-060

CDC versus CDR - Which index is appropriate for clinical evaluation beyond T2T treatment protocol in a middle term? -

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Conflict of interest: None

[Objectives] In order to compare comprehensive disease control (CDC) and comprehensive disease remission (CDR) in rheumatoid arthritis (RA) treatment, clinical results in a middle term were compared. [Methods] 392 RA patients who have been treated consecutively for more than 3 years were picked up. CDC is defined as DAS28-CRP less than 2.3, as dSHS no more than 0.5, and as HAQ-DI less than 0.5, while CDR is defined as CDAI less than 2.8, and other indices are as same as CDC. Accomplishment ratio in first treatment year (AR), sensitivity and specificity after 4th year (Se and Sp), mean values of DAS28-CRP, CDAI, dSHS, HAQ-DI, pain score (PS), MMP-3 for CDC and CDR were compared statistically with Chi square test and Mann-Whitney test. [Results] AR, Se, and Sp for CDC and CDR were 52.8% and 23.7%, 49.6% and 78.9%, 93.9% and 87.5%, respectively. Mean values of each indices for DCD were 1.67, 3.43, -0.84, 0.14, 1.65, and 69.8, while 1.50, 2.33, -0.86, 0.16, 1.30, and 64.6 for CDR, with DAS28-CRP, CDAI, dSHS, HAQ-DI, PS, and MMP-3, respectively. No statistical significant difference less than 5% have been demonstrated between the two. [Conclusions] No difference has demonstrated in clinical results. CDC is more likely to be appropriate for clinical perspectives in a middle term future.

P3-061

Comparison of rheumatoid arthritis patient with disease activity in high state

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Conflict of interest: None

Purpose: To compare RA patients according to the cause of moderate or high disease activity, who where treated at our hospital for more than half a year. Subject: In total 41 patients out of 331 RA patients who admitted our department between July to September, 2015 where examined. 34 patients with moderate disease activity and 7 patients with high disease activity were studied. Results: Mean age was 69.8 years old, 75.6% were female, and mean duration of disease was 17 years and 11month. Patients were categorized into 4 groups. 11 patients had complications such as chronic respiratory infection that gave significant effect on choosing which drugs to use (groupA). 10 patients would not agree to tight control such as using biologics (groupB). 6 patients accidentally showed flair up during observation (groupC). 14 patients were not able to divide in to these group above and were resistant to treatment (groupD). Group A had significantly high ESR compared to non group A. Group D had significantly low swelling joints, CRP, ESR, DAS28-CRP, MMP-3 compared to non group D. Discussion: Half the patients of disease activity in high state were categorized to group A or B and were not able to carry out T2T. Group D showed low inflammatory reaction and pain remaining results.

P3-062

Factors related to DAS28ESR remission at the first visit

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Conflict of interest: None

The first target of RA treatment is to reach clinical remission, and it is very useful if factors related to remission are available. We retrospectively analyzed the factors related to clinical remission at the first visit. Subjects were 435 patients with RA with the mean age of 66 years. Mean disease duration was 13.8 years (2 - 60 years). Stage 1/2/3/4 and class 1/2/3/4 were 177/129/58/70 and 164/183/69/4, respectively. ILD was graded into 0 - 3 using mainly chest CT images. MTX and PSL were used in 63.4%(mean dose 8.4mg/week) and 59.2%(mean dose 5.3mg/day), respectively. bDMARDS were used in 32.7%. Mean DAS28ESR at the first and last visit were 4.74 and 2.83, respectively. DAS28ESR remission was reached in 45.2%. Discrimant analysis was done incorporated 15 variables such as age, gender, duration of illness, stage/class, ILD grade, dose of MTX/PSL, and use of bDMARD and SSZ/BUC. Six factors were extracted related to DAS28ESR remission, i.e, stage/class, dose of MTX, use of SSZ/BUC, RF titer and eGFR, but coefficients were negative except eGFR. It is suggested that reaching remission is difficult in patients with advanced and active disease.

P3-063

Treat-to-target strategy might be available for older patients with rheumatoid arthritis -from the TOMORROW study-

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Conflict of interest: None

Background: The aim of this study was to examine the possibility of intensive therapy for older patients with RA (rheumatoid arthritis) using the data of a cohort study including 208 RA patients and age- and gender-matched 205 non-RA individuals, TOMORROW study. Methods: We compared the dose of MTX and glucocorticoid (GC), DAS28-ESR, GFR, biologics use between older (≥65) and younger (<65) patients including longitudinal changes for 5 years. Results: DAS28-ESR was significantly higher in older group (3.83±1.31) than younger group (2.91±1.49). The dose of MTX was significantly lower in older group (8.31±4.33) than younger group (10.1±3.5 mg/week). The dose of GC was higher in older group (4.3±2.8) than younger group (3.5±2.2 mg/day). Older group showed low GFR (71.1±22.1) than younger group (89.7±22.8 ml/min/1.73m^2). There was no difference in the rate of biologic use. Multiple regression analysis revealed that DAS28-ESR was associated with age, gender, and dosage of GC. The five-year change of GFR was significantly worse in non-RA subjects. Conclusions: The older RA patients were receiving lower dose of MTX and higher dose of GC. However intensive therapy might be possible for older RA patients judging from the renal function.

P3-064

Treat to Target (T2T) of Frailty in the Elderly RA patients

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Conflict of interest: None

Introduction Frailty is a term widely used to denote a multidimensional syndrome of loss of reserves (energy, physical ability, cognition, health) that gives rise to vulnerability. The prevalence of frailty estimates of 11% have been reported in non-institutionalized, community-dwelling older adults. The early recognition of frailty is important in elderly RA patients to prevent a catastrophic decline in function and health. M & M Total 34 elderly RA patients (6 of male and 28 female) were enrolled in this study. The average age was 77.6. According to the Japanese society of geriatric medicine, a person is defined as frail if 3 or more symptoms (of unintentional weight loss, feeling exhausted, weak grip strength, slow walking speed and low physical activity) are present. Results The prevalence of frailty in this study was 97% and declined significantly following the treatment to 24%. It was correlated as the DAS28 score. Discussion Consider the Treat to Target of frailty in elderly RA patients, to regulate the disease activity using biologics, enhance physical activity by rehabilitation, and support their mental states is important.

P3-065

Examination of the predictive factors of short-term treatment outcome of Certolizumab pegol in patients with rheumatoid arthritis

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Conflict of interest: None

[Object]In Certolizumab pegol (CZP) treatment, 12-week outcome is correlated with 1-year achievement of low disease activity. The object of this study is to examine predictive factors of short-term treatment outcome of CZP. [Methods]Twenty-seven patients with RA [24 females, 49.3 y, DAS28-CRP 3.6, combined MTX 6.4mg/week (74.1%), bio-naive (n=13), CZP loading 85.2%] were enrolled in this observational study. [Results]12-week continuous rate of CZP was 70.4%, and the main reasons of the discontinuation was lack of efficacy (50.0%) and loss of efficacy (25.0%). Achievement ratio of low disease activity (DAS28-CRP <2.7; 12→24 weeks) was 61.5→87.5% in bio-naïve, and 50.0→78.6% in bio-switch patients. At 12-week, low disease activity was achieved in 75.0% patients whose baseline peripheral blood lymphocytes were >75.0%, and 84.6% patients whose Body Mass Index (BMI) were <20.5 kg/m^2. Comparison between continued group (n=19) and discontinued group (n=6) at 12-week showed significant difference in baseline peripheral blood lymphocytes number and percentage (1815 vs. 1238 /μL; P=0.02/26.6 vs. 18.1 %; P=0.009). [Conclusions]Our results suggest that baseline peripheral blood lymphocytes and BMI may be possible predictive factors of 12-week low disease activity achievement by CZP.

P3-066

Results of MTX + Adalimumab (ADA) treatment (2 years) of RA patients: Factor analysis of concomitant use of MTX ≥8 mg/week concomitant use in remission cases and MTX ≤12 mg/week in non-remission cases

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Conflict of interest: None

[Objective]: To perform factor analysis of concomitant MTX ≤8 mg/wk (≤8 mg) in remission cases and MTX ≥12 mg/wk (≥12 mg) in non-remission cases in MTX+ADA treatment. [Methods]: Of 185 analyzable patients introduced to ADA from May 2009 to October 2013, 25 in the ≤8 mg and 105 in the ≥12 mg groups were enrolled. Various parameters of DAS remission and non-remission cases were compared at baseline, 4 and 8W to investigate the remission predictors and cut-off values by ROC analysis. [Results]: SJC at 4 and 8W, ESR and physician-assigned VAS at 8W, and CRP at 4W were significantly low in the remission cases of the ≤8 mg group. SJC≤4 at 4W, SJC≤3 at 8W and ESR≤16 at 8W were set as cut-off values and extracted as remission predictors. In the ≥12 mg group, use of PSL, Stage/classification, DAS, MMP3, physician-assigned VAS at 8W, and DAS28 at baseline were significantly high in the non-remission cases. ESR≤20, physician-assigned VAS ≤6, DAS28ESR ≤3.49, and DAS28CRP≤1.96 at 8W were extracted as remission predictors. [Conclusion]: The findings demonstrated that if the MTX dose is non-increasable, remission could be predicted with SJC and ESR as Merkmal at 4 and 8W even in concomitant use of ≤8 mg.

P3-068

Prognosis prediction for rheumatoid arthritis by using a novel assessment measure-joint index vector: A multicenter observational study based on the *NinJa* (National database of rheumatic diseases by IRNet in JAPAN)

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Conflict of interest: None

Background: Joint index (JI) vector, Vji is a novel 3-dimensional assessment measure for RA.**Aim:** To examine the prognosis for RA by using Vji.**Methods:** JI of upper/large (UL), upper/small (US), lower/large (LL), and lower/small (LS) was previously described[1]. Vji (x, y, z) for 10,872 patients with serial registration both in 2013 and 2014 *NinJa* database was calculated as $x = JI_{UL} + JI_{US}$, $y = JI_{LL} + JI_{LS}$, and $z = JI_{UL} + JI_{LL} - JI_{US} - JI_{LS}$. Patients were classified by $|V| = \sqrt{(x^2+y^2)}$ and z values (G1: $|V| \leqq 0.1$, G2: $|V|>0.1$ & $|z| \leqq 0.2$, G3: $|V|>0.1$ & $z<-0.2$, G4: $|V|>0.1$ & $z>0.2$).**Results:** Patients of G1 had the lowest level of SDAI and HAQ, and those of G3 had the highest SDAI level among the four groups, while patients of G4 had the longest disease duration and the highest level of HAQ. Patient rate of each group in 2013 who entered G1 in 2014 was 71.2, 32.7, 23,3, and 22.9%, respectively. Shorter disease duration and fewer steroid user rates were the predictive factor of entering G1 in 2014 for patients of G1, G2, or G4 in 2013, while upper joint superiority was the predictive factor of entering G1 in 2014 for those of G3 in 2013.**Conclusion:** Four groups classified by Vji had different prognosis and predictive factor.**Reference:** 1. Nishiyama S, et al. Rheumatol Int. 2012:32;2569-71

P3-069

Analysis of association of disease flare and functional disability in RA patients in DAS28 remission state using the IORRA cohort.

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Conflict of interest: None

[Object] To investigate association between DAS28 based flare and functional disability in RA patients in DAS28 remission. [Methods] RA patients in DAS28 remission in the IORRA cohort in April 2012 were selected and evaluated in October 2013. Flare at 6 months later was evaluated according to 4 previously reported DAS28 based flare criteria: 1)increase in DAS28 > 1.2, 2)increase in DAS28 >0.6 or DAS28 >3.2 at baseline, 3)DAS28>3.2, and 4)DAS28>2.6. Progression of J-HAQ (DJ-HAQ: J-HAQ in October 2013 - J-HAQ in April 2012) was evaluated in each patients. The association between DJ-HAQ and RA flare defined by each criteria was analyzed using multiple regression analysis. [Results] A total of 1,874 patients were analyzed. Proportions of the patients with flare were 1) 9.7%, 2)24.4%, 3)11.3%, and 4)28.1%, respectively. Multiple regression analysis confirmed that DJ-HAQ in patients with each flare criteria was 1)0.11 ($p<0.001$), 2)0.05 ($p<0.001$), 3) 0.10 ($p<0.001$), and 4)0.04 ($p<0.01$). [Conclusions] Regardless of flare criteria, RA flare was strongly associated with progression of functional disability. The flare criteria of "increase in DAS28 >0.6 or DAS28>3.2"and "DAS28>2.6"are useful to predict less progression of functional disability.

P3-070

A comparative study conducted by the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) of treatment conditions existing between hospitals and clinics of rheumatoid arthritis patients under the age of forty

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Conflict of interest: None

Purpose: The AORA analyzed whether there were differences in the states of treatment existing between clinics and hospitals in the case of rheumatoid arthritis (RA) patients within the age of forty. **Methods:** This study was based on AORA's 2014 records of registered RA patients. Out of 1,987 patients, 61 (3.1%) patients were under age forty. There were two groups which were divided between clinic-going (Group C) and hospital-going (Group H). Individuals were assessed on disease duration, their Steinbrocker classification, type of medicinal treatment, and patient's disease activity level. **Results:** No significant difference was observed between two groups in disease duration and Steinbrocker classification. The prescription ratio of MTX in Group H was 59.4%, and 58.6% in Group C. Prescribed biological products ratios were 46.9% for Group H and 20.7% for Group C. Patient disease activity levels were assessed according to DAS28 CRP and the average results for Group H and C were 2.41 and 2.12, respectively. Successful remission rates were 59.4% for Group H and 69.0% for Group C. **Conclusions:** Among RA patients within age 40, compared to Group C, there was a high inclination to prescribe biological products in Group H.

P3-071

Analysis of patient reported outcome in patients with early rheumatoid arthritis

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Conflict of interest: None

To evaluate the improvement of social role, mental components in patients with rheumatoid arthritis (RA), we measured the patient reported outcome (SF-39,HAQ-DI) DAS28, ultrasound, bone change. Physical and mental, social role by SF-36 were measured 152 patients with RA. Moreover we prospectively examined these components in SF-36 in 66 patients early RA (disease duration < 12 months).Results:early RA (mean disease duration 0.57±0.5 year, female 72%) DAS28 (4.4±1.5), HAQ-DI0.78±0.66, SF36:Physical component scale (PCS)38,2±12, Mental component scale (MCS) 50.3±7.1,Social role component scale (RCS) 40.1±13.1 (each standardized sacle in Japanese 50±10). After 24 weeks these RA patients revealed DAS28 2.3±0.6 (remission 69%, LDA21%, MDA9.6%. HDA0%) by treatment (bDMARS27%, csDMARDs20%,MTX68%) SF-36 components were showed increased PCS:3.1±11.8, RCS:9.8±11.4. Conclusion: The analysis of SF-36 component score (PCS,MCS, RCS) indicated the effect of bDMRDSs and csDMARDs on quality of life in patient reported outcome of early RA.

P3-072

No correlation between disease activity score and modified health assessment questionnaire in elder patients with rheumatoid arthritis

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Conflict of interest: None

Object. The therapy for rheumatoid arthritis (RA) has been improved by MTX and biological agents. However, the disability is serious in those who have irreversible joint destruction, even if the disease activity is improved. Declining physically with aging, the elder patients with progressed RA may have much more defects. Therefore, we investigated the connection between the activity of RA and the influence on the daily life of the elder patients treated in our hospital located in a remote rural area. **Methods.** Twenty four patients with RA who had been treated in Jinsekikogen Town Hospital from Sep. 2014 to Sep. 2015 were contained. We collected items from medical records. **Results.** The mean age was 82.8 ± 7.0. The mean of DAS 28-CRP, DAS 28-ESR, and mHAQ was 2.80 ± 1.31 (n = 13), 3.88 ± 1.24 (n = 13), and 0.56 ± 0.86 (n = 12), respectively. The ratio of patients treated with MTX was 29.4%, combination of DMARDs excluding steroids was 20.8%, only steroids was 8.3%, and biologic agents was none. There was no correlation between mHAQ and DAS 28-CRP (p = 0.788) or DAS 28-ESR (p = 0.893). **Conclusion.** The patients treated in our hospital were 82.8 years old. The activity of RA was moderate and mHAQ was 0.56. There was no correlation between mHAQ and the activity of RA.

P3-073

Predicting the responses to biological therapy by two kinds of antibodies titers against *Porphyromonas gingivalis* in RA patients

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Conflict of interest: None

Background: The prediction of clinical response to biologics (Bio) in RA patients is difficult. Recent report shows that clinical response to TNF-i was related to periodontal conditions, which might be affected by infection with *Porphyromonas gingivalis*(*P.g*). And serum antibody against *P.g* were associated with RA and periodontitis. Objectives: To evaluate whether serum antibody against *P.g* antigens and periodontal conditions are associated with clinical response to Bio in RA. Method: 20 patients were treated with Bio according to the usual regimen. Clinical background and disease parameters (RA and periodotits)were assessed at entry. DAS28CRP was evaluated at 6 months Bio treatment. Serum levels of antibodies against *P.g* sonicated extracts (SE) and hemin binding protein (HBP) of *P.g* were determined by ELIZA. Results: Most patients had active disease with DAS28CRP 4.2 (0.9) at entry, and showed an improvement of DAS28CRP 2.87 (0.82) after 6Mo. The mean serum levels of antibodies against *P. g* SE and HBP were 15.9 (52.3) and 0.632 (0.276), respectively at entry. Antibody titers against *P.g* SE gradually decreased, but anti-*P.g* HBP increased during 6 Mo. No associations were observed between changes in DAS28CRP and serum and periodontal parameters including anti- *P.g* SE and P.gHBP.

P3-074

Validity and Reliability of Hand 20 Questionnaire in Rheumatoid Arthritis Patients

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Conflict of interest: None

Objective) Objective was to validate Hand 20 questionnaire in Rheumatoid arthritis (RA) patinents. Hand 20 questionnaire was developed by Hand Frontier and was reported its usefulness for elderly patients. Patients and Methods) Hand 20 was applied to our 200 RA outpatients. Results) Total score wad 38.09, and the average of each question was 2.93. Patients answered blank in more than 3 questions was just 1%. Discussion and Summary) Hand 20 questionnaire contains 20 questions including question of hand appearance. Hand 20 was seemed suitable for evaluating upper extremeity impairments, disability.

P3-075

Polymorphism analysis to predict methotrexate efficacy in rheumatoid arthritis

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Conflict of interest: None

[Object] Methotrexate (MTX) is the first-line DMARD used for the treatment of rheumatoid arthritis (RA). However, when patients inadequately responded to it, an increase of the dosage or a switch to bDMARD is necessary as early as possible. In this context, tools that predict the response to MTX are clinically important. Thus the objective of this study is to analyze gentic polymorphisms associated with the response to MTX. [Methods] The subjects consisted of 171 cases (25 male cases, average age: 63.5 years old) of patients. The subjects were divided into two groups; the responder (n=73) who achieved low disease activity or remission with csDMARD and the non-responder (n=98) who were remained moderate/high disease activity or stepped up to bDMARDs. Ninety-six candidate SNPs were examined with the association of the groups. [Results] The minor allele of polymorphisms of the gene encoding organic anion transporting polypeptide 1B1 (SLCO1B1), rs11045879 and rs4149081, tended to be classified as non-responders (odds ratio; 0.55, 95% CI;0.33-0.88, P=0.015). [Conclusions] SLCO1B1 is a membrane transporter which is involved in the MTX efflux mechanism. SLCO1B1 polymorphisms could be a useful tool to predict patients at risk of non-responder to MTX in RA patients

P3-076

Treatment strategy approaching to maintain clinical remission by withdraw biologics

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Conflict of interest: None

The aim of this study was to assess whether withdrawal or discontinuation of biologic agents is possible after sustained remission and to discusses its effectiveness from the clinical point of view in rheumatoid arthritis patients. Disease activity score (DAS28CRP) and roentgenogram were researched in 20 rheumatoid arthritis patients (average age 58yo, morbidity duration 64 months) who were treated by biologic agents (ETN 13,ADA4, TCZ 2, ABT 1) at the start of full dose treatment (DAS28CRP 3.54) and serially after sustained remission (DAS28CRP<2.6). Withdrawal of agents were started in 11 months (DAS28CRP 1.83) after treatment and remission were remained in16 patients at final follow-up (35 months). The treatment strategy approaching to maintain clinical remission by withdraw biologics are useful for rheumatoid arthritis patients.

P3-077

Survey of biologics to treat rheumatoid arthritis (RA) patients in our related clinic

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Conflict of interest: None

[Objectives] To investigate the status of the biologics use in our related clinic. [Methods] 59 patients who treated with biologics in our related clinic were included in this study. We investigated the introduction of biologics, dosage, change of the concomitant medication, disease activity score (DAS28CRP) and MMP-3. [Results] The average age were 52.5 years old. Duration of biologics introduction from the RA onset was 67.4 months. 42 cases were introduced the biologics in this clinic. Etanercept (ETN) in 48 cases, tocilizumab and adalimumab in three cases of each were administrated at first. There were 29 cases that introduced ETN 25 mg/week, but it was only five cases that increased 50mg/week for insufficiency. In addition, there were 32 cases that reduced biologics all over the progress. The concomitant medication at the introduction was a methotrexate (MTX) 47 cases (81.4%), prednisolone (PSL) 32 cases (54.2%), but decreased with MTX 43 (72.9%), PSL 23 (39.0%) after the introduction of biologics. DAS28CRP decreased to 2.39 from 3.81 after 12 months, and MMP-3 decreased with 72.0 ng/ml from 148.7 ng/ml, also.[Conclusions] 59 cases were introduced with biologics in our patients. The efficacy of biologics was accepted even in low dose of biologics.

P3-078

Etanercept reduction in rheumatoid arthritis

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Conflict of interest: None

Objective: The aim of this study was to assess the background of patients with dose reduction or discontinuation of etanercept. Methods: We investigated DAS28,age,desease duration of 20 patients with dose reduction or discontinuation of etanercept (reduction group),39 patients with continuation of etanercept (continuation group). Results: 16 of 20 patients given 50mg/week etanercept are able to dose reduction, 1 of dese reduction patients is able to discontinuation of etanercept.4patients given 25mg/week etanercept extended to 25mg/2week.DAS28 of reduction group decrease from 4.27at baseline to 2.18 at dose reduction,but 3 patients were dose reduction with DAS28 moderate response.It significantly had a short contraction of disease duration at reduction group rather than continuation group.The facts of dose reduction were in remission (14 patients),cost effectiveness (3 patients),safety (3 patients).The facts of continuation were in steroid tapering difficulties (22 patients),not remission (10 patients),worry about loss of disease activity (7 patients). Conclusion: In a common clinical manner,it was dose reduction of etanercept about 30% patients when etanercept was continuously administered to RA patients in the long term,but some of them were dose reduction because of cost effectiveness.

P3-079

Analysis of spacing of the intravenous administration of tocilizumab(TCZ) in patients with rheumatoid arthritis(RA)

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Conflict of interest: Yes

Purpose: To analyze the efficacy of spacing of the intravenous (iv) administration of TCZ in patients with RA. **Methods**: Enrolled were 63 patients (M 11, F 52) who were administrated iv TCZ for more than 1 year. Eleven patients had shifted to subcutaneous injection and the data at the last iv infusion were analyzed. **Results**: Mean age was 57.4YO (30-78), mean body weight was 55.5kg (37-85.5), mean duration of illness was 10.7yrs (0-32), Stage were 4/12/20/27, Class were 0/41/22/0, the number of the former biologics were 0.9 (0-3), and duration of TCZ was 46.9 M (13-83). The intervals of administration were 4W: 28.6, 5W: 38.1, 6W: 17.5, 7W: 6.0, 8W: 7.9, 10W: 1.6%. Disease activities were significantly ameliorated. The remission rats were DAS28-ESR 90.5, CDAI 44.4, SDAI 42.9%, respectively. PSL were used in 50 to 38 patients ($p=0.031$), 4.2 (0-10) to 1.7 (0-5) mg/day ($p<0.0001$). MTX were used in 46 to 32 patients ($p=0.017$), 6.0 (0-18) to 3.3 (0-14)mg/W ($p<0.0001$). There were no changes in the usage of other DMARDs. **Conclusion**: TCZ significantly reduced disease activity, PSL and MTX. Spacing of the administration were done in 71.4 % of the patients. TCZ is the most inexpensive biologics, and with spacing, it is possible to reduce more cost with a good control of RA.

P3-080

A study of dose reduction of certolizumab pegol for the patients with rheumatoid arthritis

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Conflict of interest: None

【Objective】Certolizumab pegol (CZP) is PEGylated anti-TNFα biologic to treat rheumatoid arthritis patients. It has a characteristic to keep its blood level longer. Then it would be possible to reduce the dose of CZP after the remission. 【Background of patients】We studied CZP treated five RA patients with high disease activity (DAS28ESR 5.05±0.92). Their background is as follows; Male/Female: 0/6, seropositive/seronegative: 4/1, StageI/II/III/IV: 0/3/1/1, Class1/2/3/4: 1/3/1/0, average dose of MTX: 9.6±2.6mg/week, MTX/MTX+SASP: 3/2, predonisolone use: 2 cases. The average follow up period is 18.8±4.0 months after CZP treatment. 【Results】Within the first three months, patients were injected 200mg dose of CZP every two weeks after the loading dose injection. If the patients achieved the remission or LDA, they were injected 400mg CZP every four weeks. When they kept the remission or LDA at the three months after the initial injection, they were injected 200mg dose of CZP. Thereafter, patients could be kept remission or LDA after the dose reduction of CZP. 【Conclusion】When RA patients treated with CZP achieved the remission or LDA over one year, their disease activity could be controlled with 200mg dose of CZP every 4weeks with adequate dose of MTX and other csDMARD.

P3-081

Prolonged interval of TCZ administration was possible in RA patients with sustained SDAI remission by TCZ

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Conflict of interest: None

[Objectives] To investigate the possibility of interval prolongation of tocilizumab (TCZ) administration in RA patients under sustained SDAI remission. [Methods] 23 RA patients receiving TCZ more than 1 year were evaluated. After achieving SDAI remission, if SDAI remission lasted more than 6 months, the interval of TCZ administration was prolonged one week. Sustainability of SDAI remission was evaluated. Additionally, TCZ administration changed from DIV to SC injection for patients with sustained remission at longest DIV interval. [Results] SDAI remission was achieved in 20 (87%) out of 23 cases within 11.6 months. Prolonged interval of TCZ administration was possible in 17 cases. More than 7 weeks interval was achieved in 7 cases, 6 weeks interval in 5 cases, 5

weeks interval in 5 cases, but interval was not prolonged in 6 cases. Those with longer interval had short disease duration and younger age. Those with no interval prolongation had long disease duration and high disease activity. Low CRP and MMP-3 levels were observed in patients with longer TCZ interval. In 18 cases with sustained SDAI remission, switch from DIV to SC injection was possible. [Conclusion] Prolongation of TCZ injection interval was possible under sustained SDAI remission with low CRP and MMP-3 levels.

P3-082

Effects of extended dosing intervals of biologics in patients at our hospital

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Conflict of interest: None

Objective: To evaluate treatment outcomes of patients receiving biologics with extended dosing intervals at our hospital. Methods: All patients with rheumatoid arthritis who were using biologics at our hospital between September 2014 and December 2015 were divided into those who received the drug by the usual administration and by extended dosing intervals. Possible differences in treatment outcome between the different methods of drug administration, variables such as C-reactive protein, erythrocyte sedimentation rate, matrix metalloproteinase 3, Simple Disease Activity Index, Crohn's Disease Activity Index, Disease Activity Score 28, and safety, were assessed and retrospectively compared between the two groups. Results: Further evaluation appears to be necessary concerning the effects on suppression of bone destruction. There were no large differences between the two groups in hematological data or in various rheumatoid arthritis assessments. Discussion: Depending on the individual patient, the dosing interval may be unavoidably compromised for reasons such as financial burden. The present study results suggest that an extended dosing interval may be one option before temporary discontinuation.

P3-083

The interchageability from bio-original DMARD, Infliximab to biosimilar DMARD Infliximab BS

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Conflict of interest: None

Subjects and Methods Subjects were 17 RA patients who were undergoing continuing treatment with IFX in spring 2015. After signing informed consent, 11 of these patients elected treatment with IFXBS (mean age 65.2±8.0 years, mean disease duration 17.8±10.3 years). Most of these patients had advanced RA. Mean duration of treatment with IFX was 8.7 years. The simplified disease activity index (SDAI) was used to evaluate disease activity following switching treatment. Adverse events were studied as well. **Results**Mean SDAI was 6.23±4.2 prior to switching, 5.74±3.8 prior to second administration following switch, and 6.07±3.3 prior to third administration following switch, revealing no particular changes in clinical symptoms following switching to IFX-BS. Currently, all patients have received their third administration of IFX-BS, and there have been no particular infusion reactions or other adverse events. Nor have there been any laboratory test abnormalities, including liver function, renal function, or blood tests. **Discussion**IFX-BS is Japan's first biosimilar disease-modifying antirheumatic drug (DMARD). Our study demonstrated no effects of switching from IFX in terms of efficacy or safety, and the biosimilar formulation is useful in terms of healthcare economics as well.

P3-084

Intensive bio-swiching therapy by ADA as the second Biologics achieves deeper remission in DAS28 and HAQ score in RA patients

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Conflict of interest: None

【Objectives】IFX, ETN, or TCZ treatment was intensively changed to ADA to maintain clinical remision in RA patients. We estimated this trial of new Bio-switching therapy. 【Methods】Disease activity of 16 RA patients was reduced after prior treatment with IFX, ETN or TCZ, and then the patients were switched to ADA. Changes in DAS28ESR and serum MMP3 values, and HAQ scores were examined for statistically significant differences. 【Results】The mean DAS28 ESR at the screening, just before the switch, and at 52 weeks were 4.96, 2.39, and 1.95, respectively. Further deep remission was achieved from the switch to ADA. The mean serum MMP3 values were also significantly reduced from the switch. For 16 patients in whom HAQ was measured the final progress observation, patients of less than 0.5 were 11, and the mean HAQ was 0.38. 【Conclusion】The next bio-switch to ADA resulted in deeper remission rates of the clinical, functional and structural assessments on RA patients.

P3-085

Comparison of effectiveness of different biologic agents after failure of non TNF inhibitor in RA

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Conflict of interest: Yes

【Objectives】To compare the effectiveness of different biologic agents after failure of non tumor necrosis factor inhibitor (TNFi):Abatacept (ABT) and Tocilizumab (TCZ) in Rheumatoid Arthritis (RA)【Methods】This study was retrospective study in our hospital. The efficacy of the next biologics after ABT (n=30) and after TCZ (n=33) were analyzed. 【Results】The discontinuation of non TNFi,which were caused by the efficacy (primary failure, secondary failure and reducing the effect), were ABT:TCZ=76.7%:42.4%(p=0.006). In biologics switch by the reason of the efficacy, patients were switched to TNF after ABT (TNF/A: n=15), TCZ after ABT (TCZ/A: n=8), TNF after TCZ (TNF/T: n=7) and ABT after TCZ (ABT /T:n=7).The biologics after non TNFi were also stopped in 40-60% of the cases within 12months. For 12 months after switching from non TNFi, the DAS28-CRP were decreased trend in the cases of TNF/A, TCZ/A and TNF/T. While ABT/T remained roughly flat. But there was no statistical significance.【Conclusions】In switching from non TNFi by the efficacy, there were many difficult cases to continue the next biologics. In a few cases of ours, but TCZ after ABT and TNF after TCZ in using biologics after failure of non TNFi, were the relative good improvement of DAS28-CRP.

P3-086

Caution of switching to infliximab BS from infliximab in rheumatoid arthritis patients withsustained low disease activity

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Conflict of interest: None

Background)Dissemination of biosimilar is desirable from the point of view of medical economics. Methods)Use of infliximab following low disease activity (DAS28 <2.6) rheumatoid arthritis patients and maintain more than one year was changed to infliximab BS, we examined the disease activity and continuation rate after 6 months. Results)But was able to study 26 cases, the continuation rate after six months was 60%. It was infusion reactions three cases. Discussion)At the cry should change to easily infliximab BS a patient has maintained a low disease activity infliximab. Example infusion reactions three cases in which it is raised 2 to cause the infusion reactions In infliximab again, care must be taken. The easy change also lead to collapse of the relationship of trust with the pa-

tient.

P3-087

Usefulness of BIO Switch for partial responders to TNF inhibitors - Golimumab (GLM), Abatacept (ABT) and Tocilizumab (TCZ): Observation Study in a clinical setting

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Conflict of interest: None

[Objective]: Among various BIO preparations, there are 5 TNF inhibitors and 2 non-TNF inhibitors. There is no report comparing the usefulness of second TNF and non-TNF inhibitors in partial responders. The clinical usefulness of 24W treatment of GLM 100 mg/month, ABT, and TCZ in partial responders to TNF inhibitors was comparatively investigated retrospectively at this institution. [Methods]: RA patients who were BIO switched from May 2009 and March 2015 and were analyzable GLM (group G), ABT (group A) and TCZ24 (group T) patients were the subjects. Baseline disease activity (DAS28CRP) showed no significant difference between the groups. Efficacy up to 24W after BIO treatment was investigated comparatively. [Results]: △AUC DAS28CRP was defined and multiple comparative tests performed by Dunnett's method. Group G as the control group, △AUC DAS28CRP was significantly low in both groups A and B (group A: p=0.0020, group T: p=0.0347). Even in a multiple regression analysis, ΔAUC DAS28CRP revealed that improvement is likely with GLM treatment. [Conclusion]: Choice of other TNF inhibitors as a second BIO for partial responders to TNF inhibitors, was more effective than using non-TNF inhibitors such as ABT and TCZ.

P3-088

Golimumab 100mg therapy is effective for another biologic therapy drug partial responder

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Conflict of interest: None

[Purpose] We tried to clarify effect of Golimumab therapy for another biologic therapy drug (BTD) showed partial response (PR). [Methods] Patients; another biologic therapy drug PR: 12. Average disease duration; 14 mo. (5 mo. to 9 y. 9 mo.) Previously used BTD; ADA 5, ETN 3, ABT 2, CPZ 1, and IFX 1). Average age; 59.1yo. (22-81) Sex: all female. Combination use of MTX; Yes: 7, No: 5. After initiation of Golibumab 100mg therapy, effectiveness of the therapy was evaluated by CDAI, DAS28-CRP, HAQ, and persistence rate of therapy. [Results] One case was dropped due to insufficient effect; therapy persistence rate: 91.7%. Process of barometer of activity (-8 to 0 weeks vs 4 to 12 weeks after therapy) was following: CDAI (17.4 vs 9.2), DAS28-CRP (3.36 vs 2.43), and HAQ (3.26 vs 2.26). That is, previously moderate activity cases were mostly changed to low activity by Golimumab therapy. In addition, findings of color doppler echo of finger joints was also improved from 14 to 8 points, indicating improved blood flow. Adverse effect was mild dermatitis of 1 patient without severe adverse phenomenon. [Discussion] Switching of BTR to Golimumab was effective because the therapy showed high persistence rate of therapy and improved disease activity without showing any severe adverse phenomenon.

P3-089

Survey of the Status of Use of Biological Preparations to Treat Rheumatoid Arthritis Patients in our Institution (6th report)

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Conflict of interest: None

[Object] We conducted a survey on the status of use of six biological preparations to treat rheumatoid arthritis in our institution. [Methods] Biological preparations were used to treat 155 cases, and consisted of Infliximab (INF) in 69, Etanercept (ETN) in 68, Tocilizumab (TCZ) in 48, Adalimumab (ADA) in 19, Abatacept (ABA) in 19, Golimumab (GLM) in 28, and certolizumab (CZP) in 9 cases. [Results] Treatment was discontinued in 12 INF cases, 21 ETN, 9 TCZ, 4 ADA, 7 ABA, 6 GLM, and 4 CZP. Treatment was switched to another drug in 40 INF cases, 27 ETN, 14 TCZ, 13 ADA, 5 ABA, 6 GLM and 2 CZP. Cases in which more than one drug was used because of attenuated or inadequate efficacy or adverse events consisted of two cases in which 5 drugs were used, 8 cases in which 4 drugs were used, 16 cases in which 3 drugs were used, and 43 cases in which 2 drugs were used. The longest periods of use were: INF, 10 yr 7 mo; ETN, 10 yr 2 mo; TCZ, 8 yr 2 mo; ADA, 6 yr 11 mo; ABA, 3 yr 7 mo; GLM, 3 yr 7 mo; CZP, 1 yr 11 mo. [Conclusions] Attenuation or inadequate efficacy and adverse events were observed with the biological preparations, and in the future it appears necessary to adjust the dose, dose interval, etc., of each of the drugs.

P3-090

Three cases of Rheumatoid arthritis (RA) with effect attenuation of Tocilizumab (TCZ) treated successfully by TCZ and TNF blocker (TNF) bimonthly(TTBM)

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Conflict of interest: None

[objective] To assess the efficacy and safety of TTBM treatment for RA patients with effect attenuation of TCZ. [method] Three cases of RA patients with effect attenuation of TCZ treated with TCZ and Golimumab (GLM) or Certlizumab pegol (CTZ) bimonthly. [Result] Case 1:26 years old female became RA 6months ago and was treated with Adalimumab and MTX, but could not cure complete, so treated by TCZ. After the 3months, recurrent arthritis occurred and treated with TTBM. Case2: 63 year old female with 5 years of RA treated by TCZ. After 2 years of remission, she suffered from arthritis and she was treated by TCZ and GLM bimonthly. Case 3:60 years old male with three years of RA, treated with Infliximab and MTX, flared up arthritis after withdrawal of Infliximab. After a year of TCZ therapy, he had some signs of recurrence of RA, so he was inducted TTBM. [Conclusion] all are good condition,so we can probe the efficacy and safety of TTBM with suppression of TNF and IL-6. [Discussion]TCZ and GLM have a character of low immunogenicity and are hard to produce anti-bioagent antibodies. CTZ has structurally longer-lasting effect. So we can use them 2 month extension. It will be considered that there are some RA patients who can treat with suppression of both TNF and IL-6.

P3-091

Efficacy and sustained control of disease activity in rheumatoid arthritis patients switched from infliximab to golimumab

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Conflict of interest: None

Objective. To evaluate the efficacy and sustained control of disease activity of switching from infliximab (IFX) to subcutaneous (SC) golimumab (GLM) in rheumatoid arthritis (RA) patients. Methods. Eighteen patients who had treated with IFX were switched to GLM because of sustained control of RA disease activity or adverse events of IFX. All received GLM (50 mg/4 weeks). Effects of the IFX-to-GLM switch were evaluated at week 12, 24 and 52 after switching. Results. The mean age of the patients was 65.6 years, and the mean disease duration was 15.6 years. The mean DAS28-ESR of the patients was 2.8. The proportions of patients were 12 patients in remission/LDA and 6 patients in MDA. One patient withdrew due to adverse event after 24 week. DAS28-ESR scores were 2.4 at week 12, 2.5 at week 24 and 2.3 at week 52 after switching. The proportions of patients were maintained or improved at week 52. Conclusions. Efficacy is adequately sustained and improved control of

disease activity in all patients switching from IFX to GLM. Patients receiving IFX can switch to GLM-SC without serious safety concerns.

P3-092

Choice and effort of treatment for Rheumatoid arthritis based on TNF-α and IL-6

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Conflict of interest: None

[Objective] TNF-α, IL-6 are predominant inflammatory mediator in RA, we try the choice of treatment based on serum TNF-α and IL-6. [Methods] We estimated the activity at 12 weeks posttreatment in the four of ACPA-positive RA patients onset within a year, measured pretreatment TNF-α(normal value< 0.55pg/ml) and IL-6 (normal value< 4.0pg/ml). At first they were treated MTX, adding on Bio with high IL-6. [Results] 1. A 58-year-old man with onset 2 months, CDAI was 17.7, CRP 10.64mg/dl, TNF-α 2.9pg/ml and IL-6 37.4pg/ml, remission at 12 weeks treated by MTX dose 8mg/w. 2. A 58-year-old woman with onset 2 months, CDAI was 18.0, CRP 0.55mg/dl, TNF-α 0.9pg/ml and IL-6 261pg/ml, LDA at 12 weeks treated by MTX dose 10mg/w add on ABT. 3. A 46-year-old woman with onset 7 months, CDAI was 31.0, CRP 10.94mg/dl, TNF-α 1.2pg/ml and IL-6 155pg/ml, remission at 12 weeks treated by MTX dose 12mg/w add on TCZ exchanged IFX. 4. A 73-year-old woman with onset 2 months, CDAI was 19.4, CRP 10.40mg/dl, TNF-α 1.4pg/ml and IL-6 32.3pg/ml, elevating 157 pg/ml after MTX treatment, LDA at 12 weeks treated by MTX dose 8mg/w add on TOF exchanged GLM.[Discussion] There is 2 LDA and 2 remission cases. We try to add on biologics based on IL-6 values, but TNF-blocker was ineffective with TNF-α elevated.

P3-093

Switching Effect of Biologics on Gastrointestinal and Associated Articular Inflammation:A Case Report

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Conflict of interest: None

[Object]To show the switching effect of biologics to treat articular Inflammation in association with gastrointestinal inflammation. [Method] Case report study [Results]32years old woman.Ulcerative colitis occured in September 2014.She was treated by Infliximab from Febulary 2015 in successfully.But in July,she suffered from multiple joint pain, especially,bilateral ankle pain.Due to severe ankle pain,she could not walk,and consulted to our orthopaedic division.In laboratory data on first visit,CRP was revealed 19.08.We assumed that according to neutralized antibody agents of Infliximab,antiTNFalpha effect was decreasing. SoWe changed Infliximab to Adalimumab,Joint pain diminished and inflammatory indicators rapidly decreased. [Conclusions]Change of biologics in treatment of gastrointestinal inflammation may improve associated articular inflammation.

P3-094

The efficacy of Infliximab as the second bilogic in patients with rheumatoid arthritis

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Conflict of interest: None

[Object] There are not a few cases that must be changed to other biologics due to the effect attenuation and effect insufficient (partial responder). In this study, we analyzed the efficacy of IFX as the second bilogic in patients with rheumatoid arthritis who were administered IFX that was escalated dose or shorted period. [Methods] 248 patients who received IFX administration were assigned from December 2003 to December 2012 were assigned. Cases who were administered Anti-TNF therapy (etanercept (ETN), adalimumab (ADA)) as the first biologics and changed to the administration of IFX as a second biologics were 9. The average age was 61.4 years old and the average disease duration was 11.1 years. [Results] 8 cases were administrated ETN and one case was administrated ADA, 6 cases were escalated dose and 3 cases were shorted period in 9cases. Mean DAS28-CRP value was an improvement at the second time and was kept maintained good response after the third time. [Conclusions] We showed the efficacy of tight control with IFX for the effect attenuation and partial responder. We should analyzed in cases of using non anti-TNF biologics for the first biologics.

P3-095

Discontinuation of infliximab(IFX) after achieving remission in patients with rheumatoid arthritis at Niigata Rheumatic Center

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Conflict of interest: None

[Objective] To investigate the rate of patients continuing biologics-free disease control after discontinuing IFX in patients with rheumatoid arthritis (RA) at our hospital. [Methods] Of 225 patients who had been treated with IFX from 2007, 18 patients who had achieved DAS28-ESR (DAS) remission and been discontinued IFX were evaluated retrospectively. [Results] The median age was 57.5 years, the disease duration was 5.2 years and DAS was 5.06 at the induction of IFX. The total duration of IFX treatment was 183 weeks. Of 18 patients, 13 patients were evaluated for 96 weeks after discontinuation of IFX. Eight patients (61.5%) at 48 weeks and 6 patients at 96weeks maintained low disease activity (DAS<3.2). Seven patients experienced flares in 96 weeks, 5 patients of them achieved remission again due to MTX dose escalation or addition of another csDMARD. Eleven patients (84.6%) maintained biologics-free disease control at 96 weeks. By October 2015, 4 of 18 patients needed re-induction of the other biologics (golimumab, GLM for all 4 patients), all of them achieved remission promptly. [Conclusions] Continuing biologics-free control succeeded in quite a number of patients with concomitant use of csDMARDs. GLM is effective for prompt re-achievement of remission.

P3-096

Evaluation of factors associated with restart of biological therapy in patients with rheumatoid arthritis after discontinuation of bDMARD

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Conflict of interest: None

Objective: The aim of this study are to analyse predictive factor for readministration of bDMARD to maintain the low disease activity (LDA) of rheumatoid arthritis (RA) after discontinuation of bDMARD. Methods: A retrospective chart review was conducted in RA patients who discontinued bDMARD after achievement LDA. A total of 15 females were identified (mean age, 62.9±12.0 years; mean disease duration, 4.8±4.8years; mean MTX dosage, 4.8±4.8mg/week). To explore predictive factor for readministration of bDMARD, we divided the patients in two groups whether restart bDMARD or not, and tested the differences for statistical significance using the t test or the chi square test. Results: The mean CDAI was 2.8±2.7 before discontimnuation of bDMARD and 8.3±11.9 at 24 weeks after the discontimnuation. The mean withdrawal duration of bDMARD was 75.2±68.1 weeks. Eight patients (57%) were flared RA and achieved LDA after readministration of bDMARD. The predictive factor for the readministration was high value of MMP3 (64.3±23.5 vs 37.9±15.1ng/ml) at 24 weeks after the discontimnuation. Conclusion: Six (43%) patients were able to withdraw bDMARD after

achievement of LDA. Patients with low value of MMP3 at 24 weeks after the discontimnuation could maintain LDA without bDMARD.

P3-097

Bioholiday for rheumatoid arthritis patients with Clinical disease activity index remission

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Conflict of interest: None

[Objective] To investigate Bio-holiday therapy for rheumatoid arthritis patients with clinical disease activity index (CDAI) remission. [Material and Method] Thirty six RA patients whose disease activity are CDAI remission were involved. We divided them two groups. One is Bio-holiday (H group), 14 patients (ETN 4, GLM 7, TCZ 3 patients). They withdraw biologic DMARDs in CDAI remission, and restart to take Bio if they are without CDAI remission. After retaking Bio, if in CDAI remission they withdraw Bio again. The other is to continue Bio (C group), 22 patients (ETN 7, GLM 9, TCZ 6 patients). Mean age are 55.6 and 58.3 years old, H and C group respectively. Mean disease duration are 4.45 and 4.96 years, H and C group respectively. We evaluated CDAI, delta mTSS and HAQDI and compared them between among both groups.[Result] The mean withdrawal period are 12.3, 6.7, 10.0 months, GLM, ETN and TCZ respectively. Two in H group and 3 patients in C group dropped out because advertise events or ineffectiveness. In H group, we could improve all patients to be CDAI remission without delay except one case who drop out because drug ineffectiveness. There were no differences statistically in delta mTSS and HAQDI.

P3-098

Consideration of 8 cases of RA ;Discontinuation of Biologics after maintaining clinical remission(CR) for more than 12month

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Conflict of interest: None

[Objectives] To consider the condition of patients whose biologics were discontinued to aim at Bio-Free. [Methods] We investigated 8 patients who were treated with biologics and maintained CR at least for more than 6 months and then discontinued to aim at Bio-Free. All were female and average age were 45.7 (19-64), Used biologics were 6 TNF inhibitor (Infliximab (IFX) 3, Etanercept 1, Adalimumab (ADA) 2) and other 2 were Tocilizumab. Average duration of biologics treatment was 21.8 months (11-42) and of keeping CR was 14 months (6-42). Avelage DAS28CRP and DAS28ESR were 1.43 and 2.09. [Results] 6 patients maintained CR for 12 months after discontinuation of biologics, but 2 were re-treated (1 ADA after 3 month, other IFX after 6 month) and introduced CR promptly. [Conclusion] DAS28 at 3 month later of discontinuation of biologics may indicate the possibility of keeping Bio-Free for longer duration. If DAS28 increase, early re-treatment with same biolodics may introduce prompt CR.

P3-099

Biologic-free remission after etanercept therapy for patients with rheumatoid arthritis; report of two cases

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Conflict of interest: None

Case 1:36-year-old female with rheumatoid arthritis had received methotrexate at another hospital. Her disease duration was 8 years. Even though she showed low disease activety, joint destruction had progressed gradually and she referred to our department. In ultrasonography, there were some joints with the power Doppler signals, we started to treat with etanercept (ETN) 25mg per week. She achieved clinical remission and the power Doppler signals disappeared after ETN treatment. We tapered ETN at 30 weeks of ETN treatment and withdrew at 72 weeks. Her clinical remission and disappearance of power Doppler signals remain during 4 years after stopping of ETN.Case 2:61-year-old female with rheumatoid arthritis had received methotrexate 8mg per week and prednisolone 3mg, but his disease activity showed high. Her disease duration was 2 years. We had added ETN 25mg per week. Her disease activity decreased gradually, She achieved clinical remission and imaging remission at 96 weeks of ETN treatment. Five years later, we tapered ETN and withdrew at 7 years of ETN treatment. She showed stable clinical remission during 6 months after stopping of ETN.conclusionWe describe two cases of rheumatoid arthritis patients achieving biologics-free remission by treatment of etanercept.

P3-100

Examination of the rheumatoid arthritis (RA) case that discontinued infliximab(IFX) after achievement of remission

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Conflict of interest: None

【Objective】To examine the case discontinued IFX after remission in RA patients. 【Patients and Methods】After having achieved clinical remission among 52 RA patients who received IFX, we examined 4 cases that discontinued IFX. The patient at the time of IFX introduction is a woman with 4 people. Average age was 63.5 years old (55-69). Mean disease duration was 15.3 months (4-24). Steinbrocker stage I: 2 II: 1 III:1,and class2 in all cases.DAS28CRP,3.49-4.00 (averageof3.76), MMP-3 36.5-366.7ng/mL (average of 143.7 ng/mL). RF was positive (45.0IU/mL) in 1 case, and ACPA was positive in 1 case (67.9 U/mL). IFX dose was 3 mg/kg of 4 cases, and dosage period before leading to discontinuation was 22-40 months (an average of 28.3 months). MTX dose at the discontinuation was 4 mg of 4 cases and was not given steroid and DMARDs except for MTX.About above-mentioned 4 cases, we evaluated having flare or not. 【Results】One case of StageIII flare 13 months after discontinuation and was given IFX and achieved remission again.Three others maintained remission in spite of the next 5-8 months passed after discontinuation. 【Conclusion】 Discontinuation is possible in the patients who remitted using IFX, but we need attention for flare when it takes long term for induction of remission.

P3-101

The analysis of background diseases and course of pregnancy in 18 cases with Rheumatoid Arthritis(RA) at Tokyo Metropolitan Tama Medical Center

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Conflict of interest: None

[Purpose] We analyzed the background diseases and course of pregnancy (treatment and fetal complications) in 18 cases with RA at our hospital for the purpose of managing future cases. **[Method]** Of the 6739 women who underwent delivery at our hospital between March 1, 2010 and September 30, 2015, 18 cases in whom a RA was diagnosed were retrospectively analyzed. **[Results]** With regard to immunosuppressants and antirheumatic drugs, no case had started newly after pregnancy has been recognized and 5 cases (MTX 3, ETN 2) discontinued them. With regard to steroids, 3 cases received increased dosages. With regard to fetal complications, a premature birth due to imminent abortion was found in 1 case. **[Conclusion]** This research broadly reflects a reality of pregnancy and childbirth management in a Japanese tertially center with obstetrical and rheumatologic departments. Although some cases required reinforcement of the treatment, the data suggest that it is possible for cases with RA to experience a safe delivery.

P3-102

Why rheumatoid arthritis patients discontinue methotrexate

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Conflict of interest: None

Why rheumatoid arthritis patients discontinue methotrexate Rheumatology and Allergy department, Kameda medical center ○Akira Jibatake, Tamao Nakashita, Yuto Hamada, Koutaro Matsumoto, Shinji Motojima Introduction:Methotrexate (MTX) is the anchor drug for rheumatoid arthritis,we analyzed the reasons for what they discontinue it Method: prospective analysis of rheumatoid arthritis patients who received MTX from 2010 to 2015 Results: 758 patients (F591,M167) was begun with MTX and 123 patients discontinued taking MTX for more than 3 months. The cause of MTX itself is 44 patients (35%) with abnormal CBC, respiratory symptoms, gastrointestinal symptoms, elevated liver function. abruptly visiting hospital 25 patients, infection 8 patients, maglinancy 6 patients, 4 patients want to discontinue, low disease activity 3 patients, the rest is 15 patients. Conclusion:over 30 percent discontinue taking MTX with MTX itself, about 20 percent of patients dont visit clinic forever, and female patients are more likely to discontinue taking MTX than male patients. this means the understanding of disease will make their compliance better.

P3-103

Etanercept (50mg/w) for RA patients with low weight and old age is at high risk of death

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Conflict of interest: None

(Introduction) After treating rheumatoid arthritis patients with etanercept (50mg/w) in japan, many patients died due to infection and interstitial pneumonia. In the present study, we checked the safety of etanercept (50mg/w) for rheumatoid arthritis (RA) patients with low weight and old age. (Method) We check the data of 1st phase results both in Japan and United states. Low weight is designated under 50kg and old age is designated upper 65 years old. We also checked the reports which discussed the death due to Etanercept 50mg/w for RA patients with low weight and old age. (Results) In 1st phase results, the safety was examined in younger peoples (24±3 years old, Japan, 30±10 USA) and in rather heavy weight (63±5kg, Japan, 76±14kg, USA). More than 50 RA patients with low weight and old age were died of infections and interstitial pneumonia in 2 month after injection of etanercept (50mg/w). In our clinical experiences, etanercept (50mg/w) induced pancytopenia and interstitial pneumonia. (Conclusions) Etanercept (50mg/w) should not be used for RA patients with low weight and old age. Safety of Etanercept (50mg/w) in healthy controls with older and low weight peoples is to be established.

P3-104

Analysis of Prognostic Factors Associated with Death from *Pneumocystis* Pneumonia in patients with RA

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Conflict of interest: None

Background: While *Pneumocystis* pneumonia (PCP) is a severe complication of rheumatoid arthritis (RA), the prognostic factors are not well defined. **Patients and Methods:** Our hospital records from June 2008 to June 2015 were reviewed for all PCP cases. The PCP was diagnosed based on respiratory symptoms, positive radiological findings on chest computed tomography compatible with PCP, elevated serum βd-glucan levels, and positive PCR for PCP. We compared age, sex, treatment for RA, treatment for PCP, coexisting diseases, blood tests, activity of RA between survivors and non-survivors, and analyzed prognostic factors of PCP in RA patients. **Results:** Fourteen PCP cases with RA were identified. Ten of them were survivors. Coexisting interstitial pneumonia were observed 1 in 10 survivors and 4 in 4 non-survivors (p=0.0017). The dose of steroid for the treatment of RA is significantly higher in non-survivors (13.2±4.1 mg vs 2.2±3.0 mg, p=0.0062). **Conclusion:** We identified coexisting interstitial pneumonia, high dose steroids treatment for RA as prognostic factors for PCP in RA patients. These are already known as risk factors of PCP onset in RA patients. Our result emphasized the importance of prevention of PCP in RA patients who had interstitial pneumonia and received high dose steroids.

P3-105

A case suspected of methotrexate-associated lymphoproliferative disorders of the lung (MTX-LPD) during the medical treatment of pulmonary cryptococcosis in rheumatoid arthritis

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Conflict of interest: None

A 80-year- old gentleman who had been treated for 10 years with methotrexate (MTX) and steroids for rheumatoid arthritis was found to chest abnormal shadow. Chest Xray and CT scan revealed 3 nodules in the right upper and lobe incidental lung nodules detected on chest Chet Xray and CT. CT-guided lung biopsy was performed, and the pathological diagnosis was pulmonary cryptococcosis. Serum Level of cryptococcal Antigen was 1:128. Inspite of treatment with FLCZ and VRCZ,A *shadow* in the chest CT scan have got worse. So we changed treatment (L-AMB).After that, we switched to FLCZ because of maintenance therapy. Despite he had been treated with FLCZ through the previous 8 month, the chest CT revealed newly nodule in the right lower lobe. Serum Level of IL2-R was 4970U/ml He stopped taking MTX. A newly nodule in the right lower lobe. was disappear ed, and serum level of IL2-R decreased to 668u/ml. During the treatment of MTX, RA usually complicated by pulmonary cryptococcosis or (MTX-LPD). However, It is difficult to defferenciate from the comlications both pulmonary cryptococcosis and MTX-LPD.

P3-106

A case report of joint listeriosis after IFX treatment

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Conflict of interest: None

We report a case of Listeria monocytogenes knee arthritis without prosthesis, associated with infliximab (IFX) treatment for rheumatoid arthritis (RA). A 76-year old female, who had diagnosed RA in 9-month former and had started treatment with methotrexate (MTX) and corticosteroid, and followed by IFX injection therapy. After 1.5-month later first IFX injection, sub-acute arthritis occurred in her knee. Her joint fluid revealed café au lait like, and we started treatment with SBT/ABPC 12g/day, following arthroscopic joint debridement, and continuous irrigation in 5 days. After 6-week intravenous antibiotic therapy, she recovered completely and left hospital. After 1-year from operation, listeriosis has not relapsed. We review the literature, and revealed 36 reported cases of bone and joint listeriosis, and one report from France in 2012, a study of 43 consecutive cases. Depend on this report, putative risk factors are (1) age >60 years (88%), (2) presence of foreign material (84%), (3) immunosuppression and corticosteroid therapy (33%), (4) underlying neoplasia (26%), and (5) diabetes (11%). This study suggests that RA, reported in 16% of patients in this series, is a risk factor for bone and joint listeriosis. In our case too, that is true RA, age and immunosuppression therapy.

P3-107

A Case Report: Forearm Pyogenic Tendosynovitis by Administrating Certolizumab pegol

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Conflict of interest: None

OBJECTIVE: We report the case of a 65 year-old woman with rheumatoid arthritis (RA) who underwent synovectomy due to pyogenic tendosynovitis following the use of certolizumab pegol (CZP).CASE: 65 year-old woman with RA (CRP 2.03 mg/dl, MMP-3 256, RF 121, ACPA 4.7, PtGH 50/100. Class 2, Stage 4). She was treated with methotrexate 8mg, BUC 200mg and prednisolone 5mg. After 16 weeks of starting CZP, right forearm redness and swelling were observed and deep infection was suspected by sonography and MRI (WBC 11,300, CRP 4.55 mg/dl, MMP-3 96). After performing puncturing, abscess was drained. She was diagnosed with right forearm pyogenic tendosynovitis and underwent synovectomy. Causative agent was MSSA. DISCUSSION: We experienced forearm pyogenic tendosynovitis while administrating CZP. Age, use of prednisolone and diabetes are considered as major risk factors of severe infection. The patient was 65 years old, took prednisolone and experienced pyogenic tendosynovitis after 4 months of CZP. CONCLUSION: It should be considered carefully when administrating biologics to high-risk patients.

P3-108

Epstein Barr virus--DNA may be a predictive factor in methotrexate-associated lymphoproliferative disorders (MTX-LPD)

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Conflict of interest: None

Objective: MTX-LPD are important adverse events associated with MTX. We performed the Epstein-Barr virus (EBV)-DNA assay and other tests in RA patients with MTX-LPD and their association with prognosis. Methods: In all, 24 patients were included who had symptoms such as multiple lymph node enlargement, tonsillar ulcers, ileocecal mass or ulcers, multiple pulmonary nodules, fever, or hemorrhage because of MTX use. Of these, 19 were diagnosed based on histological results, and 5 were diagnosed with MTX-LPD on the basis of their clinical course. Results: The patients included 8 men and 16 women, mean age 69.4 years, mean RA disease duration 14.5 years, and mean duration of MTX use 3.8 years. EBV-DNA levels were measured in 15 patients, of whom 8 (53%) showed positive results. All patients discontinued MTX after they were diagnosed with LPD: 20 (83%) achieved remission through withdrawal alone, but 4 needed chemotherapy. All patients who had positive results for EBV-DNA achieved remission, but 3 of the 7 who showed negative results required chemotherapy, suggesting that EBV-DNA in the peripheral blood may be a prognostic predictive factor for LPD. Conclusion: Measurement of EBV-DNA levels in blood may be useful for predicting the prognosis of patients with MTX-LPD.

P3-109

A case of chronic myelomonocytic leukemia following methotrexate and etanercept combined therapy in a patient with rheumatoid arthritis

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Conflict of interest: None

It is well known that methotrexate (MTX) and TNF-α inhibitor etanercept (ETN) are occasionally accompanied by blood side effects such as lymph proliferation and lymphoma, whereas leukemia rarely occurs with these agents. We report here such a case in a patient with rheumatoid arthritis. A 48 year-old female, who suffered from pain and/or swelling of wrist joints, PIP joints, knee joints and shoulder joints, was diagnosed with RA and started initial treatment by MTX and prednisolon at the end of 2009. Three months afterwards, the dose of these agents was 8mg/week and 7.5mg/day respectively. However, her symptoms in the wrists and PIP joints remained. So, ETN and salazosulfapyridine was added 9 months after the initial treatment, which resulted in clinical remission. Her physical conditions came from RA being maintained well, although her blood cell count was sometimes high and slight anemia was observed. Five years after ETN induction, she became severely anemic in September 2015. She was diagnosed with chronic myelomonocytic leukemia (CMML-1). Her anemia improved after she was administered 1000mg/day of hydroxycarbamide. Although the etiology of leukemia by MTX and ETN therapy in RA patient is not clear, we should pay attention to such side effects.

P3-110

Analysis of patients with lymphadenopathy who were done lymph node biopsy during the treatment of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To analyze the diagnosis and clinical course of lymphadenopathy in rheumatoid arthritis. [Methods] We retrospectively analyzed the 13 patients with lymphadenopathy who were performed lymph node biopsy and treated in our hospital. [Results] Fourteen biopsies were performed in 13 patients. In pathological findings, cases were diagnosed as follows; 4 reactive hyperplasia, 4 DLBCL, 3 Hodgkin`s lymphoma, 1 MALT lymphoma, 1 diffuse and follicular lymphoma, 1 EBV-LPD. 11 cases were clinically diagnosed as MTX-LPD. Two of them (18%) needed chemotherapy as a secondary treatment. There were no significant difference between malignancy and benign lesion in blood examination results, including titers of C-reactive protein, LDH and soluble interleukin-2 receptor. There were no relation between EBV antigen in lymph node and EBV serological patterns in peripheral blood. [Conclusion] Peripheral blood findings were not useful to distinguish malignancy and benign lymphadenopathy in patients with rheumatoid arthritis. Discontinuation of MTX were effective in MTX-LPD.

P3-111

A case of lymphoproliferative disorders after treatment with oral tacrolimus for rheumatoid arthritis

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Conflict of interest: None

An 87-year-old male was diagnosed with rheumatoid arthritis (RA) in September 2014 based on the presence of polyarthritis, positive anti-CCP antibody, and increased CRP titer. Although he was treated with methotrexate (MTX) 6mg/week, MTX was switched to Tacrolimus (Tac) 3mg/day due to an adverse event at November 2014. The disease activity maintained low with PSL 4mg/day, salazosulfapyridine 1g/day, and Tac 3mg/day. He was admitted to our hospital, complaining of fever and right hypochondrial pain on June 2015. Abdominal CT showed multiple masses in the liver with no abnormal signs in other sites, which implied radiologically metastatic liver cancer of unknown primary. However, considering increased serum LDH and sIL-2R level, we estimated Tac might induce these masses as lymphoproliferative disorders (LPD). Discontinuation of Tac had resulted in the regression of masses and the decreased level of serum LDH and sIL-2R. Tac induced LPD is seldom reported when it is used for RA, while is commonly reported in the field of transplantation. MTX is known to induce LPD as iatrogenic immunodeficiency-associated LPD. As is the case with MTX, Tac induced LPD should be considered if fever without any infectious symptoms and elevation of serum LDH level are seen during administration of Tac.

P3-112

Study of twenty six cases of MTX-LPD in our hospital

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Conflict of interest: None

OBJECTIVE: Methotrexate-related lymphoproliferative disorder (MTX-LPD) is one of the MTX adverse events that have been attracting attention recently. This report is the analysis of the cases in our hospital. METHODS: Twenty six RA patients with MTX-LPD diagnosed from 2005 to 2014 are investigated by chart survey. RESULTS. Sex: male; 10, female; 16. Age at RA onset:55 ± 14 yo. Age at lymphoma onset:71 ± 6 yo. Duration of MTX use;9 ± 6y. Dose of MTX at the LPD onset:8.2 ± 2.4mg/w. Lesion area:Node;8, extranode;4, both;14. Oropharyngeal lesion (n=7) is the largest in extranodal tumor. Lymphoma clinical stage:I;5, II;4,III;5,IV;12. Histopathological examination (n=24): DLBCL;12, Hodgikin; 5 etc. EBER-ISH positive: 8/10. sIL2R value at oncet:8580 ± 10820U/ml (n=22). The remission only by MTX discontinuation is observed in 14 cases followed by 4 recurrences (1 death). Another 12 cases undergo chemotherapy and all patients have once remission, followed by 2 recurrences (1 death). Sixteen cases have been exacerbated in RA after LPD-remission. The subsequent treatment for RA: PSL;18, MTX;4, biologics;3, tacrolimus;1. CONCLUSION: Clinical picture of MTX-LPD is variegated and extranodal disease should be noted. Risk factors for MTX-LPD are desired to be revealed in the future.

P3-113

MTX-associated intravascular large B-cell lymphoma in a patient with rheumatoid arthritis

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Conflict of interest: None

A 66-year-old woman with rheumatoid arthritis who had been treated with methotrexate (MTX) 6 mg/week since 2011 presented with a high fever and fatigue. Initial laboratory tests showed elevated lactate dehydrogenase (665 IU/L) and C-reactive protein (7.24 mg/dL) and a decreased platelet count (6.3×10^4/μL). Computed tomography found no lesion or lymphadenopathy. Blood and urine cultures were negative. Positron emission tomography (PET)/CT with [^{18}F]-fluorodeoxyglucose showed hypermetabolic foci in the uterus with a maximum standard value of 6.65. During the workup, she was found to be hypotensive and her albumin level fell suddenly. She was started on pressor support with norepinephrine and 100 mg/day prednisolone. A random skin biopsy and endometrial biopsy revealed intravascular large B-cell lymphoma. After the diagnosis, she was started on the EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone) regime. Approximately 40-50% of the reported cases of MTX-lymphoproliferative disease involve extranodal sites, such as the skin, lungs, and soft tissues. To our knowledge, however, no case of MTX-associated intravascular large B-cell lymphoma has been reported.

P3-114

A case of rheumatoid arthritis developed stageIV DLBCL with large lung tumors disappeared by the discontinuation of MTX

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Conflict of interest: None

The patient is 78-year-old woman. She had been visited to our hospital in rheumatoid arthritis from 1994. She kept a low disease activity from 2008 with MTX 8-10 mg /week and a low dose of steroids. She admitted a full general malaise and food anorexia and visited our hospital on October 5. New two huge tumor shadows were in each lung in chest X-ray. One was in the right lower lobe whose diameter was about 5 cm, another was in the left lower lobe hilar whose diameter was about 4 cm. Serum soluble IL-2 receptor was 6500U/mL then MTX-related lymphoproliferative disease (MTX-LPD) was suspected and MTX was discontinued. We underwent CT guided biopsy from the tumor of the right lung. Pathological diagnosis was diffuse large cell B-cell lymphoma (DLBCL). By PET-CT, she was diagnosed as StageIV. Since after MTX discontinuation, the patient's general condition was improving, the tumors in the chest X-ray were getting smaller, and the titer of soluble IL-2 receptor decreased. So chemotherapy was suspended. Huge lung tumor s disappeared without chemotherapy. MTX-LPD is known as a rare complication of MTX. Several cases have been reported healed naturally by MTX discontinuation. Here we report a case of DLBCL Stage IV remitted only by the discontinuation of MTX.

P3-115

Progression of solid cancer by TNF inhibitor two cases report

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Conflict of interest: None

[Object] According to the ACR recommendation 2015, use of biological agents in rheumatoid arthritis (RA) who had solid cancer, can be considered same as the patient without such condition. We report two cases concluded that TNF inhibitor involved in the progression of solid cancer. [Case 1] 58y.o surgery for ovarian cancer, 62y.o. onset RA, DMARD-IR. Since operation, she had 2cm of lymph node. She had Gynecologic follow-up until 70y.o. and canceled due to no change. ETN was started, not effective enough at 4 months and switch to IFX. It was effective. 72y.o, Her lymph node showed enlargement to 6 cm and diagnosed with a recurrence of ovarian cancer. [Case 2] 38y.o. RA onset, she had high disease activity but because of HBV carrier, she could not receive enough therapy. 57y.o. ETN was started with Entecavir. 59y.o. she had uterine cancer. ETN was stopped, After operation, PET-CT revealed the uptake at bil. shoulder joints and rt. hip joint, and PET-CT after three months showed no increase, so these were recognized as synovitis. Because arthritis was worsened, she re-started ETN. After three injections, PET-CT showed the strong uptake in rt. hip joint and diagnosed as metastasis of uterine cancer. [Conclusion] TNF inhibitors were considered to induce the rapid tumor growth.

P3-116

A Case of tocilizumab-induced thrombocytopenia and methotrexate-associated lymphoproliferative disorders in patient with Rheumatoid Arthritis complicated with type 1 Diabetes

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Conflict of interest: None

Tocilizumab (TCZ) has been reported to develop anemia because of anti-Interleukin-6 effect. Methotrexate (MTX) has been reported to increase the risk of lymphoproliferative disorders (LPD). We have reported a case of TCZ-induced thrombocytopenia and MTX-associated LPD in RA complicated with type 1 diabetes. A 58-year-old man had been treated with slowly progressive insulin-dependent diabetes mellitus observed with positive IA-2 and negative GAD antibody. He had been diagnosed as RA five years ago, and treated with 12 mg/week MTX and 50 mg / week etanercept (ETN). He was introduced to our hospital on July in this year, because joint pain was getting worse. Then, ETN was switched to 162 mg TCZ every two week. He gradually became to be thrombocytopenia although joint pain and swelling was improved. When He was admitted to our department, the laboratory examination revealed thrombocytopenia, anemia, increased anti-CCP antibody, rheumatoid factor, MMP-3 levels, negative antiplatelet antibody titer, and decreased haptoglobin level. When we stopped TCZ treatment, thrombocytopenia was improved. However, he had appeared lymphadenopathy in the right occipital region. We have diagnosed as MTX- associated LPD. After stopping of MTX treatment lymphadenopathy was disappeared.

P3-117

For the development course and prognosis with the MTX-related proliferative disease that is experienced in our hospital

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Conflict of interest: None

<Purpose>Report cases of tumors that appear to be associated with MTX Associated with rheumatoid arthritis (RA) patients who experienced at our hospital <subject methods> It had obtained a remission with two cases in patients treated from patients and 2014 in the MTX + Etanercept administration from 2005 only in the MTX in the <subject methods> our hospital. <Results> both cases introduces the blood internal medicine, changes in the state of MTX-related lymphoproliferative disease tumor diseases caused by changes to the prednisolone it stops under MTX and biological formulation of diagnosis of suspected (LPD) and the disease activity of the transition of the RA, was presented for the treatment that was performed in our hospital. <Discussion> first case of cases develop in long-term administration, the two cases eyes are e effects of drug discontinuation, such as MTX not be all obtained results suggest the LPD in different test data and short-term development of a one-year It did not. <Conclusion> MTX-LPD is diverse, the course of up to definitive diagnosis by tissue type, should be determined whether the MTX canceled due to drug discontinuation effect also varies also MTX administration period, such as MTX, and I suspect.Conflict of interest. Nothing

P3-118

The clinical experience of Biologics in rheumatoid arthritis patients complicated with palumoplanter pustulosis

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Conflict of interest: None

Biologics have recently been employed in rheumatoid arthritis (RA), yielding an excellent response. But psoriasis or palumoplanter pustulosis (PPP) like eruption due to biologics were rarely observed. TNF inhibitors were used in the management of severe SAPHO syndrome, however paradoxical development of PPP has been well documented. Here we show two experiences of biologics in RA patients complicated with palumoplanter pustulosis with a review of the literature.[Case1: 56 years old woman] She developed PPP at 30 years old, and had RA at 51 years old. Predonisolon (PSL) 10mg/day and methotrexate 16mg/W were initiated. RA activity was high (DAS4-CRP4.81), Abatacept was initiated. Arthritis was recovered and PSL was tapered (2mg/day). However, there was a reappearance PPP on the bilateral palms. Subsequently, topical steroids were prescribed, leading to an improvement. Then, ABT were administered continuously.[Case2: 59 years old woman] She developed PPP at 53 years old, and had RA at 56 years old. PSL, bucillamin and salazosulfapyridine were initiated. RA activity was low (DAS4-CRP2.78), but she had severe right wrist arthritis. Tocilizumab was initiated. Arthritis was recovered and eruption was disappeared.

P3-119

A case of Sezary syndrome which became evident while being treated with biologics as psoriatic arthritis

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Conflict of interest: None

[Case] An eighty-year-old male was admitted to our hospital because of fever, erythroderma and arthralgia. From two years before this hospitalization, erythema with scales appeared to his trunk and limbs. It gradually spread over the whole body. By the dermatologist of a university hospital, he was diagnosed as psoriasis and treated with PUVA therapy for one year. But his disease did not improve. So he came to our hospital. PSL and adalimumab was started. At the beginning, his symptoms were relieved immediately, but recurred gradually. Therefore he was hospitalized for reexamination. In his peripheral blood, one thousand / μL of atypical lymphocytes with gyrus-formed nucleus were observed. Then he was diagnosed as Sezary syndrome by skin biopsy. Adalimumab was stopped and etoposide and PSL was started. As a result, his symptoms were relieved shortly and the peripheral atypical lymphocytes disappeared one month later. [Clinical meaning] It is very difficult even for skilled dermatologists to distinguish early-stage Sezary syndrome from psoriasis and drug eruption. In this case, Sezary syndrome was supposed to be smoked out by TNF inhibitor. We should be careful about the development of cutaneous lymphoma when using biologics for psoriatic erythroderma.

P3-120

A case of psoriasiform drug eruption caused by abatacept in rheumatoid arthritis

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Conflict of interest: None

A 77-year-old woman was followed for rheumatoid arthritis (RA) for 13 years. She had treated regimens of DMARDs had included methotrexate, etanercept and infliximab, but she had failed to have insufficient response to them all. When intravenous abatacept (ABT) was started, the clinical symptoms of RA were well-controlled. 2 months later she developed some scattered erythematous plaque on body. The histopathological findings of skin biopsy was consistent with psoriasis. Intravenous ABT was discontinued because the eruption made worse. After that, the eruption had almost disappeared, RA had flared up again. We decided the use of ABT with subcutaneously. Then clinical symptoms of RA were well-controlled with mild psoriasiform drug eruption on body. In these days, there are case reports of psoriasiform drug eruption caused by not only intravenous ABT but also subcutaneous ABT. We reported the case psoriasiform drug eruption caused by intravenous ABT and subcutaneous ABT in the same patient. Subcutaneous ABT makes clinical symptoms of RA well-controlled with mild psoriasiform drug eruption on body, as we have continued subcutaneous ABT. When the psoriasiform drug eruption is caused by ABT, there is the choice to change route of administration of ABT.

P3-121

A case of palmoplantar pustulosis in a rheumatoid arthritis patient treated with certolizumab pegol

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Conflict of interest: None

We report on a case of palmoplantar pustulosis (PPP) in a patient with rheumatoid arthritis (RA). The PPP was suspected to be caused by certolizumab pegol (CZP). The patient was a 52-year-old woman diagnosed with seronegative RA at age 47, and was started on a dosage of methotrexate. Subsequently, her RA activity became worse, and her medicine was changed to CZP. However, at 3 months after starting CZP treatment, a rash appeared on her palm and foot skin and left knee joint synovitis became obvious. The patient was referred to a dermatologist, but external medicines and medications were ineffective. Next, we started to administer the IL-6 inhibitor tocilizumab (Actemra), but this was also ineffective. Finally, we changed to tofacitinib (Xeljanz), and her RA activity and dermatitis control were improved and remain good to date. There have been some articles describing a paradoxical reaction with TNF inhibitor administration, but rare cases with CZP. However, we experienced a case in which tofacitinib was effective. It is considered that tofacitinib was effective as a treatment for PPP by obstructing the communication from an inflammatory cell receptor of type I interferon (TNF).

P3-122

Case report for emergence of psoriasis in a RA patient as suspected paradoxical reaction through adalimumab administration.

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Conflict of interest: None

Objectives: Anti-TNF antibodies, IFX and ADA, are known to be effective therapy for RA as well as the other inflammatory diseases such as psoriasis and IBD. However, it is also known that paradoxical skin rash like psoriasis is reported. Background: 78 years old female RA patient complained skin rash/pruritus on back and limbs. Result: Adalimumab had been started with 2mg of MTX on 2012 Sep and 1 year and half later, MTX dose was lowered to 1mg due to higher creatinine and lower WBC counts. 3 months later, there was a fracture on left humerus diaphysis and 2 days after the fracture, herpes zoster emerged on right lower limb thus discontinued ADA and MTX followed by Zovirax. 6 weeks later, red rash emerged with scabs and dander on back and limbs. Biopsy was performed and diagnosed as psoriatic vulgaris. Immunosuppressant treatment started without adalimumab and 3 months later red rash was disappeared. Discussion: This case report showed emergence of psoriatic vulgaris suspiciously by adalimumab use. Even though it is not well known mechanism and onset of skin adverse events during anti-TNF therapy, it worth to remember paradoxical reaction could happe

P3-123

Destructive thyroiditis following biologics administration led to acute renal failure in patient with rheumatoid arthritis associated with AA amyloidosis - case report

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Conflict of interest: None

Recently, several cases of thyroiditis associated with anti-TNF therapy have been reported. We treated a patient with AA amyloidosis who was diagnosed with acute renal failure following destructive thyroiditis while undergoing anti-TNF therapy for rheumatoid arthritis. A 71-year-old man had been suffering from active rheumatoid arthritis for 14 years and started Certolizumab pegol treatment. Following the fourth injection, the patient complained of a swollen neck with tenderness as well as respiratory distress. CT findings revealed an enlarged thyroid, while serum thyroid hormone (FT4, 4.31 ng/dl) and serum thyroglobulin (Tg, 1000 ng/ml) were elevated. Although neck pain was reduced after 2 weeks, he was hospitalized with acute renal failure, as well as diarrhea and nausea. Endoscopy and biopsy results revealed amyloid deposition in the duodenum and kidney. We administered Tocilizumab, and the diarrhea and arthralgia were immediately improved. We concluded that subclinical AA amyloidosis was manifested by introducing anti-TNF therapy in this case.

P3-124

Associations between Psychological Tendencies and Arthritic Pain in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] We analyzed the associations between psychological tendency and arthritic pain in patients with rheumatoid arthritis (RA). [Methods] Disease activities of 60 outpatients with RA were evaluated using DAS 28. Furthermore, synovial blood flow of the 28 joints used in DAS 28 was evaluated by joint ultrasound and scored. The total score was defined as the total signal score (TSS). Depression and anxiety were evaluated using the Japanese version of the self-rating depression scale (SDS) and the state-trait anxiety inventory (STAI). Using VAS as an indicator of pain, and TSS as an indicator of synovitis, subjects were divided into 4 groups including group I: VAS > 50mm, TSS ≥ 5, II: VAS ≥ 50mm, TSS ≥ 5, III: VAS ≤ 50mm, TSS < 5, and IV: VASmm > 50, TSS < 5. SDS and anxiety scores were compared between groups. [Results] Group I had significantly higher SDS and anxiety scores than group II. There were no differences in SDS and anxiety scores between III and IV. [Conclusion] In active RA patients, severe depression and high anxiety may cause more severe arthritic pain.

P3-125

A case of rheumatoid arthritis complicated with gluteal muscle hematoma and decreased Factor XIII activity during treatment with tocilizumab

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Conflict of interest: None

【Case】A 67-year-old woman with rheumatoid arthritis was complaining of spontaneously developed purpura and swelling on her left hip. She had been treated with tocilizumab (TCZ) for eight months. Laboratory tests revealed anemia. Computed-Tomography detected a high-density mass in her left gluteus. So she was diagnosed left gluteal muscle hematoma. With complete bed rest after admission, the hemoglobin level stopped to decrease and swelling on her hip gradually improved. The platelet count, bleeding time, prothrombin time, and activated partial thromboplastin time were within normal range. The fibrinogen level was slightly decreased and Factor XIII (FXIII) activity level was decreased to 35%(normal range 70-140%). After we discontinued TCZ, her purpura and muscle hematoma did not recur and her FXIII activity level gradually recovered. 【Discussion】TCZ is reported to suppress FXIII production. In congenital FXIII deficiency, FXIII activity level is correlated with severity of bleeding and if it is ≧ 31%, severe bleeding rarely occurs. However, three cases including our case developed muscle hematoma despite the fact that their FXIII activity levels were ≧ 31%. Physicians should consider discontinuing TCZ treatment if hemorrhagic events occur during TCZ treatment.

P3-126

Treatment of serious allergy symptoms occurring in association with enteritis in a rheumatoid arthritis patient

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Conflict of interest: None

A 64-year-old woman was diagnosed in 2009 with rheumatoid arthritis (RA). A skin biopsy performed in 2012 revealed angiitis, and she was diagnosed with malignant rheumatoid arthritis. In March 2015, she was admitted for vomiting and diarrhea along with marked dehydration and high inflammatory response. Abdominal CT indicated edema in the small intestinal wall, and a blood culture indicated gram-positive bacillus. A blood culture identified *Listeria monocytogenes*. After discharge, she frequently suffered bronchial asthma attacks, despite regular use of inhaled b-agonists. On day 8 of hospitalization, steroid dosage was increased to PSL 40 mg/day. Subsequently, her asthma symptoms improved, but on day 11 she experienced systemic urticaria. We suspected drug-induced rash and discontinued all potential inducing drugs, but her condition did not improve. On day 20, T-cell suppression resulted in improvement in allergy symptoms, and abatacept was initiated to control RA, resulting in the urticaria improvement 14 days later. Molecular targeted therapy is effective in RA treatment, but its application and innovative drug develop-

ment in the allergy field remains unexplored. This case is important as one of the first reports of abatacept use for treatment of allergy symptoms in humans.

P3-127

Fatal deterioration of interstitial pneumonia in a rheumatoid patient during Tofacitinib treatment: a case report

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Conflict of interest: None

We report a case of a rheumatoid patient who died of deteriorated interstitial pneumonia during TOF treatment. A 60-year-old-woman was suffering from RA for 7 years and had interstitial pneumonia. Although etanercept, tocilizmab, adalimumab, abatacept, golimumab were given, their effects were insufficient. The use of MTX was permitted in a university hospital. She was introduced to our hospital in April, 2014. We used TOF 5mg in July 2014, because her symptoms were not improved despite of increasing the amount of MTX to 16 mg once a week. CRP was improved from 1.4 mg/dl to 0.05 mg/dl, and DAS28-CRP was also from 4.54 to 2.11 for two months. In the middle of November, 2014, she went to see a respiratory physician complaining of fever and cough, but she was not given additional treatment because of no apparent changes on chest radiographs. In the end of November, she was transferred to our emergency room because of severe dyspnea. She was hospitalized by a diagnosis of deterioration of interstitial pneumonia. Steroid pulse therapy and antibiotics treatment were provided, but the symptoms were not improved. She died in the end of December. 9 fatal cases have been reported during TOF treatment in Japan. Doctors should give TOF to rheumatoid patients with pulmonary diseases carefully.

P3-128

A case of ANCA-negative microscopic polyangiitis with highly elevated biliary tract enzymes and necrotizing vasculitis of the liver

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Conflict of interest: None

A 40-year-old man was admitted to our hospital because of fever, muscle pain and abdominal pain which persisted for 2 months. He had weight loss of 6 kg in 2 months. He also complained numbness of his extremities. Blood pressure was 173/105 mmHg. Laboratory data revealed that urinary red blood cell 8 cells/HPF, urine protein 0.37 g/gCr, AST 83 IU/L, ALT 135 IU/L, ALP 2869 IU/L, γ-GTP 428 IU/L, Cr 0.32 mg/dL, CRP 8.29 mg/dL. HBs-Ag, HBs-Ab, MPO-ANCA, PR3-ANCA and IF-ANCA were all negative. Abdominal angiography did not show vasculitic lesions. Liver biopsy revealed fibrinoid necrosis of arteriole to small artery in the portal area. Because a slight increase of urinary protein and serum creatinine was observed, we then performed renal biopsy, which showed a cellular crescent in 1 glomerulus out of 28 glomeruli, together with fibrinoid necrosis of afferent/efferent arterioles and tubulitis. He was diagnosed as microscopic polyangiitis. After the treatment with 1mg/kg/day of prednisolone, the laboratory data improved immediately. By literature review, we found some case reports of MPO-ANCA-positive microscopic polyangiitis, in which liver dysfunction preceded renal injury. Our case showed a similar progression of the disease occurred in the absence of ANCA.

P3-129

Association between DAS28-based flare criteria and patient-oriented flare in RA patients using IORRA cohort

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Conflict of interest: None

[Object] To analyze association between DAS28-based flare criteria and patient-oriented flare in patients with RA. [Methods] RA patients participated in the IORRA cohort from April 2009 to April 2012 were selected. DAS28 at 6 months and change in DAS28 (ΔDAS28) in 6 months in each patient was evaluated. The association between 6 previously published DAS28based flare criteria (1)ΔDAS28>1.2 or ΔDAS28>0.6 if DAS28 >5.1 at baseline, 2)ΔDAS28>1.2 or ΔDAS28>0.6 if DAS28≥3.2 at baseline, 3)ΔDAS28>0.6 or DAS28>3.2 at 6 months, 4)ΔDAS28>1.2, 5)DAS28>3.2 at 6 months and 6)DAS28>2.6 at 6 months) and patient-oriented flare was analyzed using sensitivity and specificity. Patient-oriented flare was defined when patient self-rated as "worse" than 6 months before in pain using 5-point Liker scale. [Results] Among 6442 patients, 592 patients self-rated as "worse". Sensitivity/specificity (%) in each flare criteria were 1)48.5/93.9, 2)60.8/87.4, 3)91.7/60, 4)42.4/94.4, 5)85.5/64.8, and 6)94.4/41.8. In patients with DAS28 remission at baseline, those were 1)73.6/91.8, 2)79.2/88.6, 3)87.5/78.9, 4)73.6/91.8, 5)73.6/90.4, and 6)88.2/74.8, respectively. [Conclusions] This study showed that "ΔDAS28>0.6 or DAS28>3.2 at 6 months" criteria was useful for predicting patient-oriented flare.

P3-130

A study on complications of tocilizumab for rheumatoid arthritis

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Conflict of interest: None

Object We examined the efficacy and severe complications such as needing hospital treatments for using tocilizumab for rheumatoid arthritis in our hospital. Method We evaluated retrospectively rheumatoid arthritis patients (44 cases, 10 males and 34 females) treated with tocilizumab in our hospital during August 2008 to July 2015. Result All 44 cases, age average 56.1 (23-78) years old, disease duration average 14.3 (0.8-61.5) year. Biological naive 4 cases, switched 40 cases. Combination with prednisolone 18/44 cases, dose average 4.8 (1-14) mg, and with methotrexate 28/44 cases, dose average 5.1 (4-16) mg. DAS28 CRP average 3.7 to 2.0, SDAI average 19.4 to 5.5, and no response occurred only a case. Severe complications were 15 cases, include Infection 9 cases (2 cellulitis, 2 endophthalmitis, a bacterial pneumonia, a empyema, a pulmonary a tuberculosis, a septic arthritis of wrist, a necrotizing cholecystitis). Combination with steroid in infection case 5/9, and of methotrexate 3/9 cases. Other serious complications were 2 cases (intestine perforation and foxhole cardiomyopathy). There were deaths in 3 cases (empyema, pneumonia and cardiomyopathy). Conclusion Although tocilizumab was effective for RA patients, the severe complications occurred 15/44 cases, which contained fatal 3 cases.

P3-131

Hepatic tumor in the course of RA treatment with Biologic agents. Experience two rare cases

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Conflict of interest: None

Case 1:64y.o. female PI:She was diagnosed as RA in 1984, and it treated with MTX6mg/w and Infliximab (IFX)200mg/8ws from 2008.She was improved arthralgia, and RA maintained remission afterwards. She appealed for right upper quadrant pain in December, 2010. CT showed 100mm liver tumor in S5 and 50mm in S4 CC:Because MTX association lymphoproliferative disorder (MTX-related lymphoproligerative disorders, MTX-LPD) were doubted, we canceled MTX administration. We showed sIL2R degradation immediately afterwards, and the image top accepted spontaneous remission of tumors, too. In pathology by liver biopsy, we showed CD3 (+),CD4 (-), CD8 (+) monoclonal T-cell lympho-

ma. Case 2:58y.o.female PI:She was diagnosed as RA in 2011 and treated with MTX8mg/w, 870 certolizumab pegol (CZP) 100mg/2ws from January, 2012.We showed improvement of arthralgia, and RA became remissi. We finished CZP by January, 2014.. She appealed for right upper quadrant pain in May, 2015. We accepted a mass image of liver S4 40X10mm size in CT. CC:Echinococcosis was doubted by a close inspection. We recognized echinococcus antibody (ELISA / WB method) positive. It was performed hepatectomy (S4a / S8) in surgery. As for the tumor diameter, S4a50x25 mm / S8 was mm 5x5mm size.

P3-132

A case of pregnancy in a patient of rheumatoid arthritis treated by etanercept (ETN) which delivered a healthy baby.

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Conflict of interest: None

A case was a 38-year-old woman. In 2008, she was diagnosed as having rheumatoid arthritis (RA) at the age of 31, with high-titer of anti-CCP antibody (100< U/ml). She had been treated with MTX at the onset, subsequently all treatment was stopped in July 2010, because of her first planned pregnancy. She delivered a healthy baby in April 2011, but bone erosions of bilateral wrist joint was worsened. After breast-feed, drug treatment was restarted with salazosulfapyridine (SASP) in February 2013, because of her desire to conceive a second baby. But bone erosions of bilateral wrist joint was worsened further, treatment was changed to etanercept (ETN) in December. In November, she was 5 weeks pregnant. She hoped for treatment continuation by ETN. We informed that treatment of biological agent during pregnancy is not still recommended, and after getting her consent, treatment of ETN was continued. In July 2015, she delivered a female healthy baby. A length of time from pre-pregnancy through lactation period will be 2 to 3 years. In a patient with high disease activity of RA, bone destruction progresses remarkably by a no treatment or insufficient treatment during pregnancy. We report the case that patient of RA treated by biological agent during pregnancy delivered a healthy baby.

P3-133

Poor knowledge of self-administered biologics associated with male gender and shorter administration duration

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Conflict of interest: None

[Objective] To determine rheumatoid arthritis (RA) patient understanding of self-administered biologics, particularly stopping agents due to adverse events. [Methods] A total of 101 patients with RA using self-administered biologics were asked 26 questions about self-administered biologics including the following questions: Do you temporally stop biologics when serious infection occurs (Q18) or in the perioperative period (Q19)? The impacts of characteristics on understanding were assessed with logistic regression model. [Results] Patients were predominantly female (87%), and had a mean age of 56 years, disease duration of 14 years, DAS28-CRP of 2.3, and administration duration of 5 years. 64% of patients understood Q18, and 39% of patients understood Q19. Multivariate analysis revealed that male gender (OR: 5.23, 95% CI: 1.47-18.60) and administration duration (OR: 0.85/year, 95% CI: 0.74-0.99) were independently associated with no understanding of Q18 and Q19, respectively [Conclusions] Male gender and shorter administration duration are factors associated with poor knowledge.

P3-134

The differences of eGFR decline among biologics in RA patients

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Conflict of interest: None

[Object]Comparing the differences of the degree of the estimated glomerular filtration (eGFR) decline in RA patients among bio. [Methods]RA patients in our section using same bio continuously at least 18 months from April 2011 to March 2014. We calculated eGFR in the period, and compared the change between TCZ group and TNF inhibitor group (IFX ADA GLM), ETN group and ABT group, respectively. [Results]73 examples (62 female). There were 14 patients in TCZ group, 8 in IFX, 38 in ETN, 7 in ADA, 3 in ABT, and 3 in GLM. The average age was 61.2±12 years old. The serum creatinine value in the beginning of observation period was 0.67±0.16 mg/dL. Among the period, the eGFR decline in TCZ group was -6.1±7.8, in TNF inhibitor group 0.7±9.3, in ETN group 1.5±15.0, and in ABT group -1.5±8.5 ml/min/1.73m^2 per year, respectively. In TCZ group, the average CRP value in the observation period was lower than others. [Conclusions] In TCZ group, eGFR decline was the lowest compared with others.

P3-135

Minimally invasive treatment with controlled release of recombinant human basic fibroblast growth factor for patients with early idiopathic osteonecrosis of the femoral head

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Conflict of interest: None

Idiopathic osteonecrosis of femora head (ONFH) is a multifactorial disease which is common among young people in their 30s and 40s, that can cause femoral head collapse and have to undergo total hip arthroplasty. Treatment with recombinant basic fibroblast growth factor (bFGF) in animal experiments has been shown to increase bone mass in deficit areas of ONFH. A pilot study with recombinant human bFGF for patients with precllapse ONFH was conducted at Kyoto University Hospital in 2013-2014. In the trial, ten patients with early stage of ONFH received a single local administration of 800μg of recombinant human bFGF impregnated gelatin hydrogel and were followed up for one year. The surgery was performed using a minimally invasive technique. Five patients experienced 14 adverse events, however all the patients completely recovered from all the adverse events. The mean clinical scores significantly improved by one year postoperatively compared with the preoperative scores. There was one case of femoral head collapse. Stage progression and collapse did not occur in the other nine cases. It is planned to conduct an investigator initiated multicenter trial to evaluate the efficacy of gelatin hydrogel containing 800μg of recombinant human bFGF for patients with precollapse ONFH.

P3-136

Two cases of seronegative rheumatoid arthritis with onset of monoarthritic form treated by etanercept

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Conflict of interest: None

[Objective] To report about two cases of seronegative rheumatoid arthritis (SNRA) developed with monoarthritis treated by etanercept.[Case 1] Sixty-seven years male complained his right elbow pain occurred gradually during a year. CRP level was 1.08 mg/dl and both RF and ACPA were negative. The X-ray photograph and MRI of right elbow showed bone erosion. In the pathology of resected tissue, synovium was increased. Microbial tissue, including mycobacterium, culture was also negative. The diagnosis was SNRA. Recurrence of synovium was occurred even after medication with conventional DMARDs, but it was reduced by etanercept. [Case 2] Sixty-five years male complained his wrist pain after falling down on skiing. The X-ray photograph of right hand showed multiple cystic lesions of carpal bones. CRP level was within

normal limits and both RF and ACPA were negative. In the pathology, synovium was increased. Tissue culture was also negative. He was also diagnosed as SNRA. Destruction of carpal bones was progressed even after application of MTX, but it was prevented by etanercept. [Discussion] Progressions of disease were shown in both cases, which were treated by conventional DMARDs. We need to treat with biologics even for SNRA developed with monoarthritis, if they were progressed.

P3-137

Clinical significance and challenges of old and new classification criteria of collagen diseases including overlap syndrome

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Conflict of interest: None

[purpose] To examine the differences in patient classification between old and new criteria for collagen diseases. [Methods]We enrolled 781 patients visiting our department in this study. The following criteria were applied: 1997 revised ACR criteria and 2012 SLICC criteria for SLE, 1980 ACR criteriaand 2013 ACR/EULAR criteria for SSc, 1997 ACR criteria and 2011 ACR/EULAR criteria for RA, Bohan and Peter criteria, definite or probable, for PM/DM. [Result] 74 and 83 SLE patients were identified by 1997 ACR criteria and 2012 SLICC criteria,respectively; 32 and 38 SSc patients by 1980 ACR criteria and 2013 ACR/EULAR criteria, respectively; 188 and 284 RA patients by 1987 ACR criteria and 2011 ACR/EULAR criteria, respectively; and 11 PM and 7 DM patients. Patients with overlap syndrome were 13 and 33 by old and new criteria, respectively. When we excluded RA, 3 SLE-SSc and 3 SLE-PM patients were classified by old criteria, and additional 4 SLE-SSc patients and 1 SLE-PM patient by new criteria. [conclusion] Although revised classification criteria showed increased sensitivity, the importance of differential diagnosis and the handling of overlap patients in 2011 ACR/EULAR criteria for RA was reconfirmed. In addtion, SLE-SSc was the most frequent overlap in collagen diseases other than RA.

P3-138

A case of the overlap syndrome of systemic lupus erythematosus (SLE) and dermatomyositis (DM)

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Conflict of interest: None

A -27years-old man visited to our hospital for facial rash that appeared after sunburn and fever and cough in June 2015. He was suspected as dermatomyositis from rash and Gottoron's signs and elevation of creatine kinase. He did not complicated with interstitial pneumonia. It showed myositis and fasciitis findings on lower leg in the MRI. The laboratory test revealed pancytopenia and low C3 and C4. Anti-DNA and anti-RNP and anti-Sm antibodies were positive. Anti-Jo-1 antibody was negative. Hematuria and proteinuria were found in the urine test. He was diagnosed with lupus nephritis, ISN/RPN class IIIA in renal biopsy. Although anti-U1RNP antibody was positive, he was diagnosed as overlap syndrome of SLE and DM from the typical skin findings and anti-dsDNA antibody positive and lupus nephritis. He was treated with methylprednisolone pulse therapy (1000mg daily, 3 days) and following oral PSL 60mg daily. Treatment with prednisolone was successful. SLE is often overlap with scleroderma and Sjogren's syndrome, it is rare to overlap with DM. We report here a rare case of overlap syndrome of SLE and DM which showed a characteristic skin findings in DM.

P3-139

A case of mixed connective tissue disease associated with HHV-6 reactivation after intravenous administration of cyclophosphamide (IVCY)

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Conflict of interest: None

33 years-old woman suffering from polyarthralgia, followed by Raynaud's phenomenon, edema of face and extremities, and alopecia for seven months, was referred to our hospital. The patient disclosed facial rush, sausage-like swelling of fingers, mild skin sclerosis of hands. Laboratory findings revealed WBC 3100/μl, CH50 17.5 U/ml, ANF (speckled) 1280x, anti-RNP >500 U/ml, anti-Sm 58.2 U/ml. Pulmonary hypertension was suspected according to the findings of right heart catheterization. Finally she diagnosed of having MCTD, and the administration of PSL 50mg was started. Three days after IVCY 700mg on PSL 40mg, there developed fever, skin rush and transaminase elevation of AST 144 IU/L and ALT 167 IU/L, which spontaneously subsided over 2 weeks. Further examination revealed HHV-6 positive detected by the urinary real-time PCR method, and measles virus negative. Parvoviral B19 was detected serologically negative. 4 weeks later, the same episodes of fever, and transaminase elevation was repeatedly developed 3 days after 2nd IVCY on PSL 30mg, but was resolved spontaneously likewise. Thereafter the disease activity of the patient was controlled with PSL administration. It is interesting in HHV-6 reactivation induced by IVCY, we report some considerations about these conditions.

P3-140

A case of mixed connective tissue disease (MCTD) complicated with Sjogren's syndrome (SS) and microscopic polyangiitis (MPA)

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Conflict of interest: None

【case】71-year-old woman was diagnosed as having MCTD and Sjogren's syndrome with Raynaud phenomenon, sclerodactyly, pulmonary fibrosis, leukopenia, sicca syndrome, positive test for serum anti-U1 RNP antibody and anti-Ro/SSA antibody in 1999. Microscopic hematuria and proteinuria were pointed out for the first time in May 2011 and in August 2011 respectively. Renal biopsy revealed crescentic glomerulonephritis without deposit of immune complex. Titer of serum MPO-ANCA was 130 U/ml. Serum PR3-ANCA, anti-GBM antibody and hypocomplementemia were not observed. She was diagnosed with MPA. Steroid pulse therapy and azathioprine were started, and she was doing well. 【conclusion】Pathological characteristics of kidney found in MCTD patients are usually immune-complex glomerulonephritis as SLE-like features or intimal thickening of small arteries found in systemic sclerosis patients. MPO-ANCA positive crescentic glomerulonephritis in MCTD patients was rarely reported. To our knowledge, it is the second case in which MPA was demonstrated in a patient with MCTD and SS.

P3-141

Two cases of dermatomyositis associated with lung cancer

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Conflict of interest: None

Two cases of dermatomyositis associated with advanced lung cancer, histologically non small cell carcinoma were reported. In one case, dermatomyositis was well controlled by the systemic chemotherapy of lung cancer which made the tumor shrink in size. In each case, the patient passed away becouse we could not heve the systemic chemotherapy. Primarily the presence of an autoimmune mechanism was suggested in the relationship between lung cancer and dermatomyositis.

P3-142

A case of dermatomyositis with primary cardiac lymphoma showing central nervous system relapse

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Conflict of interest: None

【Case】 A 69-year old woman presented skin rash, myalgia, muscle weakness, arthralgia, elevated creatinine kinase (CK). A diagnosis of dermatomyositis (DM) was made and corticosteroid and methotrexate was started with prompt response. Two years later, she experienced syncope. CT scan showed intracardiac mass, and cardiac biopsies demonstrated primary cardiac lymphoma (PCL). Six cycles of R-CHOP was started with complete response. Six month later, she experienced myalgia with right leg and elevated CK. A diagnosis of recurrence of DM and immunosuppressive therapy was intensified. However, she showed headache and disorientation and she admitted to our hospital. Although we started to treatment of infectious and metabolic cerebritis, she have increasing disorientation, respiratory failure and died in 10 days after admission. We underwent her autopsy and found pathologically lymphoma cell with her brain and fatty tissue around her cardiac muscle.【Conclusion】We reported a rare case of DM with PCL that showed central nervous system relapse.

P3-143

The autopsy case of polymyositis that was complicated with a respiratory muscle disorder

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Conflict of interest: None

The patient was age of 66 years old female. She got interstitial pneumonia at the age of 52, and polymyositis at the age of 56. She was treated with 30mg of prednisolone and cyclosporine daily, became remission state. She got prednisolone tapering and was followed up. She got small intestine ileus at the age of 60 was similar to systemic sclerosis. She received conservative therapy for this pseudo ileus. She came to our hospital at the age of 62, was pointed out anti-EJ antibody positive and treated with 14mg of prednisolone and 2mg of tacrolimus daily for maintenance therapy. She was urgently hospitalized with E. coli sepsis this time. Sepsis was improved by antibiotics after hospitalization immediately, but is complicated with takotsubo cardiomyopathy after seven days of hospitalization. It became the intubation and mechanical ventilation for poor breathing state. We put tracheotomy and continued mechanical ventilation for a compound factor of push up of diaphragm due to pseudo ileus, heart failure and interstitial pneumonia. However, her muscle weakness progressed, and the spontaneous breathing became gradually weak. There was no effect that high dose steroid therapy, she died after 79 days of hospitalization. We examine her with autopsy.

P3-144

A fulminant case of polymyositis and fascitis complicating thrombotic microangiopathy and alveolar hemorrhage

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Conflict of interest: None

A 34-year-old female was admitted to our hospital with finger edema and myalgia, muscle weakness. She was found to have an anti-Scl-70 antibody, increased muscular enzymes, but she didn't have sclerema and Raynaud phenomenon. MRI revealed myositis and fasciitis. But we was not obtained diagnosis by muscle biopsy. We clinically diagnosed as polymyositis and fascitis and treated by prednisolone, cyclosporine, methylprednisolone pulse therapy. But they were not sign of improving symptoms. Thrombocytopenia, hemolytic anemia and red cell fragments were present in peripheral blood on the 32th hospital day, so thrombotic microangiopathy (TMA) was diagnosed. Anemia progressed and bloody sputum and hypoxia were observed, and CT revealed diffuse pulmonary infiltrative shadow on both lung fields, so alveolar hemorrhage was diagnosed on the 34th hospital day. She was treated by plasma exchange therapy. She died of progressive respiratory failure and circulatory failure on the 36th hospital day. In autopsy we showed a lot of pericardial fluid and pulmonary hemorrhage. We discuss polymyositis, fasciitis and scleroderma without sclerema as the underlying disease of TMA and alveolar hemorrhage.

P3-145

One case that led to the diagnosis of CADM (clinically amyopathic dermatomyositis) from intractable skin ulcer

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Conflict of interest: None

A 38 year old woman, in November, 2014, had a symptom of sore throat, cough, femoral myalgia, and thenal eruption. The range of the erythema with pain increased gradually, and it appeared on the neck, the both upper arms, the both thighs and around the nail. The eruption of neck aggravated and formed an ulcer, and also an ulcer formed into gums. She was diagnosed as lupus erythematosus profundus on the basis of skin biopsy of the eruption of the upper right arm, received 30mg of Prednisolone daily. However the improvement of the symptom was poor, she was hospitalized for diagnosis and treatment. Finally we diagnosed CADM (clinically amyopathic dermatomyositis) because anti Jo-1 antibody and anti ARS antibody were negative, anti MDA-5 antibody and Gottron's sign were positive, test value of CK increased a little, and there was not muscular weakness. Ferritin was 120 and slight high, but anti MDA-5 antibody was positive and she had interstitial pneumonia so we treated trimodality therapy. Nonetheless she didn't have malignancy. The eruption experienced an improvement gradually and the pain was reduced. There is not exacerbation of interstitial pneumonia currently. We report a rare case that refractory skin ulcer suggested the existence of CADM with literature review.

P3-146

The efficacy of additional cyclophosphamide for interstitial pneumonia complicated with dermatomyositis/polymyositis after early initiation of calcineurin inhibitor

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Conflict of interest: None

Objective: We evaluated the efficacy of additional intravenous cyclophosphamide (IVCY) for progressive interstitial pneumonia complicated with dermatomyositis / polymyositis (IP-DM/PM). Methods: We studied 33 patients with ILD-DM/PM. All patients initially received co-administration of calcineurin inhibitor (CNI) with corticosteroid. When a patient presented exacerbation of IP, IVCY was additionally administrated. Patients were classified into three independent severities (severe-, moderate- and mild-IP). Clinical outcomes were compared with those of 21 patients who had been previously treated in our hospital before starting this therapeutic strategy, as the historical comparison group. Results: IVCY was administrated to 11 patients (8 in severe (89%), 2 in moderate (29%), and one in mild-IP (6%)). In the severe-IP, IVCY was given to 6 patients within 14 days after the initiation of CNI. On the other hand, the mortality rate in the severe-IP was significantly improved compared with the historical comparison group (22.2% vs. 85.7%, $P < 0.05$). Conclusion:

Under stabilizing the blood concentration of CNI, additional administration of IVCY in the early phase of the illness is a reasonable combination therapy for repressing the disease activity in severe IP-DM/PM.

P3-147

Lung prognosis in interstitial lung disease in patients with anti-Jo-1 positive and anti-EJ antibody positive polymyositis/dermatomyositis

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Depertment of internal medicine

Conflict of interest: None

【**objective**】To examine the prognosis of interstitial lung disease (ILD) in patients with anti-Jo-1 and anti-EJ positive polymyositis/dermatomyositis (PM/DM). 【**methods**】29 of PM/DM patients with anti-Jo-1 antibody or anti-EJ antibody who were seen at Tokai University hospital between April 2011 to March 2015 were retrospectively evaluated for induction rate of home oxygen therapy (HOT), mortality rate and recurrence rate of ILD. Antibodies were measured using immunoprecipitation assay. 【**results**】Of the 29 patients, 19 had anti-Jo-1 antibody and 10 had anti-EJ antibody. Induction rates of HOT, mortality rates and recurrence rates of anti-Jo-1 positive group were 10.5%, 15.8% and 26.3% and those of anti-EJ positive group were 30.0%, 30.0% and 50.0%, respectively. 【**conclusions**】These results suggest that the lung prognosis in patients with anti-EJ antibody might be worse than that of patients with anti-Jo-1 antibody.

P3-148

A case of Banker type juvenile dermatomyositis with an ileocecal arteriovenous fistula

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Conflict of interest: None

The patient developed exudative erythemas on his face and extremities, and myositis at 7 years of age. These symptoms improved after administration of prednisolone (PSL). Small intestine bleeding from the ileal was diagnosed by the lower digestive tract endoscope and abdominal CT for the first time at age 10. His prominent symptoms characterized by recurrent intestinal bleeding due to a vasculitis, lipodystrophy, subcutaneous calcification, joint contraction, suggested Banker type juvenile dermatomyositis (JDM). His recurrent gastrointestinal bleeding was refractory to PSL and several immunosuppressive agents, such as cyclophosphamide pulse therapy and mycophenolate mofetil, until 25 years of age. Although his arteriovenous fistula located in the ileocecal developed and became greater, his gastrointestinal bleeding and nutritional status had shown marked improvement with ascending colon resection and a colostomy at 26 years of age. In conclusion, our case might suggest that Banker type JDM imposed resistance to an immunotherapy of gastrointestinal bleeding due to vasculitis. Thus, it is particularly important to treat for vasculitis of JDM in the early stage.

P3-149

Successful treatment with adalimumab for dermatomyositis with calcinosis universalis and acquired Brown's syndrome: a case report

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Conflict of interest: None

We present a 49-year-old woman diagnosed as dermatomyositis with calcinosis universalis. At 36 years old, the Gottron's sign, heliotrope rash and dactylitis appeared, and laboratory data revealed elevated serum CK and positive anti-Jo-1 antibody. High-dose glucocorticoid improved her symptoms, but a number of csDMARDs failed to maintain remission and spare the steroid dosage. At 40 years old, calcification on her chest wall and IP joint capsules, fever and myalgia developed. At 46 years old, administration of infliximab was initiated and she achieved remission. At 48 years old, infliximab was suspended due to an operation, and her fever and myalgia relapsed. Panniculitis on her chest wall, that might precede the development of calcification, appeared. She also felt difficulty in looking upward, which was diagnosed with acquired Brown's syndrome. We supposed the long interval of infliximab might cause the secondary failure. We switched infliximab to adalimumab, and her symptoms, including panniculitis and acquired Brown's syndrome, resolved again. There are a few case reports that show the effectiveness of anti-TNF-alpha inhibitors on refractory dermatomyositis. This case suggests the utility of adalimumab on refractory dermatomyositis, especially with calcinosis universalis.

P3-150

A case of thrombotic microangiopathy complicated by polymyositis successfully treated with rituximab

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Conflict of interest: None

A 40-year-old woman presented with muscle pain in her limbs for a week. Observed proximal limb muscle weakness, elevated muscle enzymes, electromyogram findings and MRI results led to the diagnosis of polymyositis. Initially, prednisolone 60mg/day was prescribed. 19 days after starting the treatment, her myalgia was suddenly exacerbated and was accompanied by an elevation of creatine kinase and severe thrombocytopenia. Since exacerbation of polymyositis was suspected, a 3-day course of intravenous methylprednisolone was prescribed. Because laboratory analysis suggested microangiopathic hemolytic anemia, we strongly suspected a complication of thrombotic microangiopathy (TMA) and started to treat with plasmapheresis. Given the resistance to the treatment, we decided to start an additional treatment with rituximab administration. After treatment with ten plasmapheresis sessions and 4 weekly doses of rituximab, platelet counts and creatine kinase levels were normalized. To the best of our knowledge, this is the first case report of TMA complicated by polymyositis that has been successfully treated with rituximab and plasmapheresis. It is possible that rituximab is effective for treating TMA complicated by polymyositis.

P3-151

A case of polymyositis with anti-polymyositis-scleroderma(PM-Scl) antibody

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Conflict of interest: None

A 57-year-old male began to have muscle pains at lower legs and arthralgia at knee joints on October 2014, following by Raynaud's phenomenon symptoms, swelling of fingers, dyspnea and trismus. With the exacerbation of the symptoms, he referred to our hospital on July 2015. His physical examination showed not typical skin symptoms of dermatomyositis nor sclerema, but sausage-like swelling of fingers and nailfold telangiectasia. He revealed muscle weakness at proximal muscles and dysphagia with high titers of CK (2106 IU/L) and aldolase (41.5 U/L). The serological exams showed ×1280 ANA, negative for anti-JO-1, ARS, RNP and Scl-70 antibodies. His chest X-ray showed interstitial pneumonia. We diagnosed him as polymyositis by the electromyogram, although muscle biopsy was normal. We treated him with steroid pulse therapy, following by 50mg/day PSL and 150mg/day CyA. His additional exams showed positive for anti-PM-Scl antibody by immunoprecipitation. His muscle symptoms were improved with normalization of CK. Anti-PM-Scl antibodies are specific for myositis, especially seen in overlap syndrome with PM and SSc. This antibody has a relationship with HLADRB0131 and the type of HLA is only 0.14%, resulting very rare in

Japan. We report this rare case with some previous reports.

P3-152

A case of rapidly progressive interstitial lung disease associated with amyopathic dermatomyositis preceded by fulminant type 1 diabetes

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Conflict of interest: None

[Case] A man in his 40s was diagnosed with fulminant type 1 diabetes mellitus when he was 30 years old. Anti-GAD antibody was negative. 3 months before admission, he noticed edematous erythema on his eyelids, cheeks, arms and back. He was not aware of any weakness of muscles. Chest HRCT showed consolidations at basal segment of both lungs. After admission, serum ferritin level was 601 ng/ml and chest HRCT revealed the development of consolidations. He was diagnosed with rapidly progressive interstitial lung disease associated with amyopathic dermatomyositis. He was treated with prednisolone 60 mg per day, cyclosporine 225mg per day and intravenous cyclophosphamide (500 mg/m^2, every 3 week). The erythema, consolidations of chest HRCT and serum ferritin level gradually improved. **[Clinical Significance]** The mechanism of onset of fulminant type 1 diabetes is considered to excessive immune response after the viral infection, with a specific type of *HLA* or *CTLA4*. That of amyopathic dermatomyositis is also related to the host response to viruses. It is of interest to consider the patient's characteristics of autoimmune disease like this case.

P3-153

Idiopathic portal hypertension as one of rare causes of hepatic involvement associated with polymyositis

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Conflict of interest: None

A man was diagnosed with polymyositis (PM) at 44-year-old. PSL was started and IVCY was followed for interstitial pneumonitis associated with PM. Then he was treated with PSL 7mg and Tac 3mg daily as maintenance. He developed myalgia and muscle weakness with CPK 717U/L and CRP 5.8mg/dl at 61-year-old, therefore was admitted for flare-up of PM. Therapy with PSL 40mg and Tac 4mg daily improved his symptoms. However, hepatic dysfunction prolonged and he suffered from progressive ascites. Hepatic biopsy was performed after negative tests of viral hepatitis, portal thrombosis and malignancy. Biopsy specimen showed fibrotic change of portal vein without hepatitis, suggesting idiopathic portal hypertension (IPH). Hepatic venography demonstrated hepatic vein-to-vein anastomoses with "weeping willow" appearance and direct measurement of portal pressure was elevated at 28mmHg, and therefore he was diagnosis with IPH. Additional ascites drainage and olmesartan for reducing portal pressure improved laboratory data and ascites. IPH associated with autoimmune disease was shown by several reports showed, and it is suggested that autoimmunity is possibly related to pathophysiology of IPH. We should remind to consider IPH as a rare cause of prolonged hepatic dysfunction associated with PM.

P3-154

A cases of anti-NXP-2 antibody(anti-MJ antibody) positive dermatomyositis, which merged in large cell lung cancer

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Conflict of interest: None

【Object】To report a cases of anti-NXP-2 antibody positive dermatomyositis, which merged in large cell lung cancer.【Method】Case report of a 44-year-old man,with edema,muscle pain,and fever. It showed a tumor lesion of diameter 60mm in the right upper lobe on chest CT,and WBC5780/μl,CRP4.07mg/dl,CK6432 U/l (CK-MM98%),high intensity lesion in muscle MRI.【Result】We diagnosed with non-small-cell lung cancer in bronchoscopy, and muscle fibers of mild various sizes,the infiltration of slight inflammatory cells from muscle biopsy.We went radical resection after radiation therapy (40 gray) and chemotherapy (carboplatin-paclitaxel 6 Cool) enforcement. The final diagnosis was found with large cell lung cancer (pT2aN0M0, stageIB). Promptly inspection and clinical symptoms after the start of chemotherapy were improved.Anti-NXP-2 antibody was found to be positive in this case after.【Conclusion】This case was an example of a successful treatment of paraneoplastic syndromes edema and CK value of limbs due to lung cancer radical was also remission.

P3-155

Clinical features of myositis patients with intramuscular bleeding; an association of anti-MDA5 antibody with muscular bleeding

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Conflict of interest: None

Objective: Muscle bleeding is a rare complication in Polymyositis (PM) / Dermatomyositis (DM). We examined clinical features of patients with/without intramuscular bleeding Methods: Subjects were 40 patients of PM/DM who received muscle biopsy for the diagnosis from January 2011 to August 2015. Results: Subjects receiving muscle biopsy were 40 patients (PM; 13, DM; 18, clinically amyopathic DM (ADM); 9) which included 14 males and 26 females. Among them, 9 were positive for anti-MDA5 antibody. Intramuscular bleeding occurred in 4 cases. One case was PM with intramuscular hemorrhage during anti-coagulant therapy for atrial fibrillation. Another 3 cases were ADM; muscle bleeding was developed at the site of biopsy in 2 cases and fatal spontaneous multiple massive bleeding occurred in the 1 case. Interestingly, All cases of ADM with muscle bleeding were positive for anti-MDA5 antibody. Conclusion: Intramuscular bleeding was specifically occurred in ADM patients positive for anti-MDA5 antibody, which suggests muscle bleeding is one manifestation of anti-MDA5 syndrome that injured micro-vessels.

P3-156

A case of peripheral fasciitis as one of the significant manifestations in polymyositis

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Conflict of interest: None

【Case】A 52 years old woman came our hospital with muscle weakness of lower limb. She also had myalgia and elevated level of serum CPK. Computed tomography showed interstitial pneumonia. Biopsy specimen from lower limb muscle showed infiltration of inflammatory cells and degeneration of muscle fiber. She was diagnosed as anti-ARS antibody positive polymyositis (PM) and treated with predonisolone (PSL) and cyclosporin (CyA). Her symptoms and elevated CPK level improved. In X-1 year, she continued treatment with PSL 10mg and CyA 100mg daily. On October, she developed pain and swelling of her left lower leg. MRI with fat-supressed T2 weighted image demonstrated high intensity in left anterior tibial fascia, indicating fasciitis. FDG-PET/CT showed high FDG uptake in bilateral anterior tibial fascia. Biopsy specimen showed infiltration of imflammatory cells to fascia, suggesting fasciitis associated with PM. Additional PSL was administrated and her symptoms and MRI finding dramatically improved. 【Discussion】Though fasciitis can be associated with PM, peripheral fasciitis is rare. We report with considerations from literature.

P3-157

Examination about the association between result of a measurement level of Euroline Myositis profile 3 and disease activity in the rheumatic disease

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Conflict of interest: None

[purpose] Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP, PM-Scl100, PM-Scl75, Ku, Ro-52 are included in Euroline Myositis profile 3. We consider an association between result of a measurement level and disease activity in the rheumatic disease. [method] About the cases that measured Euroline Myositis profile 3 several times, among approximately 140 cases in our course, I examined the association between change of the result of a measurement level and clinical course. [result] After assessing a result of a measurement level of Euroline Myositis profile 3 for the same case over time, a change was confirmed. [conclusion] The usefulness as the index when we evaluate disease activity,.may be found by examining a result of a measurement level of Euroline Myositis profile 3 in more large number of cases.

P3-158

Case report : two cases of cancer associated dermatomyositis improved with resection of underlining malignancy

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Conflict of interest: None

[Methods] case 1: 39 year old female. 5 months before admission, she was pointed out breast mass and she was diagnosed stage 2 breast cancer. There was worsening of skin rash and liver enzyme when she started neoadjuvant chemotherapy. She was referred and diagnosed as cancer-associated dermatomyositis. Her skin rash completely disappeared after resection of cancer. case 2: 66 years old male. Two months before admission, skin rash appeared on his face and neck. Although he was prescribed topical steroid, his rash persisted and referred. We diagnosed Stage 3 gastric cancer and cancer-associated dermatomyositis. After resection, rash and myositis were disappeared, though dysphagia was remained so we have to administer steroid and IVIg. [Results] Skin rash and myositis disappeared after resection of cancer, though dysphagia persisted even after resection about case 2. [Conclusions]There is possibility of clinical improvement when cancer is resected in early phase. We can consider about performing surgery for non-organ threatening myositis before immunosuppressive treatment.

P3-159

Demographics and clinical features of patients with dermatomyositis (DM) over the past decade - A single institute study

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Conflict of interest: None

Background: Recently we feel that we have encountered more patients (pts) with DM than before. Japan intractable disease information center reported that the number of pts with PM/DM was ca. 6,000 in 1991, which increased to 17,000 in 2009. Methods: We retrospectively examined clinical features of inpatients with newly developed DM. Results: The average annual number of DM pts from 2005 to 2014 was significantly higher than that prior to 2004. There were variations (1-5 per year) in the annual incidence, which was higher in 2006-07 and 2012-13. As for 23 inpatients in the past 10 years (onset age; 56.7, female; 15), ANA was positive in 19, while anti-Jo1 was negative. Malignancy and interstitial lung disease (ILD) were seen in 7 and 11, respectively, and smoking was significantly associated with ILD. Corticosteroid (CS) was the main therapy, and immunosuppressant and IVIG were used in some. The prognosis was poor in DM with malignancy. Regarding pts with ILD, some developed pneumomediastinum and required cyclophosphamide and cyclosoprin plus CS. However, overall prognosis was fair. Conclusion: DM is increasing over the past decade, in which smoking, infection and malignancy could presumably be involved. Further studies to investigate the extrinsic factors would be warranted.

P3-160

A case report of dermatomyositis with germ cell tumor

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Conflict of interest: None

A 20 year old Japanese man developed an erythematous rash over his face, both upper and lower extremities. His rash worsened over the next month and bilateral proximal muscle pain and weakness of upper and lower extremities developed. With an acute right upper quadrant abdominal pain, he was hospitalized to our faculty. Investigations revealed CK 3649 IU/L and abnormalities on muscle biopsy consistent with dermatomyositis (DM). Symmetric proximal muscle weakness, elevated serum muscle enzymes, typical rash of DM and typical histological feature fulfilled the Bohan and Peter diagnostic criteria for the diagnosis of DM. Steroid therapy led to improvement in his rash and weakness with return to normal level of CK in a week, but over the next week his skin rash flared and the decline of LDH stopped. Abdominal echo test and CT scan revealed and retroperitoneal mass. Without elevation of tumor marker such as HCG, AFP and sIL2-R, FDG-PET showed abnormal uptake (SUV-Max=19.6). A biopsy of mass revealed germ cell tumor. He was discharged from our hospital to start chemotherapy. Although the association between DM and malignancy are well reported, there are few reports of DM with germ cell tumor. We report a case report of DM and germ cell tumor based on the past literature.

P3-161

A difficult case of anti-SRP-positive polymyositis, who were tried to treat with the combination therapy of mycophenolate mofetil (MMF)

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Conflict of interest: None

A woman was diagnosed as having polymyositis at age of 27. She was treated with methylprednisolone pulse therapy, following with prednisolone (PSL) 40mg and methotrexate (MTX) 8 mg per week. When the dose of PSL was tapered to 10 mg, her polymyositis was flared. The therapy of PSL + MTX + tacrolimus (Tac) was started but the effect was restricted. At the age of 32, her condition became worse and she moved to other hospital for further examination. She was confirmed a diagnosis of active necrotizing myopathy with anti-SRP antibodies and she was treated with high dose of immunoglobulin infusion and PSL. Because the effect was restricted, they restarted the PSL + MTX + Tac therapy and she came back to our clinic. At the age of 34, her muscle weakness worsened again with an increase in creatine kinase (CK) level to approx. 3,000 and low serum IgG. Because the Hospital Ethics Committee permitted the use of MMF, she and us decided to stop MTX and to start MMF 1,000 mg, which was increased finally to 2,500 mg. Her muscle weakness, CK level and serum IgG slowly improved and she returned back to work without an obvious side effect.

P3-162

Two cases of dermatomyositis complicated by relatively rare malignancies

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Conflict of interest: None

Case 1. a woman in her 40s was diagnosed with uterine body cancer of clinical stageIIIc in January, 2014. She was operated and achieved complete remission (CR) after six courses of adjuvant chemotherapy. One year after, PET revealed FDG uptake in a solitary lymph node near the internal iliac artery. One month later, she noted skin rashes on her face and the back of both hands, and proximal muscle weakness of her extremities. The metastasis of uterine body cancer to the lymph node was confirmed by open biopsy. Dermatomyositis was the diagnosis after detail examinations. We started prednisolone concurrently with chemotherapy for the metastatic uterine body cancer. After six courses of the chemotherapy, she attained CR again. Case 2. A woman in her 70s was admitted to our hospital because of skin rashes on her face and both upper arms in September 2014. One month later, she felt progressive proximal muscle weakness of her extremities. Dermatomyositis was the diagnosis after detail examinations. PET revealed FDG uptake in an anterior mediastinal mass and multiple lymph nodes around the mass. Operation was performed. Thymic cancer was diagnosed pathologically. Radiotherapy was performed after the operation, but multiple metastasis in the liver was found four months later.

P3-163

A case of steroid-refractory polymyositis complicated with lung carcinoma who responded well to IVIG

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Conflict of interest: None

A 71-year-old male noticed general fatigue in February 2015. He visited a hospital complaining of proximal muscle pain and weakness. He was transffered to our hospital because of polyarthralgia and high creatine kinase (CK) level. Serum CK level was 10437 IU/l. Anti-nuclear and anti- ARS antibodies were negative. Manual muscle testing of the bilateral proximal muscles revealed grade 3/5. A diagnosis of polymyositis was made. After a daily dose of 1000 mg of mPSL for three days, the patient was given at PSL 60 mg/day. He presented a resistant polymyositis with sever muscle weakness, so high dose intravenous immunoglobulin (IVIG) were intiated after failure of steroid. His muscle weakness and myalgia gradually improved. In May CT scan showed enlaged neck lymph nodes and mediastinal tumor. Fine needle aspiration of the neck lymph node revealed adenocarcinoma. He was diagnosed as adenomatous lung carcinoma. He underwent radiotherapy, however chest CT scan showed a large amount of pericardial and pleural effusion. The cytology of effusion revealed low differentiated adenocarcinoma. He received the best supportive care. Good muscular control was achieved following the initiation of PSL 30mg/day.We suggest that IVIG may useful in active and refractory polymyositis with malignancy.

P3-164

A Case of Dermatomyositis with Interstitial Pneumonia Complicated by Chylothorax

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Conflict of interest: None

[Case report] A 77-years-old woman had rash of back of her hands, muscular pain of upper arms and femurs, getting-worse dyspnea and cough. Three month later, she visited our hospital, and was diagnosed as dermatomyositis (DM)complicated wit subacute interstitial pneumonia (IP). Her rash, myositis and IP were gradually improved after initiation of prednisolone, tacrolimus and intravenous pulse cyclophosphamide (IVCY). Unilateral pleural effusion, which was finally diagnosed as idiopathic chylothrax, appeared on about the 40th hospital day. Somatostatin analog and fat-restiricted diet were not able to improve the chylothrax, but fasting therapy and total parenteral nutrition for about a month were able. But bilateral leakly pleural effusion gradually increased and IP was exacerbated. IP was exacerbated more despite of changing tacrolimus to cyclosporine and additional IVCY, and thrombotic thrombocytopenic purpura and fulminant hepatitis were complicated. She died on 92th hospital day. [Discussion] Subacute IP complicated with DM is a poor prognostic disease. Recently, combination of prednisolone, calcineurin inhibitor and IVCY was reported to improve DM-IP prognosis. We reported a very rare and bad prognostic DM-IP case complicated with chylothorax.

P3-165

The association between interstitial pneumonia and blood coagulation disorders in patients with polymyositis / dermatomyositis

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Conflict of interest: None

Objectives: The purpose of this study was to clarify the relationship between the activity of interstitial pneumonia (IP) with polymyositis / dermatomyositis (PM/DM) and blood coagulation abnormalities. Methods: This study is retrospective observation study. Twenty-two patients who were diagnosed as having PM/DM admitted to our hospital from April 2012 to March 2015 were reviewed (median age: 50.5, female ratio: 81.8%). Diagnosis of IP was evaluated by chest high-resolution CT. We reviewed the laboratory findings associated with PM/DM and IP. Results: Nineteen of 22 (86.4%) patients with PM/DM were diagnosed as having IP. All of IP patients with PM/DM were positive for anti-ARS autoantibody or anti-MDA5 autoantibody. The levels of serum KL-6 is 508 U/mL in PM/DM patients with IP. There is significantly positive correlation in the levels of between serum KL-6 and plasma D-dimer ($R=0.61$, $p= 0.0003$). However, there is no correlation between serum KL-6 and blood coagulation tests, such as prothrombin time (%) and activated thromboplastin time. Conclusion: Our data suggested that plasma D-dimer levels are associated with activity and/or severity of IP in patients with PM/DM.

P3-166

A case of adult dermatomyositis with unusual calcinosis

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Conflict of interest: None

We present a case of adult dermatomyositis (DM) with unusual calcinosis unlike often found in juvenile DM. We resected the calcinosis existed in between right first and second metatarsal bones. A 76-year-old woman who has been suffering from DM for twenty years was treated with only external medicine. Hard tumors had appeared in her right forefoot (45mm wide calcinosis detected by X-ray) and in both fingers, and caused a refractory callus of her right foot sole in 2009. The callus caused severe pain in load and repeated local infections, so we resected the calcinosis in 2012. Because we could resect most of the calcinosis, the callus disappeared and local infection got well. And the calcinosis has stayed silent three years after the resection. Clinical significance: Unusual calcinosis in adult DM is rare, only a few reports say the treatments against it may be oral intake or injection of corticosteroid. In case of dermatitis such fistulas or local repeated infections, the surgical resection might be useful. But recurrence of calcinosis was often reported. In our case, no recurrence of calcinosis for three years may be because the activity of her DM has been under good control. Surgical resection of calcinosis in adult DM might be a good option depending on cases like ours.

P3-167

Two Cases of Patients with Antisynthetase Antibodies Presenting Different Clinical Courses

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Conflict of interest: None

[Introduction] Antisynthtase syndrome (ASSD) is characterized by clinical manifestations including myositis, interstitial lung disease (ILD), arthritis, fever, Raynaud phenomenon and mechanic's hands. We report two cases of patients with antisynthetase antibodies (ASA).[Case1] A 59 year-old man with ILD was treated with glucocorticoid (GC) at another hospital. Following the taper and discontinuation of GC, polyarthritis developed and his ILD worsened. He was then referred to our hospital and laboratory test revealed a positive result for ASA. He was treated with GC, tacrolimus and mizoribine. After this course of treatment his, ILD and arthritis improved. [Case2] A 41 year-old woman visited our hospital with complaint of intermittent polyarthritis and fever. Muscle symptoms, skin rash and ILD were all absent. She was found to have ASA. These symptoms were not relieved with NSAID. Following the treatment with systemic GC, fever and polyarthritis improved rapidly. [Conclusion] Previously it was reported that some patients with ASA presented only single manifestation of ASSD, and other symptoms occurred during the clinical courses. It's important to rule out ASSD among patients presenting with arthritis or ILD as single manifestation.

P3-168

A case of flare up of interstitial pneumonia associated with clinically amyopathic dermatomyositis which was thought to be triggered by rapidly decreasing dose of corticosteroid

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Conflict of interest: None

A 42-year-old man was referred to Department of Respiratory Medicine of our hospital for fever, general fatigue, and dyspnea. He was clinically diagnosed as having idiopathic interstitial pneumonia, and histological examination of bronchoscopic lung biopsy specimen showed nonspecific interstitial pneumonia (NSIP). Corticosteroid therapy had been effective, but reduction of PSL caused disease recurrence. He was referred to our Department of rheumatology because of appearance of skin eruption on face and extremities. A diagnosis of clinically amyopathic dermatomyositis (CADM) was made based on characteristic skin lesion, polyarthritis, fever, abnormal feature of electromyogram, elevated CPK levels and anti Jo1 antibody positive. Muscle symptom was not obviously. The patient's clinical condition was very similar to the first episode, and is improving in response to the same therapy again but with slowly reducing dose of corticosteroid. Even though the details are not clear, rapidly decreasing dose of corticosteroid might trigger a flare up of CADM in this patient.

P3-169

Effects and safeties of oral Tacrolimus as a rapid induction therapy in progressive interstitial pneumonia with dermatomyositis

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Conflict of interest: None

【Objective】We examined the efficacy and safety of rapid induction therapy with oral tacrolimus (Tac) for progressive interstitial pneumonia in dermatomyositis (DM-PIP). 【Method】 Twelve patients with DM-PIP treated with tacrolimus were enrolled in this study. We initiated tacrolimus and maintained the trough level 15~20 ng/ml. We assessed laboratory findings and respiratory function test results before and 4, 12, 24 months after tacrolims initiation. 【Results】 The median age was 66 (38-79) and eleven were femail. Eight patients were clinically ADM (CADM). One was acute progressive type, and the others were subacute progressive type. Median diseases duration was 14 weeks (1-350). The frequencies of anti-ARS-antibody (Ab) positivity and anti-MDA5-Ab positivity were 58.3%, 16.7% respectively. One patient died during 24 weeks follow-up period, and the cause of death was encephalitis. Fungal infection was shown in 1, and upper respiratory infection in 1 patient. No patient had renal damage. 【Conclusions】 Rapid induction therapy with oral Tac is effective and well- toleranted for treatment of DM-PIP.

P3-170

Membranoproliferative glomerulonephritis in a patient with systemic sclerosis -polymyositis overlap syndrome

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Conflict of interest: None

We describe 78-year-old Japanese man. He was well treated with 3mg of Prednisolone (PSL) and 3mg of tacrolimus because of systemic sclerosis (SSc) and polymyositis (PM) for ten years. When he was 78 years old, he showed decline of renal function and increase urinary protein. PSL was increased to 5mg, but it did not have effect. He underwent renal biopsy, which presented immune-complex-mediated membranoproliferative glomerulonephritis (IC-MPGN). Autoantibody was rechecked and anti-signal recognition particle antibody was positive. PSL was increased to 1 mg/kg/day and he underwent intravenous cyclophosphamide pulse therapy, and urinary protein was decreased. However, he had oliguria, then he developed respiratory failure. He finally died, although he underwent continuous hemodiafiltration and mechanical ventilation. IC-MPGN results from the deposite of immune complex in the glomerulus. The immune complex-mediated type is secondary to autoimmune diseases, chronic infections, or blood disease. Pragmatic considerations suggest that patients with IC-MPGN should undergo treatments of underlying disease. MPGN occurs in a number of autoimmune disease, which include SLE, SjS and RA. SSc or PM/DM rarely associate with glomerulonephritis or nephrotic syndrome, especially with MPGN.

P3-171

Microscopic polyangiitis diagnosed by muscle biopsy

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Conflict of interest: None

The histological proof of necrotizing vasculitis is the most important part of the diagnosis of vasculitis syndromes. When systemic vasculitis is suspected, the lesion of skin, kidney or nerve is a candidate of tissue biopsy. However, constitutional syndromes such as fever, weight loss or fatigue can be the predominant and only symptoms in systemic vasculitis. We repot two elderly patients with MPA, whose necrotizing fibrinoid vasculitis were demonstrated by muscle biopsies.【Case 1】A 85-year-old female was refered because of general fatigue, impaired ADL, anemia, elevated CRP. There were neither skin eruption, neurological disturbance, ear problem, ILD nor kidney injury. MPO-ANCA was 165 U/ml. A biopsy of lateral quadriceps muscle showed necrotizing fibrinoid vasculitis. The patient was treated with moderate amount of PSL.【Case 2】A 93-year-old female was referred to out hospital because of weight loss, fatigue and fever. The physical examination, laboratory data and imaging studies including PET-CT did not show any significant abnormality except for elevated MPO-ANCA 61 U/ml. The muscle biopsy showed necrotizing fibrinoid vasculitis.【Conclusion】These cases demonstrate the possible utility of muscle biopsy in diagnosis of MPA presenting only with constitutional symptoms.

P3-172

A case of effective intravenous immunoglobulin for peripheral neuropathy in steroid-resistant eosinophilic granulomatosis with polyangitis

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Conflict of interest: None

A 66-year-old female, having suffered from bronchial asthma for 20 years, was admitted with purpura in her lower legs. She presented with sensory impairment, numbness and muscle weakness in the distal regions of her extremities. Laboratory data were: peripheral blood eosinophil count (Eosin), 10,200 /μL; serum IgE, 3979 IU/mL; and the MPO-ANCA, 39.4 U/mL. Nerve conduction tests revealed a decrease of the amplitude of the compound muscle action potential in median, tibial, sural regions. Skin biopsy showed perivascular inflammation with neutrophils and eosinophils. Based on above, we diagnosed her with eosinophilic granulomatosis with polyangitis (EGPA). We initially treated steroid pulse therapy (methylprednisolone 1 g for 3 consecutive days), followed by oral prednisolone at 1 mg/kg/day. Eosin, IgE, and MPO-ANCA was decreased, and muscle weakness was gradually getting better. The sensory impairment and numbness, however, did not exhibit a prompt response. We, therefore, administrated intravenous immunoglobulin (IVIg) at dose of 400mg/kg/day for 5 days after four weeks of steroid therapy, and the neuropathy improved immediately afterwards. We describe a case of EGPA with steroid-resistant peripheral neuropathy which improved after IVIg.

P3-173

Case of peripheral neuropathy developed after the remission induction therapy in eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

A 45-year-old man with a month history of epigastric pain and history of bronchial asthma, allergic rhinitis, prominent eosinphilia, and vasculitis symptoms visited our department with suspected eosinophilic granulomatosis with polyangiitis (EGPA). Digestive tract biopsy findings revealed perivascular infiltration with eosinophils. His history and symptoms were consistent with the characteristic clinical course of EGPA and satisfied the diagnostic criteria by the Japan Ministry of Health, Labour and Welfare. Steroid pulse therapy and steroid (PSL; 1 mg/kg/day) were started, which normalized peripheral blood eosinophil count and improved gastrointestinal symptoms. BVAS improved from 9 to 0.On the 47th hospital day, when PSL was tapered to 40 mg/day, sensory nerve and left leg movement disorder developed without eosinophilia and serologic exacerbation; this was diagnosed as neurogenic disorder by electromyography. CNS and other peripheral neuropathy diseases were ruled out, and EGPA-induced peripheral neuropathy was diagnosed. Intravenous immunoglobulin therapy was started; dysbasia improved, and he was discharged on the 74th hospital day. Peripheral neuropathy develops as an initial symptom in 93% of patients with EGPA; however, in this case it developed after disease remission.

P3-174

A case of granulomatosis with polyangitis presenting the rapid progressive palpable purpura

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Conflict of interest: None

A 51-year-old woman with MCTD had suffered from arthritis, and refractory digital ulcers. In 2007, she was diagnosed as MCTD overlapped with granulomatosis with polyangitis (GPA) by the granulomatous mass of her nasal cavity and the skin biopsy. Prednisolone (PSL) and intravenous cyclophosphamide followed by methotrexate + etanercept (MTX + ETN) resulted in remission of her symptom. In May 2015, she presented with congestion and was diagnosed with sinusitis. Within two months, she developed arthritis and palpable purpura in lower and upper limbs with erosive bullae. Skin biopsy showed vasculitis with perivascular infiltration by leukocytes in upper dermis, which lead to diagnostic confusion with Henoch-Schonlein purpura, but she was diagnosed as relapse of GPA with nose symptoms. 1 mg/kg PSL resulted in improvement of nasal and the skin lesions, then PSL was tapered and MTX+ETN was re-started. GPA is a necrotizing systemic vasculitis of the small sized blood vessels. This case initially had vasculitis in the deep dermis, which lead digital ulcers, and then had vasculitis in the upper dermis, which showed palpable purpura, leading to diagnostic confusion with HSP. Awareness of various presentation of GPA vasculitis is important to the appreciate management of this disease

P3-175

One case of ANCA-associated vasculitis complicated with Central retinal artery occlusion, glomerulonephritis, interstitial pneumonia, cerebral infarction, hypertrophic dura flame

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Conflict of interest: None

The patient was 70-year-old man. And our department introduction visit to scrutiny purpose from MPO-ANCA positive. Before hospitalization, the right eye of vision loss occurred and nearest ophthalmologist observed the place red cherry spot and diagnosed central retinal artery occlusion.On admittion,We listened to both sides of the fine crackle, acknowledged vibratory sensation decrease of both sides lower limbs, in both lower limbs showed the purpura. Labolatory data showed the inflammatory response in blood tests, CRP8.7mg / dl, ESR 60 mm/min and MPO-ANCA 115U/ml.Urine protein 96mg/dl and urine red blood cells 5-9/HPF,and chest CT showed ground-glass shadow of lower lobe, the head contrast MRI showed dura thickened and deeply stained image of the cerebellum.Although biopsied purpura site of the lower limbs is not observed evidence of vasculitis,we diagnosed ANCA-associated vasculitis from the above findings.We started prednisolone oral and cyclophosphamide intravenous drip infusion therapy. Because it showed asymptomatic cerebral infarction during hospitalization course in contrast MRI test, we added aspirin oral. Due to the inflammatory response improved,the patient returned for follow-up visit. We report this case with bibliographic consideration.

P3-176

A case of eosinophilic granulomatosis with polyangitis (EGPA) similar to IgG4-related disease

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Conflict of interest: None

A 48-year-old Japanese man with a long history of allergic rhinitis was administrated in our hospital. He began to have fever and malaise a few month ago, followed by edema and purpura in extemities. In another hospital, blood tests showed eosinophilia (10.3% 1359/μl), hypocomplementemia (C3 64 mg/dl, CH50 <7U/ml),elevated C-reactive protein (10 mg/dl), positive rheumatoid factor (21 U/ml) and hypergammaglobulinemia (IgG 3000mg/dl, IgE 774IU/ml, IgG4 717mg/dl). Skin biopsy showed leukocytoclastic vasculitis. Therefore, he was transferred to our hospital for further evaluation. Hyper sensitivity of the airway was found and Gallium scintigraphy showed remarkable integration in both sides of the kidney and salivary glands. Renal biopsy showed a tubulointerstitial nephritis with marked infiltration of eosinophils. He was thought as having EGPA. Increased eosinophilia and serum IgG4 level, swelling of the kidneys were improved after administration PSL (1mg/kg). This case shows the features of both of IgG4-related disease and EGPA. This case seems a very rare case that shows only tubulointerstitial nephritis without

glomerular injury.

P3-177

Development of granulomatosis with polyangitis 5-year after diagnosis of polymyalgia rheumatica

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Conflict of interest: None

We report a 75-year-old woman with 5-year history of polymyalgia rheumatica (PMR) developing granulomatosis with polyangitis. In 2010, she was diagnosed as PMR. The treatment with prednisolone (10 mg/day) was started, which showed a good response and the dose of prednisolone had been gradually tapered. In 2015, the patient noticed the pains of bilateral shoulders and thighs. She was diagnosed as exacerbation of PMR and dose of prednisolone was increased up to 20 mg/day, which was resulted to be ineffective, so she was admitted to our hospital for further examinations. Laboratory findings revealed the positive for C-ANCA and we performed FDG-PET/CT and found the accumulation of FDG in right nasal region and bilateral lung nodules. The biopsy of right nasal concha was done and demonstrated necrotizing granulomatous vasculitis. She was diagnosed as granulomatosis with polyangitis and treated with a pulse therapy of 1 g methylprednisolone, followed by daily prednisolone (40 mg/day) and monthly intravenous cyclophosphamide (500 mg), which was proved to be effective.

P3-178

A case of Thrombotic thrombocyteopenic purpura caused by Polyarteritis nodosa

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Conflict of interest: None

A 63-year-old female was admitted to our hospital because of fever, livedo racemosa, arthritis and polyneuropathy. She had 5-year history of joint pain, neuralgia and fever and had history of treatment with predonisolone (PSL). Several months before admission to our hospital, she had developed livedo racemosa, arthritis and polyneuropathy. Examination showed the presence of sacroiliitis and multiple inflammatory lesions on the axial spine. A diagnose of undifferentiated spondyloarthritis was made. On post-admission Day12 (Day12), she became acutely ill with a temperature of over 38˚C and renal failure. Enhanced CT showed features of microaneurysms and renal infraction. We diagnosed polyarteritis nodosa (PAN) and she was treated with PSL. However, laboratory test on Day23 showed thrombocytopenia, features of hemolytic anemia and reduction in the serum haptoglobin. And we detected reduced activity of ADAMTS 13. A diagnosis of thrombotic thrombocyteopenic purpura (TTP) was made. She was treated with plasma exchange and Rituximab. Despite the intensive treatment, the patient died due to intraventricular hemorrhage. Our case suggests the possibility of secondary TTP caused by PAN. This is the rare case of PAN complicated by TTP.

P3-179

Rhabdomyolysis in a patient with polyarteritis nodosa

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Conflict of interest: None

A 71-year-old man was hospitalized because of muscle weakness of lower limbs persistent for a month. On physical examinations, rapidly progressive lower proximal muscle weakness and bilateral drop foot were observed. His blood test showed an elevation of CRP (19.5 mg/dL), CK (13000 IU/L). CT angiogrm showed stenosis of the left renal artery. Electromyogram indicated mono-neuritis multiplex pattern, and enhanced MRI demonstrated discretely granular hyperintensities on T2 in his femoral muscles. Femoral muscle-biopsy specimen revealed fibrinoid necrosis of medium-sized vessels and disruption of elastic lamina of the vessel wall in fascia. Muscle necrosis was localized depending on arterial distribution, suggesting the ischemic change of muscles. Collectively, he was diagnosed as polyarteritis nodosa (PAN) with rhabdomyolysis and treated with methyl-prednisolone pulse therapy followed by oral prednisolone of 50 mg/day. He was additionally treated with monthly intravenous cyclophosphamide of 500 mg. Sustained remission has been obtained for 2 months after the treatment. Although rhabdomyolysis is rarely manifested with PAN, it should be included in a differential diagnosis of febrile patients presenting with acute myalgia and weakness with CK elevation.

P3-180

Successful immunosuppressive therapy for the recurrence of headache in a case of primary angiitis of cerebral nervous system (PACNS)

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Conflict of interest: None

The patient was 40s woman. She had headache 3 years ago, and 3 months later paralysis was occurred in her left face and upper limb. FLAIR and DWI of brain MRI revealed high intensity in the right frontal and parietal lobes. The right middle cerebral artery, bilateral basilar and internal carotid arteries showed irregularity in enhanced CT. The number of cell in CSF was elevated. CRP was elevated up to 0.8 mg/dl. She had no symptoms of any other organs and autoantibodies were all negative. She was diagnosed PACNS and treated with prednisolone 60 mg per day. Headache was temporarily improved after treatment, but relapsed with tapering. She was admitted again because of severe headache. Brain CT and CSF did not reveal any activities, but she was diagnosed the recurrence of PACNS because of continuous headache. She was treated with prednisolone and intravenous cyclophosphamide. Headache had improved quickly and CRP level decreased after treatment. Brain biopsy is needed for the diagnosis of PACNS, but it is not done in many cases. The standard treatment of PACNS is high dose glucocorticoid, and combined intravenous cyclophosphamide. It is difficult to diagnose and evaluate PACNS if headache is the only symptom, but it is possible that a series of headache warns a severe symptom.

P3-181

IgA-dominant Postinfectious Glomerulonephritis Associated with Cholecystitis caused by *Klebsiella pneumoniae*

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Conflict of interest: None

A 54-year-old man with a medical history of type 2 diabetes mellitus presented to our emergency room with a complaint of fever and right upper quadrant pain. He was diagnosed with cholecystitis and treated with antibiotics and percutaneous transhepatic gallbladder aspiration. *Klebsiella pneumoniae*(*K.pneumoniae*) was detected in the bile culuture. Although his abdominal pain and imaging findings were improved, fever continued. On day 9, palpable purpura on both of his legs, renal dysfunction, proteinuria and hematuria appeared. On day 19, we biopsied his kidney and initiated methyl prednisolone (PSL) pulse followed by PSL at 60mg/day. The pathological findings showed endocapillary proliferation and deposit of IgA and C3 on mesangium. We diagnosed the patient with IgA-dominant postinfectious glomerulonephritis (PIGN). After the initiation of corticosteroid therapy, he rapidly became afebrile, and his serum creatinine level returned to his baseline. His proteinuria and hematuria disappeared. He was discharged on day 29. IgA-dominant PIGN caused by gram negative bacilli is rare. Our patient is the second case caused by *K.penumoniae*. We herein report a case of IgA-dominant PIGN associated with Cholecystitis caused by *K.pneumoniae* successfully treated with

corticosteroid.

P3-182

A case of rheumatoid vasculitis in which diagnosis was delayed because of prior treatment of polymyalgia rheumatica

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Conflict of interest: None

This is a case of a 76-year-old man who was diagnosed with Polymyalgia rheumatica and initiated steroid therapy in X-3. After the treatment, the symptoms were gradually disappeared and steroid therapy was discontinued. But it recurred, so the treatment was resumed. In March X-1 he was admitted for mandibular osteitis,infectious endocarditis and infectious endocarditis. During admission, her steroid dosage was reduced for the treatment of infections. But his numbness and pain in the extremities gradually enhanced and he couldn't walk very well. His physical findings showed sensory impairment, muscle weakness of his extremities and his laboratory data showed CRP,RF and anti-CCP antibody were high. His X-ray showed joint destruction of his wrist joints largely. Nerve conduction study revealed mononeuritis multiplex and sural nerve biopsy showed vasculitis with fibirinoid necrosis, so he was finally diagnosed as rheumatoid vasculitis. His arthralgia was masked by steroid and NSAIDs initiated him, so result in delayed diagnosis and his disease progressed to vasculitis. We present a case of rheumatoid vasculitis in which diagnosis was delayed because of prior treatment of polymyalgia rheumatica.

P3-183

A case of IgA vasculitis with an atypical course accompanied by protein-losing gastroenteropathy

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Conflict of interest: None

[Case] A 60-yo female [Chief complaints] abdominal pain [Course] In April of the year X, she was diagnosed of MCTD and received PSL 20 mg for finger pain. Despite reduced symptoms, she had onset of abdominal pain from late May and was transferred to our hospital on June 11. Abdominal CT scan showed thickening of the small-intestinal wall, and gastroendoscopy identified mucosal erosion in the small intestine. Although no purpura was noted at the time of admission, IgA vasculitis was diagnosed for reduced activity of coagulation factor XIII, and PSL 60 mg was administrated on June 17. After the start of administration, purpura developed in four extremities, and skin biopsy showed findings of leukocytoclastic vasculitis. Although steroid administration improved abdominal symptoms, hypoproteinemia protracted. The 99mTc-HSA-D scintigraphy showed intestinal leakage, resulting in a diagnosis of protein-losing gastroenteropathy. [Discussion] Since she had no purpura at the time of admission, it was important to differentiate from lupus enteritis initially. Also, although protein-losing gastroenteropathy rarely occurs as a complication of IgA vasculitis, this pathology needs to be kept in mind when protein-losing gastroenteropathy protracts after the improvement of abdominal symptom.

P3-184

A case of drug-induced cutaneous leukocytoclastic angiitis related to azathioprine

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Conflict of interest: None

A 60-year-old woman had skin sclerosis of her fingers since 56-year-old. At 59-year-old, she was referred to our hospital as having possible interstitial pneumonia. She presented with the skin sclerosis confined to her fingers and the chest CT scan indicated interstitial pneumonia. The skin biopsy from her fingers revealed the increased collagen fiber and the atrophic changes of the adnexa at dermis. She was diagnosed with limited systemic sclerosis and treated with oral cyclophosphamide (CY) 50mg daily. Following the treatment, her cough improved gradually. Fourteen months later, CY were changed to oral azathioprine (AZA) 50mg daily to prevent the accumulation of CY. Eight days after the initiation of AZA, she had painful erythema and papules in her extremities. One week after the discontinuation of AZA, her skin symptoms and the elevation of serum C-reactive protein levels were ameliorated. Pathological findings of the erythema indicated leukocytoclastic vasculitis, and she was diagnosed with cutaneous leukocytoclastic angiitis (CLA) related to AZA. In Chapel Hill Consensus Conference 2012, it was classified into single-organ vasculitis. We should keep in mind that CLA could be induced by the immunosuppressive agents along with the treatment of connective tissue disease.

P3-185

Clinical course of IgA vasculitis complicated with SAPHO syndrome after the treatment of apical periodontitis : a case report

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Conflict of interest: None

(Background) SAPHO syndrome is an uncommon disease characterized by synovitis, acne, pustulosis, hyperostosis and osteitis. On the other hand, IgA vasculitis is a systemic small vessel vasculitis caused by immune complex deposits mainly consisting of IgA. Both diseases are suspected to associate with focal infection like tonsillitis and apical periodontitis. We report a rare case of a SAPHO syndrome patient who developed IgA vasculitis and whose apical periodontitis was treated by dental surgeory. (Case) A 53 year-old male with SAPHO was admitted to our hospital due to a hemorrhagic duodenal ulcer. He showed apparent frontal chest pain, pastulosis and elevated C-reactive protein. On the 4th day, palpable purpura appeared on his shins and microscopic hematuria which implied glomerulonephritis developed. Screening of focal infection in ear, nose, throat and dental area showed three chronic apical periodontitis. Frontal chest pain, palpable purpura and elevated C-reactive protein decreased significantly after treatment for apical periodontitis though microscopic hematuria persisted. Renal biopsy showed mesangial proliferative glomerulonephritis, suggesting that glomerular inflammation caused by IgA vasculitis was not suppressed well.

P3-186

A case of vasculitis suspected of association with streptococcus pyogenes infections

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Conflict of interest: None

19 years old female who had been suspected of rheumatic fever due to fever, arthritis, and rash in childhood and diagnosed with IgA nephritis due to hematuria and renal biopsy was admitted to our hospital with fever, myalgic pain of extrimities and painful purpura on the palmar and sole of foot. She had been took fourth generation cephem antibiotics during eleven days before admission. Because of her pharyngeal culture revealed streptococcus pyogenes two days before admission, she received antibiotics at first, but her symptoms became persistent. Although ANCA was negative, we performed skin and muscle biopsy and made a diagnoses of vasculitis due to leukoclastic vasculitis in skin and muscular tissue. Therefore, she received corticosteroid and azathioprine, and response to the therapy was good. Few reports suggested poststreptococcal vasculitis in childhood. This case also developed vasculitis after streptoccus infections, therefore the mechanism of developing vasculitis was associated with streptococcus infections. Here we demonstrate the case who was 19 years old female of vasculitis associated with streptococcus infections.

P3-187

Successful treatment of pulmonaryrenal syndrome associated with ANCA-negative angiitis with early application of plasmapheresis

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Conflict of interest: None

A case is a 72 years-old woman. She was referred to our hospital from a local physician because of renal dysfunction and hemoptysis. Chest CT scan on admission revealed findings suggestive of diffuse alveolar hemorrhage, but no granuloma or cavity was observed over the lung fields. Tests for antineutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane antibodies, and other immunologic studies were all negative. A renal biopsy was performed on 6th day of hospitalization and revealedcrescent formation and tubulo-interstitial change. She was diagnosed with ANCA-negative microscopic poly-angiitis. She was treated with plasmapheresis and prednisolone (PSL) 50 mg after the steroid pulse therapy. The patient underwent nine sessions in total of plasmapheresis andintravenous cyclophosphamide.Her renal function improved gradually with creatinine level. With this treatment, hemoptysis did not recur. Pulmonaryrenal syndrome is life-threatening condition that requires rapid and appropriate treatment. Plasmapheresis proved excellent therapeutic effects in our patients who had ANCA-negative microscopic polyangiitis. When we treat pulmonaryrenal syndrome caused by ANCA-negative angiitis, we should actively select plasmapheresis to ensure better outcome.

P3-188

Clinical characteristics of the patients with large vessel vasculitis diagnosed over 50 years of age

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Conflict of interest: None

[Object] To investigate clinical characteristics of the patients with large vessel vasculitis (LVV) diagnosed over 50 years of age. [Methods] Patients who were diagnosed with LVV between January 1995 and October 2014 were retrospectively reviewed. [Results] 38 patients were retrieved from the clinical charts. 21 patients (55%) satisfied the American College of Rheumatology criteria for giant cell arteritis (GCA), and the remaining 17 (45%) did not (called as LVV-GCA). Clinical features between the patients with GCA and those with LVV-GCA are the followings: mean age (years): 71, 65; female: 62%, 71%; constitutional symptoms (fever, malaise, anorexia, or weight loss): 67%, 76%; ESR (median): 128 mm/h, 118 mm/h; and CRP (median): 7.8 mg/dl, 7.4 mg/dl. The frequency of arterial involvement between the two is the followings: vertebral: 10%, 35%; common carotid: 10%, 71%; subclavian: 24%, 71%; thoracic aorta: 24%, 88%; abdominal aorta: 33%, 59%; and common iliac: 5%, 35%. [Conclusions] Although the clinical features and the inflammatory markers were comparable, the frequency of involved vascular sites was different between GCA and LVV-GCA.

P3-189

Clinical characteristics of elderly-onset Takayasu's arteritis

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Conflict of interest: None

[Background] The difference of the disease category between Takayasu's Arteritis (TAK) and Giant cell arteritis (GCA) has been in discussion. Although young patients are more susceptible to TAK than GCA, there are some elderly-onset TAK patients. [Purpose and Method] Eighteen cases of TAK, which were newly diagnosed or flared in our hospital were examined retrospectively. To clarify the clinical characteristics of elderly-onset TAK patients, we examined age, sex, disease legion, initial symptoms, and complication of temporal artery disease or polymyalgia rheumatica (PMR). [Results] Average age of 18 cases was 32.7±18.2 (9-73) years. Five cases (18%) were newly diagnosed TAK above 40 years old and 4 (80%) of them were categorized typeV. No cases were complicated by PMR, and only 1 case (5.6%) was complicated by temporal artery disease. Fever was a chief complaint at the onset in 10 cases. Initial treatments were glucocorticoid alone (13 cases), glucocorticoid pulse therapy (3 cases), and immunosuppressive therapy with glucocorticoid (2 cases). [Conclusion] There were only a few case of elderly-onset TAK, and a chief complaint was fever in most cases. No cases were complicated by PMR, suggesting that TAK has different clinical characteristics from GCA.

P3-190

Validation of the effectiveness of the previous predictive score for positive temporal artery biopsy results for giant cell arteritis

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Conflict of interest: None

Backgrounds: A previous study (Younge BR et al. Mayo Clin Proc 2004) suggested a predictive score for positive temporal artery biopsy (TAB) results, but its effectiveness is unknown. Objectives: We analyzed clinical data at diagnosis and examined the effectiveness of the prospective score for positive TAB results. **Methods**: Of 12 patients who underwent TAB between 2003 and 2015, we retrospectively studied 9 patients who met the ACR 1990 criteria. We collected patient data including clinical symptoms, laboratory data, and images. Then, we calculated the predictive score consisting of 6 selected variables (headache, jaw claudication, scalp tenderness, ischemic optic neuropathy, age, and ESR). For patients with a low score, we examined other factors that contributed to performing biopsy. **Results**: The patients were 5 men and 4 women (mean age, 76.4±9.7 years). Headache appeared in all patients, jaw claudication in 4, scalp tenderness in 5, and ischemic optic neuropathy in 3. The mean ESR level was 103.4±18.3 mm/hr. Four of 8 patients with positive TAB results and 1 of 1 patient with negative TAB results showed a high predictive score. **Conclusions**: Patients with low predictive score also showed positive TAB results.

P3-191

A Case of Large Vessel Vasculitis in which integrations of FDG-PET were detected with brachial or femoral artery level but not aortic level

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Conflict of interest: None

An eighty-year-old man developed bilateral lower leg pain. Elevated leukocyte, CRP and elevated creatinine kinase was observed. Blood culture, antinuclear antibody, or ANCA was negative. Femoral muscle showed lower density in CT and edematous change in MRI (STIR). Biopsy of right vastus lateralis muscle showed myositis with invasion of T cells. PET-CT indicated integrations in brachial or femoral artery but not aortic level, and enhanced CT and MRI showed irregular wall thickening of deep femoral artery and internal iliac artery. He was diagnosed as vasculitis complicated with myositis. After the administration with high dose corticosteroid, symptoms and examination results improved and remission was maintained. Temporal artery biopsy after the treatment didn't show evidence of vasculitis. A study reported that giant cell arteritis sometimes develops symptoms only in lower extremity and 37% showed enhanced integration of FDG in femoral and iliac artery. Although there

was no histological evidence, this case appears to suggest the possibility of PET-CT for diagnosis of large vessel vasculitis.

P3-192

The evaluation of large vessel vasculitis by using FDG-PET

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Conflict of interest: None

(Objectives) To evaluate the localization of large vessel vasculitis by using FDG-PET (Methods) Retrospective study.Compare FDG uptakes of aorta and the branch between large vessel vasculitis and non large vessel vasculitis (Results) FDG uptakes of Aorta and the branch were higher in patients of large vessel vasculitis than in non large vessel vasculitis. In all 9 patients of large vessel vasculitis,FDG uptakes in lesion were same or higher than that of each liver (Conclusion and Clnical significance) FDG uptakes of Aorta and the branch were higher in patients of large vessel vasculitis than in non large vessel vasculitis. The same or higher FDG uptakes of Aorta and the branch compared with FDG uptakes of each liver may be significant finding as vessel lesion

P3-193

Five cases of refractory large vessel vasculitis treated with biologics.

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Conflict of interest: None

[Objective] To evaluate the efficacy of biologics (BIO) for refractory large vessel vasculitis (LVV). [Methods] This study comprised 5 cases of LVV (Takayasu's arteritis (TA) and giant-cell arteritis (GCA)) treated with BIO, who were admitted to the department of rheumatology in our hospitals from August 2013 to June 2015. Clinical characteristics, clinical and laboratory findings including CRP, ESR, and treatment were retrospectively assessed. [Results] All five cases were diagnosed as TA and were resistant to treatment with glucocorticoid and immunosuppressant. Mean age at the initiation of BIO was 51.2 years old, and mean observation period was 14 months. Two cases were treated with Infliximab, one with Adalimumab, one with Golimumab and one with Tocilizumab, respectively. The one case with Golimumab showed no improvement on PET-CT. The other four cases continued BIO during the observation period. The mean CRP and ESR improved from 0.460 mg/dl to 0.035 mg/dl and 53.7 mm to 7.5 mm, respectively, and mean glucocorticoid dosage was reduced from 0.38 mg/kg to 0.23 mg/kg, 3 months after the initiation of BIO. [Conclution] Recently, it is reported that the BIO are effective for LVV such as TA and GCA. This case series suggests that BIO are effective for refractory LVV.

P3-194

A case of Cogan syndrome complicated with systemic sclerosis and aortitis

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Conflict of interest: None

A seventy-three-year-old woman had Raynaud's phenomenon from 1996. Treatment was begun with antihypertensive medicine from 2002. She had vertigo repeatedly from April, 2014. Furthermore, she developed arthritis, maniphalanx edema, ringing in the ears and hearing loss in October. She had a diagnosis of iritis from pain and hyperaemia of her left eye. Laboratory examinations revealed WBC 9300 μl and CRP 3.34mg/dl. She had turning to the right horizontal nystagmus and bilateral sensorineural hearing loss from vertiginous testing. The head MRI and the auditory brainstem response were normal. She was diagnosed with atypical Cogan syndrome because she had iritis, vestibule hearing loss and negative of antibody, MPO-ANCA and PR3-ANCA. She was complicated with aortitis, a cystography CT showed a well hypertrophy of left subclavian artery and superior mesenteric artery. Treatment with prednisolone (40mg/d) improved her symptoms of maniphalanx edema, vertigo, tinnitus and arthritis. She had a diagnosis of systemic sclerosis from Raynaud's phenomenon, sclerema, anti-centromere antibody and a skin biopsy. There were no organ lesions of scleroderma besides skin. There is a rare case with Cogan syndrome, syetemic sclerosis and aortitis.

P3-195

Utility of ^{18}F-fluorodexoxyglucose positron emission tomography/computed tomography in distinguishing polymyalgia accompanied with giant cell arteritis from polymyalgia rheumatica

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Conflict of interest: None

[Objectives] Giant cell arteritis (GCA) is a form of systemic granulomatous inflammation that affects large and medium-sized arteries. GCA is typically accompanied by symptoms of arthralgia and myalgia (termed polymyalgia-like symptoms) and is often diagnosed as GCA complicated with polymyalgia rheumatica (PMR). However, whether the same mechanisms underlie the pathogenesis of polymyalgia-like symptoms accompanied by GCA and PMR remains unclear. Therefore, we examined two cases of GCA that met the diagnostic criteria of PMR with ^{18}F-fluorodexoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT). [Methods] Two cases of GCA that fulfilled the diagnostic criteria of PMR were analyzed by FDG-PET/CT. The distribution of FDG uptake in each case was compared with that observed in PMR alone and GCA alone. [Results] Both cases of GCA accompanied by polymyalgia-like symptoms demonstrated high FDG uptakes in carotid arteries, femoral arteries, and large joints. No FDG uptake was observed in PMR-specific FDG uptake sites including the spinous processes, ischial tuberosities, and trochanters. [Conclusion] The FDG-PET/CT findings in this study suggest that polymyalgia-like symptoms observed in GCA patients are associated with arteritis and are distinct from PMR.

P3-196

A case of giant cell arteritis with eosinophilic infiltration in temporal artery biopsy

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Conflict of interest: None

A 70-year-old man was admitted to our hospital with fever, edema in the limbs, chest pain and temporal artery vasodilation. Laboratory data was as follows WBC 17590/μl, Eos 57.0%, CRP 14.0mg/dl, IgE-RIST 1830IU/ml, TARC 588pg/ml, IgG 2234mg/dl, IgG4 86mg/dl, cytoplasmic- anti -neutrophil cytoplasmic autoantibody (C-ANCA) negative, perinuclear-anti -neutrophil cytoplasmic autoantibody (P-ANCA) negative. Chest computerized tomography showed pleural effusion. These properties were leaky (protein 3.1g/dl, LDH 71U/l) with much eosinophils (77%). Temporal artery biopsy showed the infiltration with mainly lymphocytes and neutrophils, partially eosinophils in all layers of the temporary artery wall. He received prednisolone 50mg/day and his symptom became promptly improved. Laboratory data also improved. In conclusion, we report a case of giant cell arteritis with eosinophilic infiltration in temporal artery.

P3-197

A case of Silent type Giant Cell Arteritis was suspected

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Conflict of interest: None

[Introduction] Giant cell arteritis have classic symptoms.For example, headache, induration of the temporal artery, PMR, anterior ischemic optic neuropathy etc. It has been reported silent GCA having only fever,lacking the classic symptoms in recent years. [Case]70-year-old man,chief complaints is bloating of maniphalanx and right shoulder pain. He became our department introduction consultation,because his chief compaints were caused by PMR in September 2015. Admission blood tests WBC9130/μl,RBC285×10⁴/μl,Plt52.4×10⁴/μl,CRP17.45mg/dl.We doubted that he had RS3PE syndrome or PMR and bolted his body. Although findings such as headache, blurred vision, neck vessel noise was not observed, we consulted department of ophthalmology purposes of vasculitis.There was a soft vitiligo and nipple bleeding in both the fundus. No evidence of obvious GCA such as induration of the temporal artery, findings of carotid echo and head MRI even vasculitis was not.Although We couldn't biopsy and diagnostic criteria are not met., We diagnosed GCA comprehensively.We administered mPSL pulse 500mg×3 days,aftertreatment PSL50mg.After PSL administration his symptoms were banished. [Conclusion]This case was silent GCA without classic symptoms,so I repot it added to the literature reports.

P3-198

A case of Large Vessel Vasculitis with renal dysfunction was diagnosed by FDG-PET

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Conflict of interest: None

[Object] Large Vessel Vasculitis is characteristically affects the aorta and its major branches. The systemic arteriopathy results in stenotic or occlusive lesions predisposing to symptomatic end-organ ischaemia.We report the case of Large Vessel Vasculitis complicated with renal dysfunction. [Case] An 82-year-old woman was admitted to our hospital because of renal dysfunction. The physical examination was not remarkable, and laboratory data on admission showed high level of serum creactive protein (CRP). Infections and malignancies was not observed. FDG-PET revealed accumulation of FDG in her thoracic and abdominal aorta. In the renogram, it was recognized a reduction peak of the left kidney. After treatment with oral prednisolone (40mg/day), her CRP level returned to normal and renal function was improved. [Conclusions] Renal dysfunction and hypertension are known that complications of Large Vessel Vasculitis. It is necessary to consider the possibility of vasculitis when occurs renal dysfunction with inflammatory. FDG-PET is useful for its diagnosis.

P3-199

A case of aortitis syndrome with acute onset in the right carotid artery aneurysm that has brought the right common carotid artery occlusion

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Conflict of interest: None

The patient,22-year-old man was admitted to our hospital with right neck pain, headache and fever lasting two weeks. Ultrasound examination shows right common carotid artery was diffuse the remarkable expansion, thickening the walls of accepted CRP, blood clots, same day emergency hospitalization. No brain infarction with MRI, CT scan showed remarkable extension of the brachiocephalic artery and the right common carotid artery wall thickening, wall thickening of the aortic arch and descending aorta and abdominal aorta. Aortitis, right carotid artery aneurysm that prednisone 50 mg / day (1 mg / kg), aspirin 100 mg / day in therapy. CT scan plus the fainting symptoms fever soon afterwards but improved CRP showed the right carotid artery occlusion. No brain infarction with MRI and angiography in carotid artery bifurcation of a high ranking (5th cervical level), from carotid artery on recognized thyroid artery branch, on collateral by the thyroid artery blood flow in the right carotid artery occlusion distal confirmed. Rapid onset and right carotid artery obstruction on a case of aortitis with securing the cerebral blood flow was experienced due to a rare branch of thyroid artery, so also report and literature review.

P3-200

A case of aortitis syndrome that was diagnosed as rheumatoid arthritis

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Conflict of interest: None

Case: A 65-year-old woman History of present illness: Symptoms appeared six months ago The patient was diagnosed with rheumatoid arthritis (RA) at a nearby hospital. She received methotrexate 8 mg/week and prednisolone 5 mg /day for 3 months. However, since improvements were not observed, the patient was referred to our hospital for the purpose of undergoing treatment with biologics. At initial examination, a widened mediastinum was detected on chest X-ray, an extensive aortic aneurysm was detected on computed tomography, and inflammation of the vascular wall was observed with gallium scintigraphy, leading to the present diagnosis. Although steroid pulse therapy and **cyclophosphamide** pulse therapy were subsequently administered, the patient died suddenly due to aortic rupture. It is essential to eliminate possibilities of other collagen disorders in patients diagnosed with RA. Here, we present our experience as a didactic example along with a literature review.

P3-201

A case of pulmonary hypertension as an initial manifestation of Takayasu Arteritis

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Conflict of interest: None

[Case] When she was 44 year old, she was diagnosed as asthma and treated with intermittent steroids. Bronchoscopies revealed negative. When she was 61 year old, she exhibited hypoxia and the chest CT scan showed "ground glass opacity". Her hypoxia worsened progressively associated with sustained elevation of CRP, V/Q mismatch, aortic regurgitation and pulmonary hypertension (PH), to which home oxygen therapy, warfarin and riociguat were started. She was referred to us for further work-up. CRP and ESR were 2.88 mg/dl and 107 mm/hr, respectively. Enhanced CT and MRA of the chest showed the inflammation in the aorta and the pulmonary artery, severe right pulmonary arterial stenosis and mosaic pattern in the lung field. FDG-PET scan showed uptake in the aorta and the lung fields. Based on these findings, Takayasu arteritis (TA) was diagnosed. The inflammation improved promptly after starting high dose steroids and methotrexate but PH sustained. [Clinical significance] PH caused by pulmonary arteritis is a rare complication of TA. Early diagnosis and medical treatment including immunosuppressive agents are essential to improve prognosis. Surgical or catheter interventions may be required in advanced cases with PH.

P3-202

Multidisciplinary therapy for Takayasu arteritis with the right pulmonary artery occlusion and pulmonary hypertention: A case report

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Conflict of interest: None

Case: A 49-year-old female had been concerned by dyspnea on exertion for 2 years. She was admitted to the former hospital to diagnose the reason of dyspnea 6 months ago. Pulmonary hypertention (PH) was diagnosed by right heart catheterization, which showed mean pulmonary arterial pressure (mPAP) was 48 mmHg and her right main pulmonary artery was completely occluded. Soluble guanylate cyclase (sGC) stimulator and anticoagulant therapy were started to treat chronic thromboembolic pulmonary hypertension (CTEPH). During the course, serum level of CRP and ESR was elevated, and contrast enhanced computed tomography (CT) showed not only pulmonary arteries' involvement but also diffuse wall thickening of aortic arch and cervical branches. Suspected Takayasu arteritis (TA), she was consulted to our hospital. We diagnosed TA on the basis of the typical CT findings and HLA typing analysis (B52 positive). It was considered that both medical and surgical treatment should be conducted. We started to treat with PSL 30 mg/day, resulting in immediate improvement of CRP. After reducing the dose of corticosteroids, she is going to have pulmonary endarterectomy. Conclusion: TA with PH is rare but often mortal. Here we report a case of TA with severe PH needed multidisciplinary therapy.

P3-203

A case of aortic dissection caused by large vessel vasculitis

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Conflict of interest: None

A previously healthy 48 year-old-woman was brought to ER with a complaint of sudden onset sharp back pain followed by paraplegia. CATscan showed that her aorta was dissected from the origin of left subclavian artery to the infrarenal region. After admission she had fever up to 39.0℃.Complete blood counts and serum chemistry laboratory test showed anemia with elevated inflammatory markers: erythrocyte sedimentation rate (ESR) of 114 mm/hr and C-reactive protein (CRP) of 12.91 mg/dl. Follow-up CAT scan with contrast revealed her aortic dissection extended despite normal blood pressure with bed resting. The enhancement of adventitia of aorta was also noted. Antinuclear antibody (ANA), ANCA, and anti SS-A/B antibodies were all negative. IgG4 was also normal. Because of worsening aortic dissection, methylpredonisolone pulse therapy was started. After treatment, her fever abated and the value of inflammatory markers and radiographic finding were also improved. Aortic dissection caused by large vessel vasculitis is very rare and there have existed few reports involving aortic dissection. The incidence of large vessel vasculitis in this population is low compared with Takayasu arteritis in young female and GCA in the elderly.We report this case with some literature review.

P3-204

Takayasu's arteritis concomitant with Marfan Syndrome

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Conflict of interest: None

[Case]A 45 year old female presented to our hospital's ophthalmology department with lens location in both eyes. At that time distention of the ascending aorta as well as annulo-aortic ectasia was found upon examination and a diagnosis of Marfan's syndrome was made after confirming a family history of the disease. In October of 2015 the patient presented again to the hospital. Upon physical examination a difference in upper limb blood pressures was observed along with bruit of the common carotid artery. CT with contrast of the left common carotid artery showed stenosis and ultra sound revealed an occlusion of the left common carotid, and stenosis of the right (positive macaroni sign); these findings met the 1990 ACR criteria and a subsequent diagnosis of Takayasu's ateritis was made.[Discussion]the presence of both these disorders in the same patient is a rare occurrence, and is thought to be a coincidence, it is possible that genetic mutations in Marfan's syndrome causing protein abnormalities of the extracellular matrix and the autoimmune component of Takayasu's areritis may be related.

P3-205

Takayasu aortitis complicated with aseptic meningitis and sensorineural hearing loss in a patient with ulcerative colitis

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Conflict of interest: None

A 74-year-old woman with ulcerative colitis (UC) was admitted because of exacerbation of abdominal pain, high fever, headache, vertigo, and hearing loss. Computerized tomography (CT) and Positron- Emission tomography revealed inflammatory thickening of abdominal aorta and bilateral iliac artery, and diagnosed as aortitis. Bilateral sensorineural healing loss was detected, but ocular disorders were not. Neither cerebrovascular disease nor hypertrophic pachymeningitis was revealed by imaging tests. Aseptic meningitis was detected by the examinations of cerebrospinal fluid. As the maximum intensity point of her headache was in the front and left side, left temporal arteries was biopsied, but not observed vasculitis. Together with the finding to carry human leukocyte antigens (HLA)-B52, she diagnosed as Takayasu Aortitis, and oral prednisolone (40 mg/day) was administrated. All of her symptoms were improved, and the value of C reactive protein was decreased from 18.1 to 0.4 mg/dl within 2 weeks, and still keeps remission. There is some case reports of Takayasu aortitis associated with UC, especially from Japan. Here, we report a rare case, which also complicated with aseptic meningitis and hearing loss, may be pre-phase of Cogan's syndrome. Accumulating more reports is expected.

P3-206

A Case of Takayasu-like Large Vessel Vasculitis after Pneumococcal Vaccination

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Conflict of interest: None

We report a 65-year-old man with Takayasu-like large vessel vasculitis after pneumococcal vaccination. He presented fever and malaise after immunization of pneumococcal vaccine. He consulted our hospital because of sustained fever with no response to antibiotics. Laboratory tests showed a high level of serum CRP and abnormal hepatic function, but negative test of ANCA and anti-nuclear antibody. Computed tomography (CT) showed arterial wall thickening (aorta, right brachiocephalic trunk, left common carotid artery and left subclavian artery). FDG PET/CT revealed inflammation of aorta and carotid artery. We made a diagnosis of drug-induced vasculitis and liver injury after pneumococcal vaccination. Although he was not treated with prednisolone, the symptoms, laboratory data and arterial wall thickening were improved. The present case suggests that pneumococcal vaccination may cause large vessel vasculitis. This patient is the first case of vasculitis after pneumococcal vaccination. Careful attention should be paid to severe adverse effects such as systemic vasculitis after pneumococcal vaccination.

P3-207

Predictor of efficacy and safety of mizoribine in Sjögren's syndrome

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Conflict of interest: None

Recently immunosuppressive therapy such as mizoribine or rituximab was reported to be valid to Sjogren's Syndrome (SS), the lymphocytic infiltrate of minor salivary glands is shown in Mizoribine, and it is shown that it is advanced and effectiveness is high in not the fibrosis and atrophy. 80 SS patients were diagnosed in the Tokyo medical center department of internal medicine and the progress of necessary various examinations was observed and it was assumed 42 gotten samples in the analysis of the predictor of the treatment responses glandulae labiales biopsy. Inspection item for verification of predictor;.Schirmer test, serological test (anti-S S·A, anti-S S·B antibody, Rheumatic factor and blood serum IgG), peripheral blood lymphocytes number, IL-2 receptor, and serum β2 microglobulins, etc. The response rate of MZR was significant high in the decrement group like 65.2% in the decrement group and 27.8% in a negative group. Serum IgG level amd serum β2 microglobulin. Were not Significant..

P3-208

Case of Sjogren's syndrome successfully treated with intravenous immunoglobulin and intermittent intra-venous cyclophosphamide therapy for diverse neurological manifestations

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Conflict of interest: None

Sjogren's syndrome sometimes showed neurological manifestations and all nerve system could be affected other than peripheral neuropathy. Neurological disorder due to the vasculitis could be the target for immunosuppressive therapy whereas the efficacy of intravenous immunoglobulin (IVIg) for ganglionitis has been reported. A 40-years-old woman recognized back pain, myalgia paresthesias of the extremities and right facial palsy in March 2015. Head MRI examination revealed no sign of infarction and she was diagnosed as bell paralysis. Her symptoms did not improved despite of the initiation of 30mg of prednisolone (PSL) daily. Clinical examination indicated that she had trigeminal nerve disorder and autonomic neuropathy. Electromyogram revealed the presence of demyelinating neuropathy, cerebrospinal fluid puncture showed protein cell dissociation and cauda equina lesion was suspected by spinal cord MRI. She was diagnosed as Sjogren syndrome on the basis of dry eye, pathological findings of lip biopsy and positivity of anti-SS-A antibody. No other cause of her diverse neurological manifestations were detected except for SjS. High dose PSL with intermittent intra-venous cyclophosphamide and IVIg combination therapy was initiated and her neurological symptoms were improved gradually.

P3-209

Successful Treatment of Protein-Losing Gastroenteropathy related to Sjögren Syndrome with Steroid and Cyclophosphamide Therapy

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Conflict of interest: None

We report a case of a 46-year-old female who developed facial and systemic edema together with severe hypoproteinemia. On the basis of 99mTc-human serum albumin scintigraphy, she was diagnosed with protein-losing gastroenteropathy. Furthermore, she was diagnosed with Sjögren syndrome on the basis of eye dryness, positive result with anti-SS-A antibody, and salivary gland biopsy. Her symptoms improved with the use of intravenous cyclophosphamide following intravenous steroid therapy. Therefore, intravenous cyclophosphamide may be considered as possible effective treatment strategies for refractory protein-losing gastroenteropathy related to Sjögren syndrome.

P3-210

The case report of inclusion body myositis observed in Sjogren syndrome

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Conflict of interest: None

sIBM is one of the inflammatory myopathies together with dermatomyositis and polymyositis. While some similarities with latter two, sIBM uniquely represents both the degenerative characteristics and refractory to all treatments effective for others. In this regard, precise diagnosis of sIBM is critical for the further patient cares. We present the case of 62 years old (y.o) primary Sjogren syndrome patient showing the difficulties in turning in bed and walking. Initially at 42 y.o, she was diagnosed as primary Sjogren syndrome. Subsequently at around 60 y.o, she gradually noticed the hardening in stretching up of arms as well as standing up spontaneously. The worsening symptoms made her re-evaluation in this hospital. She barely walked with device, with muscle atrophy and weakness in proximal extremities. Additionally she represented the weakness in finger flexors. The laboratory examination revealed abnormalities such as CPK=291 IU/L, CRP=0.19 mg/dL and ESR=92 mm/hour, while EMG showed the resting spontaneous discharge. Subsequent muscle biopsy studies revealed the presence of CD8 positive cells around the muscle fibers together with the rimmed vacuoles. The immunohistochemical staining showed the p62-positive non-necrotic muscle fiber, leading to the diagnosis of sIBM.

P3-211

A case of cryoglobulinemic vasculitis associated with asymptomatic Sjögren's syndrome

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Conflict of interest: None

A 76-year-old woman was admitted to local hospital for ulcers of right forefinger and left leg, in April 2014. She had exhibited purpura on the lower extremities for 3 years, which spread to whole body from last year. Skin biopsy showed leukocytoclastic vasculitis. Oral steroid therapy (PSL10mg/day) was started, but skin lesions were not improved. She was transferred to our hospital in July, and subsequent investigations revealed type II cryoglobulinemia [cryocrit 22.5%, monoclonal IgM (κ) and polyclonal IgG], immune abnormalities with ANA (1:2560) and anti-SSA antibody (396.2 U/ml), positivity of Saxon and Schirmer tests, and lymphocyte accumulation around the minor salivary gland ducts. She was diagnosed as Sjögren's syndrome (SjS) though dry syndrome was asymptomatic. Renal biopsy showed subendothelial deposits formed by tubular structures corresponding to cryoglobulins, suggesting cryoglobulinemic vasculitis. Increase of PSL dose (35mg/day) decreased cryocrit (11%), but finger necrosis deteriorated. After introduction of weekly cryofiltration, her skin lesions were improved gradually. SjS could cause life-threatening cryoglobulinemic vasculitis even if it is asymptomatic, therefore these patients have to be followed-up carefully.

P3-212

A case of Sjogren's syndrome complicated by idiopathic portal hypertension and pulmonary hypertension

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Conflict of interest: None

Case: An 18-year-old woman was referred to our hospital at January 2015 for general fatigue, pancytopenia, liver dysfunction (AST 61 IU/L, ALT 30 IU/L), elevated IgG levels (3252 mg/dL) and positive for anti SS-A antibodies (185 IU/L). Chest X-ray showed cardiomegaly with slight pulmonary congestion. Echocardiogram demonstrated elevated TRPG (66mmHg), which indicated presence of pulmonary hypertension (PH). Computed tomography showed ascites, splenomegaly and gastric varices with increased blood flow of extrahepatic portal veins and collateral vessels. She was positive for Antinuclear antibodies (×160, speckled), Schirmer test, and fluorecein staining. Taken together, she had a diagnosis of Sjogren's syndrome with pulmonary and portal hypertension. Methylprednisolone pulse therapy, high-dose prednisolone and diuretics ameliorated PH symptoms and ascites. A liver biopsy was performed after endoscopic injection sclerotherapy. The specimen showed aberrant hepatic veins and narrowing of portal vein with fibrosis, which indicated typical idiopathic portal hypertension. Discussion: Although idiopathic portal hypertension and pulmonary hypertension with autoimmune diseases are refractory to conventional therapy, steroid administration may be affective in some patients.

P3-213

Sjögren's syndrome-associated MALT lymphoma complicated by hyperviscosity syndrome

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Conflict of interest: None

【Introduction】Hyperviscosity syndrome (HVS) is an extremely rare complication of Sjögren's syndrome (SjS). A measurement of blood viscosity is not available in general practice. We report SjS-associated MALT lymphoma complicated by HVS, the diagnosis prompted by the unexceptionally extended time of blood sampling with evacuated blood collection tubes.【Case】A 75-year-old female was referred to our hospital because of visual impairment, bleeding tendency and dyspnea on exertion. SjS had been diagnosed 10 years before. Sicca symptoms and asymptomatic ILD were noted. Ophthalmologic tests demonstrated central retinal vein occlusion, serous retinal detachments. An evacuated blood sampling took much longer time than usual. IgG 3,496 mg/dl, IgA 3,180 mg/dl, IgM 197 mg/dl, anti-SSA and SSB positive. CT demonstrated bilateral enlargement of parotid glands and generalizes lymphadenopathy. Salivary gland biopsy showed inflammatory cell infiltration. Parotid gland biopsy showed MALT lymphoma. SjS-associated MALT lymphoma complicated by HVS was diagnosed. Rituximab monotherapy was administered.【Conclusion】An extremely extended time of an evacuated blood tube sampling may point to the possibility of HVS. MALT lymphoma should be considered when SjS is complicated by HVS.

P3-214

A case of Sjögren's syndrome (SS) with retroperitoneal fibrosis (RPF) mimicking IgG4-related disease (IgG4-RD)

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Conflict of interest: None

A 73-year-old man visited our hospital with the complaint of lumbago due to hydronephrosis. CT scan revealed a retroperitoneal soft-tissue mass, which biopsy showed RPF. Serum IgG4 level was extremely high (IgG4 157mg/dl, IgG4/IgG ratio7.8%). His retroperitoneal lesion were contained sever fibrosis and marked lymphoplasmacytic infiltration with IgG4 + plasmacells. However,IgG4 +/IgG + plasmacell ratio was less than 40 %. These histopathological findings were not compatible with IgG4-RD. On the other hand, ANA were markedly elevated (X640), anti SSA/Ro Ab (240>U/ml) and anti SSB/La Ab (90.2U/ml) were also positive with high titer. These serological features and salivary gland (biopsy,scintigraphy) findings strongly suggested SS. We diagnosed this case as SS with RPF mimickingIgG4-RD and treated with prednisolone 35mg/day. His symptoms disappeared and the serum IgG4 level became normal. To our knowledge, this is the first case SS with IgG4 + plasma infiltration in RPF. A few cases of SS with high serum level of IgG4 were reported and SS has things in common pathogenesis with IgG4-RD.This case give us a hint of possibility of a close association exists between SS and IgG4-RD.

P3-215

A case of osteomalacia caused by tubulointerstitial nephritis associated with Sjögren syndrome

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Conflict of interest: None

A 76-year-old woman was visited with unimproved left upper extremity pain and lumbago. Blood examination showed hyper alkaline phosphatasia, hypocalcemia, hypophosphatemia, renal dysfunction, decrease of serum concentration of 25 (OH) vitamin D. Bone scintigraphy revealed accumulations in multiple joints and ribs. We suspected osteomalacia induced vitamin D deficiency. Since she was also attended ophthalmological clinic for dry eye, the presence of Sjögren syndrome was suspected. Antinuclear antibodies were markedly elevated, anti-SSA/Ro antibody was positive, and the Saxson test was also positive. The presence of hypokalemia and hyperchloremia was lead to the diagnosis of renal tubular acidosis. Arterial blood gas analysis disclosed acidosis at level of pH 7.254 with the anion gap of 12.7mEq/L. Renal biopsy showed lymphocytes infiltration of tubulointerstitial tissue without glomerular lesions. We diagnosed osteomalacia caused by tubulointerstitial nephritis associated with Sjögren syndrome, and treated with alfacalcidol, calcium l-aspartate, potassium citrate. Tubulointerstitial nephritis is one of the extraglandular complications of Sjögren syndrome and it is rare osteomalacia was associated with this disease.

P3-216

A case of primary Sjögren's syndrome, complicated by crescentic glomerulonephritis

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Conflict of interest: None

Glomerulonephritis in primary Sjögren's syndrome is rarely reported. We report A 44-year-old woman with cryoglobulinemic glomerulonephritis in primary Sjögren's syndrome. 3 years ago livedo reticularis occurred and she visited a dermatologist. Skin biopsy revealed necrotizing vasculitis.Vasculitis due to Sjogren's syndrome was diagnosed by antiSSA antibody positive, Saxon test positive, and it was under the medical treatment with diaphenylsulfone, colchicine, prednisolone (7.5 mg/day).She noticed lower limb edema one month ago,and tendency to weight gain for three months.In acknowledgment of proteinuria and hypoalbuminemia, nephrotic syndrome was suspected,and she visted our hospital.Prednisolone (1mg/kg/day) was provided after renal biopsy, but did not induce the complete remission. Renal biopsy revealed crescentic glomerulonephritis and tubulointerstitial nephritis.Cryoglobulinemia was denied in previous hospital, but we reexamined and confirmed cryoglobulin. Thereby crescentic glomerulonephritis with the cryoglobulinemia-related vasculitis was diagnosed as a cause of the nephrotic syndrome.A combination therapy comprising predonisolone and Cyclophosphamide pulse induced complete remission.

P3-217

A case of anti-aquaporin-4 antibody-positive Sjögren's syndrome with a relapsed myelitis

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Conflict of interest: None

We report immunosuppressive therapy improved neuropathic symptoms in anti-aquaporin-4 antibody-positive Sjögren's syndrome with a relapsed myelitis. A 67year old woman,she noticed bilateral precordial numbness from three months ago, and the expansion of the numbness site tends subsequently. She visited an orthopedist. The MRI findings suspected demyelination in Th2~10. The abnormality of the motor nervous system was absent, but sensory disturbance was present.Because of spontaneous improvement of symptoms she followed up with no medeication for two months. Right leg paralysis developed from one month ago. She noticed a desensitization of the left leg and the trunk part and dysesthesia. AntiSS-A, SS-B antibody were positive and dry eye and dry mouse were present, she was suspected a myelitis complicated by Sjogren's syndrome. AntiAQP4 antibody was positive but optic neuritis was absent.We diagnosed as an anti AQP4 antibody-positive Sjögren's syndrome with a myelitis. After two times mPSL1g pulse therapy neuro-abnormal symptoms were improved.The administration of oral prednisolone (0.5mg/kg/day) conducting azathioprine combination was effective in preventing the recurrence of myelitis,and dysesthesia improved tendency by pregabalin, baclofen, tizanidine combination therapy.

P3-218

A case of pulmonary arterial hypertension associated with Primary Sjogren's syndrome which Macitentan seemed to be effective

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Conflict of interest: None

A 52-year-old woman was admitted to our hospital because of dyspnea on exertion. Echocardiography revealed right-heart overload. Ventilation/perfusion lung scanning showed no signs of pulmonary embolism. She had complained of eye and mouth dryness since two months before first visit, she underwent lip biopsy. This specimen showed infiltration of lymphocytes into the salivary glands. Laboratory findings showed hypergammaglobulinemia and anti Ro/SSA and La/SSB antibodies positive. She had not any signs of other connective tissue disease. We diagnosed Primary Sjogren's syndrome (pSS) on the basis of a positive serological test and the findings of lip biopsy. Right heart catheterization studies revealed pulmonary arterial hypertension (PAH). From these findings, we gave her a diagnosis of PAH with pSS. Her general condition has not improved fully with therapy followed by oral administration of corticosteroids and cyclophosphamide and tadalafil. After 4 months of therapy, her WHO-PH functional class remains to II, so we administrated Macitentan. Two months later, WHO-PH functional class improved from IItoIand her complain disappeared. <Conclusion> We have presented a case of PAH associated with pSS which Macitentan seemed to be effective and adding review of the literatures.

P3-219

Lymphocytic interstitial pneumonitis, chronic thyroiditis, renal tubular acidosis, and morphea in Sjögren's syndrome

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Conflict of interest: None

A 78-year-old female presented with 2-year history of redness and thickening of the skin of lower legs and recurrent respiratory infections. On admission, her lungs showed bibasilar crackles. She had sclerotic palaques with violaceous border. Serum protein electrophoresis revealed polyclonal hypergammaglobulinemia. Anti-Ro antibodies (Ab), anti-SSB/La Ab, anti-TPO Ab, and Anti-TG Ab were positive. Plasma bicarbonate indicated metabolic acidosis. A CT scan of the chest revealed multiple cystic changes and peripheral septal thickening throughout lungs. The lip biopsy was compatible with Sjögren's syndrome (SS). Based on the above, the patient's diagnosis was lymphocytic interstitial pneumonitis (LIP), chronic thyroiditis, and type 1 renal tubular acidosis (RTA) secondary to primary SS. Skin biopsy showed densely packed collagen fibers in the dermis. She was diagnosed with generalized morphea by the absence of sclerodactyly. She was initially treated with predonisolone 30 mg/day,and the skin lesion improved. The present patient was a rare case of multiple organ involvements including LIP, type 1 RTA, and chronic thyroiditis in primary SS. The patient had generalized morphea incidentally. A CT suggested that the reccurent respiratory infections were caused by anatomical changes of LIP.

P3-220

A case of Sjogren syndrome with MALT lymphoma and Lymphocytic interstitial pneumoniae

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Conflict of interest: None

Sjogren syndrome is an autoimmune disease with exocrine glands dysfunction and systemic involvement. Lung involvement, especially interstitial pneumoniae, is relatively common, and represents usually nonspecific interstitial pneumoniae (NSIP) or lymphocytic interstitial pneumoniae (LIP). The disease is also correlated with increased risk of lymphoproliferative disorder, particularly B cell lymphoma. We present a case of Sjogren syndrome complicated with Mucosa-Associated Lymphoid Tissue (MALT) lymphoma in a tongue, also with LIP. The latter was difficult to diagnose because its finding of chest CT images represented similar pattern with MALT lymphoma, and required an incisional biopsy for its diagnosis. After diagnosing pathologically, MALT lymphoma was treated surgically and LIP with glucocorticoid and immunosuppressive agent, of which clinical course is good.

P3-221

Aneurysm of the vertebral artery by atlantoaxial subluxation in a patient with rheumatoid arthritis

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Conflict of interest: None

A 67-years old woman was admitted to our hospital because of polyarthritis for 10years in May 2014. The diagnosis of rheumatoid arthritis was made, her Steinbrocker classification was Stages IV, functional class was class4 and atlantoaxial subluxation (AAS) was complicated. Oral prednisolone 5mg/day was administrated, and cervical collar was applied. However, her condition gradually worsened and swallowing diificulty, neck pain, and dyspnea appeared in November 2014. Her AAS has progressed and vertical suluxation of the axis was observed. Moreover she presented soft tissue swelling of her left neck and thorax, because of minor rupture of the aneurysm of the vertebral artery at the level of C1 and C2. Coil embolization of the aneurysm could get hemostasis, and 9 months Halo Vest fixation produced agglutination of C1 and C2. Finally she could discharge hospital on October 2015. AAS is a common complication of rheumatoid arthritis, however aneurysm of the vertebral artery associated with AAS has been reported only in one case that presented subarachnoid hemorrhage. Our case showed that we should take care of the aneurysm of the vertebral artery in case with AAS.

P3-222

Case report: Two cases of chronic tophaceous gouty arthritis due to HGprt-related hyperuricemia (HRH)

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Conflict of interest: None

Although gout is a multifactorial disease mostly, it could be presented as a monogenic disorder. Here, we report two cases of chronic tophaceous gouty arthritis due to HGprt-related hyperuricemia (HRH). Case 1 is a 19-year-old man who developed acute arthritis on a PIP joint of his finger, which subsided within 2 weeks at the age of 13. When he subsequently experienced the attacks on his knees and ankles, he was diagnosed as having gout at the age of 16. As he developed chronic polyarthritis with gouty tophi, he visited our clinic. The mixed type hyperuricemia together with a c.100A>T mutation in *HPRT1* led to the diagnosis of HRH. Case 2 is a 43-year-old man who developed acute mono-arthritis on a first MTP joint of his toe and was diagnosed as having gout at the age of 19. He experienced gout attacks once in two years afterwards. At the age of 43, he visited our clinic.Hyperuricemia classified into urate overproduction type was detected. Along with a mutation of c.584A>G in *HPRT1*, he was diagnosed with HRH. HRH is a rare cause of gout and presents with severe arthritis, with onset in early adult life. It is also complicated with kidney damage and nephrolithiasis. [Conclusions]HRH must be taken into consideration on the diagnosis of young-onset severe gouty arthritis.

P3-223

Nasal colonization of patients with rheumatoid arthritis

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Conflict of interest: None

【Object】 Knee arthroplasty has good results are obtained in the majority of patients. It can be said that very useful surgery in rheumatoid arthritis (RA) patients. However, it has become a major problem developed postoperative infection in a few cases. In our hospital is going preoperative nasal culture of knee arthroplasty patients as part of infection control from 2010.We were compared to consider whether there is a difference in the colonization of the nasal cavity in patients with RA and non-RA patients.【Methods】We investigated 588 cases (RA group 57 cases, non-RA group 531 cases) that was performed knee arthroplasty in 2010 to 2015. We investigated the colonized state performs preoperative nasal culture examined in all patients. 【Results】Preoperative nasal culture: RA patients; MSSA the 15 cases, MRSA the one cases, CNS the 29 cases, other bacteria 35 cases, 4 cases of the negative.Non-RA patients; MSSA the 74 cases, MRSA the nine cases, CNS the 267 cases, other bacteria the 112 cases, negative and 75 cases. MSSA colonization had a higher prevalence in the RA group ($p < 0.05$) 【Conclusion】It should be noted a higher prevalence of the nasal cavity in RA patients of medical care.

P3-224

The comorbidities and complications needed for hospital treatment in the Rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Recent study indicate that the number of Rheumatoid arthritis (RA) patients needed for operation decreased and the other needed for hospital treatment increased. The object of the report is to clarify the current state and risk in letter group in our hospital**. [Methods]** 44 patients needed for hospital treatment were conducted in the study among 206 RA patients who treated at our hospital during Jan. 2014 until Nov. 2015. **[Results]** 27 patients (61%) were female, mean age was 72 years, disease duration was 13 years. Among the patients pulmonary disease in 15 patients (34%), malignant disease in 6 (14%), malignant lymphoma in 3 (7%), renal disease in 3, HZV in 3, heart disease 2 (5%), UTI in 2, severe drug eruption in 2, and others. Lung associated comorbidities existing in the patients of pulmonary disease group were 4 chronic bronchitis / bronchiectasis, 4 interstitial pneumonia, 4 old TB, one Asthma. Total CCI was 1.5, CCI of single hospital treatment group was 1.2, over 2 groups were 2.8. In 16 patients, drug induced or related adverse effects were observed. 4 in biologics, 16 in MTX, one in MZR. 11 patients were needed for treatment. **[Conclusion]** Appropriate treatments were need to be selected based on evaluation of comorbidities and complications.

P3-225

Successful treatment with tocilizumab in a patient with AA amyloidosis and rheumatoid arthritis

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Conflict of interest: None

Case report: A 60 year-old woman with rheumatoid arthritis (RA) was admitted for acute arthritis with massive proteinuria and worsening of renal function. She had about 40-year history of RA and chemotherapy for methotrexate-associated lymphoma at 58. Because renal biopsy revealed the deposition of AA amyloid along the capillary walls and tubular basement membranes, she was diagnosed as AA amyloidosis. Tocilizumab 400 mg/month was started with amelioration of proteinuria and renal function and stable joint symptoms. **Summary:** Tocilizumab could improve renal involvements of AA amyloidosis complicated by RA, and we report this case with literature review for the treatment of AA amyloidosis.

P3-226

A case of pseudoxantoma elasticum diagnosed during the follow up of rheumatoid arthritis

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Conflict of interest: None

Pseudoxantoma elasticum (PXE) is a rare autosomal recessive genetic disorder which affects skin, eyes, cardiovascular system and gastrointestinal system. The underlying defect is a pathogenic mutation in the *ABCC6* gene on chromosome 16, which results in abnormal calcification and fragmentation of elastic fibers. To date, no case of PXE complicated with rheumatoid arthritis (RA) has been documented. We report the first case of PXE which was diagnosed during the follow up of RA. A 62-year-old woman was attending to the outpatient clinic of our department for the treatment of RA. On February 16, 2015, she visited ophthalmology clinic complaining of impaired vision of her right eye. On funduscopic examination, retinal hemorrhage from choroidal neovascularization was noted, along with angioid streak, which are specific for PXE. Yellowish papules were found on her neck, axillae, and groin. Biopsy specimen from the axillae papule revealed fragmentation and calcification of elastic fibers, which were consistent with PXE. Mutation on Ex.9 of *ABCC6* gene (c.1132 C>T, p. Q378X) was detected by genetic testing at Nagasaki University. No coronary artery disease was found at the moment. However, close monitoring is necessary since she is at considerably high risk of cardiovascular diseases.

P3-227

Certolizumab Pegol Effective Case of Rheumatoid Arthritis Patient with Skin Ulceration of the Leg

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Conflict of interest: None

[Introduction] Rheumatoid arthritis (RA)-associated skin ulceration is caused by vasculitis or vasculitis not-related reason. Thus, we should carefully determine cause of ulceration. In the present report, we experienced a Certolizumab Pegol (CZP) effective RA case with persistent skin ulceration of the leg. [Case] Thirty-eight y.o. female was diagnosed as RA on 2007 and took MTX therapy. A half year after therapy, persistent skin ulceration of the leg was emerged, then she consulted our hospital. DMARDs therapy was not effective. On Nov 2013, she was admitted to our hospital due to high CRP and purpura on the leg. Purpura was diag-

nosed as leukocyte clastic vasculitis, then 40mg of Steroid was initiated. Purpura alone was cured, ulceration was remained, and the arthritis was worsened. Either Abatacept or Tocilizumab showed little effect, then CZP therapy was initiated. CZP therapy achieved Clinical complete response and marked improvement of ulceration. [Conclusion] Due to delayed determinsation of skin ulceration cause, introduction of biologic therapy was delayed. Although TNF inhibitor like CZP was effective for RA with vasculitis, it has been reported some case of opposite result. Therefore, we should carefully follow up the patient during the anti-TNF therapy.

P3-228

A case of sarcoid aortitis revealed by FDG-PET

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Conflict of interest: None

A 62-year-old Japanese woman admitted due to A-V block and was implanted the pacemaker. She was treated by prednisolone as SLE for 14 years, and diagnosed as sarcoidosis for bilateral hilar lymphadenopathy and lung lesions six years before. FDG-PET was examined as a survey of cardiac sarcoidosis. FDG accumulation was detected in mediastinal lymphnodes, lung field, myocardium, and abdominal aorta. Because of the activities of SLE was stable, it was considered that the aortitis was one of the symptom of sarcoidosis. And it was successfully treated with prednisolone therapy.

P3-229

The case report: Tocilizumab (TCZ) was used for a renal Amyloidosis during rheumatoid arthritis

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Conflict of interest: None

66 y.o. female was treated Rheumatoid Arthritis from 48 y. o. by the local medical doctor. Her renal function was normal until august X-2 year (sCre 0.55mg/dl). She was introduced our hospital at X-1 year August, since renal function was deteriorated gradually (November 0.96g/dl, January 1.48g/dl, April 1.63g/dl, June 1.83g/dl, August 2.16g/dl). She showed leg edema and massive proteinuria (4.68g/day), therefore we diagnosed Nephrotic syndrome and rheumatoid arthritis. She was admitted for careful inspection because we found positive of PR3-ANCA (21.5 IU/l). Renal biopsy was carried out. 11 glomeluli were observed. 1 glomeruli was showed a small crescent. Some other glomeruli were showed amyloid deposition. So we diagnosed she was renal amylidosis. Renal amyloid was AA amyloid, and they were deposited digestive organ and heart too. Because PR3-ANCA titer indicated higher level, we treated PSL therapy. As a result, PR3-ANCA titer was down, but remarkably hypogammopathy was revealed and she infected CMV. TCZ therapy (162mg) was started after we treated CMV infection. Proteinuria of 25g/gCre decreases to 9.9g/gCre without the kidney function decline progress but nephrotic state was going on. [Conclusion]: We could think the validity of TCZ was high to an AA amyloidosis.

P3-230

A case of effusion lymphoma associated with rheumatoid arthritis

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Conflict of interest: None

An 82-year-old woman, who had been diagnosed as rheumatoid arthritis (RA) and Sjögren's Syndrome (SS) in 1988, was treated with PSL 5mg/day and Bucillamine over twenty years. She admitted to our hospital in May 2015 because of fever, dyspnea and bilateral chest pain. Due to an elevated level of serum CRP (13.5 mg/dl), consolidations of bilateral lungs and right pleural effusion on CT, She was started to treat with an antibacterial agent, but it didn't effect at all. Although the cytological examination of the pleural effusion and the bone marrow revealed class II-Iatypical lymphocytes, there are no swelling lymph nodes. She was diagnosed as to have effusion lymphoma based on the histological finding from the pleural effusion cell block. Primary effusion lymphoma (PEL) is a rare subset of lymphoma localized to serous body cavities without tumor mass or nodal involvement. HIV negative common effusion lymphoma (HENCEL) is classified as PEL-like lymphoma, associated with old age and immunosuppressant. In our case, immunosuppressive state by long term administration of steroid may cause HENCEL in addition to risk of LPD along with RA and SS. We should therefore take the possibility of LPD into consideration in case of elevated CRP in elderly RA patients without arthritis activity.

P3-231

Pneumocystus carinii pneumonia (PCP), cytomegalovirus (CMV) related hemophagocytic syndrome as a manifestation of immuno reconstitution syndrome (IRIS) in patient with systemic lupus erytematosus (SLE)

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Conflict of interest: None

56 years old woman was admitted to our department Sep 2015 because of fever and rush. She was diagnosed with SLE in 1994 and treated with prednisolone (PSL) alone for WHO class IV nephritis. She had been taken PSL 2.5mg/day since 2012, but proteinuria appeared from April 2015. Renal biopsy showed ISN/RPS class II nephritis, she started to take PSL 20mg/day and azathioprine. After the dosage of PSL was decreased 20mg/day to 15mg/day, fever and erythema multiforme exudativum appeared. We suspected that as a drug eruption, we stopped all the medications other than PSL and that led erythema improved. One week later PCP was developed and then she needed administration of Sulfamethoxazole/Trimetoprim and PSL. PCP was improved soon, but after PSL tapered to 20mg/day, fever and erythema were developed again. And at the same time, CMV related hemophagocytic syndrome also appeared. We thought rush, PCP and CMV reactivation were a part of IRIS, we decided to start high dose PSL, intravenous immunoglobulin and anti- CMV drugs. These treatments were effective. Now we are teparing her predonisolone carefully. We report this case because it gives a good opportunity for us to think the pathology of IRIS in Rheumatic disease patients.

P3-232

A case of intravascular lymphoma developing 2 months after the initiation of methotrexate for rheumatoid arthritis

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Conflict of interest: None

A 75-year-old woman was admitted to our hospital because of high fever and nausea. She had been diagnosed with seropositive rheumatoid arthritis (RA) 4 months before. Methotrexate (MTX) was initiated 2 months before and discontinued one week prior to the admission. Her laboratory examination showed high LDH and soluble interleukin-2 receptor (sIL-2R) values (LDH 1164 IU/L, sIL-2R 1210 U/mL), progres-

sive anemia, and positive cold agglutinin with a titer of 1:131072, however, there were no findings of infection, interstitial pneumonitis or lymphadenopathy. After hospitalization, high fever with nausea persisted for a week. Bone marrow aspiration and random skin biopsy revealed intravascular large B-cell lymphoma (IVLBCL). Tumor cells also detected in the cerebrospinal fluid and chemotherapy (R-hyper CVAD/R-MA regimen) was started immediately. Half a year later, she achieved complete remission of both IVLBCL and cold autoimmune hemolytic anemia. We reported a rare case of IVLBCL with RA taking MTX only for two months. In this case, we considered that MTX might accelerate the development of lymphoma. We discussed based on an analysis of our 15 previous cases of MTX associated lymphoma and a review of the literature.

P3-233

Epstein-Barr virus-encoded RNA 1 positive immunodeficiency-associated Hodgkin lymphoma in a patient with rheumatoid arthritis treated with tacrolimus

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Conflict of interest: None

A 65-year-old man with a four year history of rheumatoid arthritis (RA), was admitted to our division because of a prolonged fever. He had been treated with tacrolimus (TAC) 2 mg/day and prednisolone 2 mg on alternate days for 14 months. On admission, his temperature was 38.8° C. Physical examination revealed palpable lymph nodes in his left supraclavicular fossa. He had no sign of arthritis. CRP was 19.82 mg/dL and sIL-2R was 12,100 U/ml. A CT scan revealed systemic lymphadenopathy. An excision biopsy of a left supraclavicular lymph node revealed proliferation of lymphoid cells with Reed-Sternberg cells, leading to a diagnosis of Hodgkin lymphoma. The tumor cells were positive for EBV-encoded RNA 1 (EBER 1). The patient was diagnosed with immunodeficiency-associated Hodgkin lymphoma due to EBV reactivation triggered by TAC. TAC was discontinued, but his symptoms persisted. He was treated with chemotherapy (ABVD) on day 14 after admission. Six courses of chemotherapy were completed and complete remission was obtained. There are case reports of post-transplant lymphoproliferative disorders related to EBV reactivation while on TAC. However, there is no case report of RA patients who developed immunodeficiency-associated lymphoma during the treatment with TAC.

P3-234

A case of EBV-positive cutaneous ulcers in a patient with rheumatoid arthritis

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Conflict of interest: None

We report a Japanese woman with rheumatoid arthritis (RA) complicated by multiple cutaneous ulcers. RA first occurred at the age of 64 years. At the age of 66 years, she was treated with 10mg/w of methotrexate and low dose-corticosteroids. Although she was maintained in low disease activity at the age of 76 years, she was admitted to our hospital because of exacerbation of multiple cutaneous isolated sharply circumscribed ulcers on the lims and herpes zoster on the left leg. The herpes zoster was cured by acyclovir treatment. While, the ulcers lesions were histologically characterized by atypical large B-cell blasts with strong EBER positivity. Thus we diagnosed with the EBV positive mucocutaneous ulcer. After only the discontinuation of MTX, the ulcers were spontaneously resolved. [Clinical significance] In 2010, EBV-positive mucocutaneous ulcer was reported as a newly recognized clinico-pathologic entity associated with various type of immunosuppression such as MTX, generally responding well to conservative management. We report this case because of the usefulness for differential diagnosis of cutaneous ulcers in patients with RA.

P3-235

Successful treatment of pulmonary mucormycosis with cavities and active rheumatoid vasculitis with a combination of antifungal therapy, a reduction of immunosuppressive therapy, LCAP, IVIg and PE-a case report

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Conflict of interest: None

We report a man with rheumatoid vasculitis complicated with pulmonary mucomycosis. RA first occurred at the 63 years, and he was originally complicated with multiple bullas in both lungs. At the age of 67 years, he treated with MTX 12mg/w and PSL 20mg/day.After one year, he was added tacrolimus and ETN. Although PSL was able to decrease to 12mg/day, he was admitted to our hospital because of exacerbation of the arthralgia and peripheral neuropathy at the age of 69 years. His monitoring chest CT showed several cavitary nodules in both lungs. TBLB was carried out using bronchoscopy. We diagnosed the pathogen of lung disease as mucor from the result of lung tissue staining and the morphology under the microscope, but the culture was negative. Then the patient was immediately L-AmB on the fifth day of admission. On the 17th day of admission, he was added caspofungin because of the progression of the lung shadows. After those combined antifungal therapies and withdrawing tacrolimus and ETN, the lung shadows were gradually decreased. While, on rheumatoid vasculitis, he was successfully treated with a combination of LCAP, IVIg and PE. [Clinical significance] We propose that those combined therapy may be a new option for management of rheumatoid vasculitis complicated with an infection.

P3-236

A Case of MTX-associated lymphoproliferative disorder (MTX-LPD) localized to the lung

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Conflict of interest: None

A 77-year-old woman with rheumatoid arthritis (RA) for 18 years had been treated solely with prednisolone (PSL) 10 mg/day. Methotrexate (MTX) and infliximab have been additionally administered since 2009, and thereafter, RA has been in remission. She complained fatigue and appetite loss from 4 months prior to admission. The upper endoscopic examination did not show any particular findings. On the other hand, CT of the chest reportedly revealed multiple pulmonary nodular shadows (the total amount of MTX: 1782 mg). Infection of tuberculosis or nontuberculous mycobacteriosis was negative from the result of the tuberculosis-specific ELISPOT assay or the culture test. Laboratory data showed that LDH was 342 IU/L and the value of soluble IL-2 receptor was abnormally high with 2630 U/ml. The chest X-ray after MTX was discontinued showed disappearance or reduction in opacity; therefore, the possibility of lung cancer was negative. MTX-LPD was eventually diagnosed. Having had MTX discontinued, CT revealed that all lung nodular shadows disappeared after 3 months. Thereafter, she has no sign of recurrence. We experienced a rare case of MTX-LPD with a lesion only in the lung. We should take MTX-LPD into consideration when lung lesions were found in subjects treated with MTX or biologics.

P3-237

Methotrexate-associated lymphoproliferative disorder in a patient presenting with bilateral pulmonary infiltrates during rheumatoid arthritis treatment

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Conflict of interest: None

A 76-year-old woman with a 12-year history of rheumatoid arthritis who was maintained in clinical remission with 6 mg methotrexate and 2.5 mg prednisolone presented with fever, cough, and dyspnea. Initial chest computed tomography (CT) demonstrated multiple infiltrates in bilateral lung fields. Antibacterial therapy in combination with steroid was initiated because of gradually worsening respiratory status. Subsequent bronchoscopy demonstrated edematous and friable mucosa of the bronchus. Pathological examination of a transbronchial lung biopsy specimen demonstrated dense lymphocyte infiltrates along the peribronchioli and alveolar walls, with immunostaining identifying the presence of LMP1-positive cells. From these results, a diagnosis of methotrexate-associated lymphoproliferative disorder (MTX-LPD) was made. CT findings and subjective symptoms progressively improved in response to treatment, and the steroid dose was gradually tapered. In the lung, MTX-LPD typically presents as nodular and mass shadows on CT imaging, with cases presenting with multiple infiltrates considered extremely rare. The present case is of particular interest as it demonstrates an atypical presentation of MTX-LPD with multiple infiltrates on CT imaging that complicated the initial diagnosis.

P3-238

A case of IgG4-related patient with Guillain-Barre syndrome after cytomegalovirus infection

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Conflict of interest: None

We describe a 78-year-old man with IgG4-related disease complicated by cytomegalovirus (CMV) associated Guillain-Barre syndrome (GBS). He was admitted to our hospital after relapse of IgG4-related dacryoadenitis. After oral steroid therapy, the swelling of his lacrimal glands were improved and he was discharged. In the next day after hospital discharge, he suddenly developed urinary retention,constipation and mild muscular weakness in his distal limbs. He was admitted to our hospital again. His deep tendon reflexes were mildly diminished in the lower extremities. He was diagnosed with GBS in the result of nerve conduciton velocity test and cerebrospinal fluid examination. Because he had positive CMV antigenemia test before the onset of neurological symptoms, he was diagnosed as CMV asssociated GBS. He received a course of ganciclovir and intravenous immunogloblin, so weakness of his limbs were gradually improved. CMV reactivation frequently develops in immunosuppressed patients by corticosteroid. In conclusion, GBS due to CMV reactivation is a rare neurological complication on immunosuppressed patients. However we may need to consider GBS when peripheral neuropathy after CMV reactivation occurs in immunosuppressed patients.

P3-239

Pulmonary diseases caused by *Mycobacterium abscessus* that developed in a patient with rheumatoid arthritis treated by non-biologic DMARDs

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Conflict of interest: None

<Introduction> *Mycobacterium abscessus (M.abscessus)* is one of the non- tuberculous mycobacteria. Since effective drug is less, it may require surgical resection when the antibiotic treatment is not successful.<Case>A 52-year-old woman was diagnosed RA 4 years ago and methotrexate (MTX) was started. Three years ago it pointed out the infiltration in the upper right lobe on chest CT and bronchoscopy was performed. Pathological examination showed inflammatory granulomas and no pathogen. Suspected drug-induced reaction by MTX, MTX was interrupted. In regular chest X-ray, the shadow was repeated progression and improvement naturally. From 3 weeks ago, intermittent fever and dry cough were emerged. Chest CT showed new shadows of the right midlower lobe in addition to deterioration of existing shadow. Bronchoscopy was performed, *M.abscessus* was detected. No amelioration was seen by 3 weeks therapy of clarithromycin, imipenem and amikacin, the patient was transferred for surgical resections.<Discussion>With respect to pulmonary disease with *M.abscessus*, there was no certain view on the timing of surgical resection. We report the past pulmonary disease of *M.abscessus* in RA and the timing of surgical intervention against refractory lesions with literature reviews.

P3-240

Survey of latent tuberculosis infection (LTBI) in patients with rheumatoid arthritis; Retrospective observational study

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Conflict of interest: None

<Purpose> Since the occurrence of tuberculosis (TB) is high in Japanese RA patients, proper management of TB is required when treatment with MTX and biological agent (BA). By assessing the present condition of LTBI, we have considered the appropriate screening method in clinical practice. <Method> Using medical record, we investigated the 345 cases of RA newly diagnosed from Apr 2013 to Oct 2015 at our department. We used the interferon-Gamma release assays (IGRA), T-SPOT and QFT, as TB screening. We examined follows: implementation rate and positive rate of IGRA; treatment of LTBI in IGRA positive RA. <Result> IGRA screening rate was 27%(93/345) in total RA patients. Overall IGRA positive rate was 16%(15/93). There were neither consistent trend in IGRA-positive ratio stratified by age nor IGRA positive case over the age of 81 (1 undeterminate, 1 borderline, 9 negative). We prescribed Isoniazid to 9 IGRA-positive cases. There was no developed TB onset. Out of 15 IGRA-positive cases, 8 MTX, 3 BA was used. MTX dose (average 7.75g/week) wasn't significantly different from IGRA negative. <Conclusion> For LTBI prevalence in RA may be higher than the general population, LTBI screening is needed. RA with LTBI as well as without LTBI could be treated under appropriate management of LTBI.

P3-241

Severe *Mycobacterium kansasii* pneumonia in a patient with rheumatoid arthritis

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Conflict of interest: None

We report a case of 67-year-old male with a history of rheumatoid arthritis (RA) for 23 years, who suffered from rapidly progressive severe *Mycobacterium kansasii* pneumonia. He was taking daily 6.5 mg of predonisolone (PSL), 100mg of bucillamine, and 50mg of iguratimod. He was referred to our hospital due to worsening fever and disturbance of consciousness from the morning. Chest X-ray and CT showed consolidation with cavity on upper and lower lobe of the right lung. Intravenous meropenem (MEPM) was initiated. Later direct smear examination of the sputum showed positive acid-fast bacilli, isoniazid (INH), rifampicin (RFP), ethambutol (EB), pyrazinamide (PZA), and clarithromycin (CAM) was added. On the day 35 *Mycobacterium kansasii* was detected by sputum culture, MEPM was discontinued, and INH + RFP + EB were continued. Although antimicrobial agents improved pneumonia, the patient's general condition gradually deteriorated due to multiple cerebral infarcts and catheter-related sepsis, and he died on the day 182. Pulmonary *Mycobacterium kansasii* infection is usually manifested as a slowly progress-

ing nodule or cavity formation of the lung, but should be considered as a cause of rapidly progressive severe pneumonia in a immunosuppressive condition such as this case.

P3-242

A case of pulmonary tuberculosis during treatment with biologics for rheumatoid arthritis

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Conflict of interest: None

A 68-year-old woman was diagnosed with rheumatoid arthritis (RA) on Dec 2014. She was treated with prednisolone 5mg/day and salazosulfapyridine 1000mg/day. Certolizumab pegol (CZP) was initiated on Feb 2015. But treatment with CZP was replaced with Golimumab on April for insufficient efficacy. She presented with cough from mid-May. Chest CT scan on 20th May, showed consolidation in right lingular segment, but there were no cavity formation suggesting pulmonary tuberculosis. Antibiotic and steroid therapy was started. However her condition did not improved. Chest scan on 29th June, showed multiple cavity formation in bilateral lobe, suggesting NTM or pulmonary tuberculosis. Smear examination of gastric juice was positive (Gaffky scale, 5) and PCR assay was positive for Mycobacterium tuberculosis. She was treated with four antitubercular agents, namely, INH, RFP, PZA, SM. Her symptoms improved. We should pay close attention to the possibility of pulmonary tuberculosis in the treatment of RA with biologics.

P3-243

Pseudothrombophlebitis caused by rupture of bilateral popliteal cysts during cessation of tocilizmab therapy before odontectomy in rheumatoid arthritis: a case report

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Conflict of interest: None

Acute disease flare during cessation of tocilizmab (TCZ) therapy is not rare in RA. Presented here is a case of RA with pseudothrombophlebitis (PT) caused by rupture of bilateral popliteal cysts during the drug cessation before odontectomy. A 35-year-old woman with a 6-year history of RA presented to our emergency room with bilateral calf pain, high fever, and gait disturbance 4 days after odontectomy. She stopped TCZ therapy 24 days before the dental treatment. CRP and DAS28-CRP was 0.06 mg/dl and 2.79, respectively, before cessation. On examination bilateral calves were remarkably swollen, and the calf circumstance on the right and left was 33 cm and 36.5 cm, respectively. CRP was elevated at 10.7 mg/dl. MRI demonstrated fluid retention in the medial aspects of both calves communicating with the knee joints. Culture of fluid obtained on aspiration was negative. The patient was diagnosed with PT caused by rupture of bilateral popliteal cysts after rule out of DVT on enhanced CT. The symptoms were improved by local corticosteroid injection and retreatment of TCZ. It is difficult to differentiate PT from DVT and calf abscess clinically, and MRI is useful for differential diagnosis. Cessation of biologics including TCZ is not always necessary before odontectomy in RA.

P3-244

Pneumocystis pneumonia in patients with rheumatoid arthritis in received biological agents-Nurses role in serious infecition triage Department of orthopedic surgery,Takatsuki Red Cross hospital Ikuyo Noguchi,Kosaku Oda

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Conflict of interest: None

[Obiect]Adverse events were prevented to go to next naursing education in order not to generate serious AEs.[Methods]Patient who developed PCP while receiving biological agents were given an interivew,we had told the frree talk such as the corresponding selfjudgment and synptoms of adverse events look back.Case:64-yearold woman in RA,after adalimumab three months palpitaion, dyspnea. The telrphone consultayion in our hospital RA nurse.Patient hope Department of Cardiology visits from palpitations and chest tighness is the same as the previous angina sympotoms.Nurse is also considered the possibility of respiratory infection recommends the Department of Respiratory medicine,at last admitted to our hospital general interal medicine,The diagnosis of PCP chest HRCT,to hospitalization.The clincal outcome was favorable[Conclusions]The possibility of PCP should be intensively investigated in RA patients developing while receiving biological agents. First contact with patients were RA nurse,therefore RA nurse present information in a sharing of information,and repeatedly patient of education.

P3-245

A case report of pyogenic arthritis of both knees and elbows in patient with rheumatoid arthritis(RA)

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Conflict of interest: None

Infections are major concerns for patient with RA, using biological drugs are reported to increase the risk of infection. We report a pyogenic arthritis case of RA 50years old male patient. He used tocilizmab (TCZ) intravenous injection. 5years after the beginning of TCZ injection, he had a cellulitis in right elbow. TCZ injection was skipped. After his cellulitis looked better, TCZ injection was restarted. After 1month, when he entered hospital for injection, he had pain and swelling in both knees. He had neither fever nor fatigue. Muddy fluid was obtained by both knees punctures, and MSSA was detected in both knee fluid. Therefore both knees irrigation was decided. Just before the surgery, he felt pain in both elbows. Muddy fluid was obtained by both elbows punctures. For these reasons, both knees and elbows irrigation was done. After using antibiotics for 4 weeks, no recurrence was recognized. TCZ is reported for good effect on the suppression of RA activity and also reported for masking effect on inflammatory and clinical reaction. Though TCZ has not been reported to increase infection rates in comparison with other biological drugs, patients using TCZ show irregular responses. When we use TCZ, we should check signs of infection carefully and lead to the remissions.

P3-246

A case of rheumatoid arthritis with ulcerative colitis during adalimumab therapy

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Conflict of interest: None

Conflict of interest: None [Purpose]In June, 2013, Adalimumab (ADA) acquired the approval of the therapeutic drug for the ulcerative colitis (UC) in Japan. It becomes one of the therapeutic drugs for moderate to severe UC now. We report the case of rheumatoid arthritis (RA) with UC during ADA therapy. [Object]A 55-year-old woman. She had a diagnosis of RA at 42 years old. And we started the ADA therapy at 49 years old. She developed abdominal pain, diarrhea, bloody stool at 54 years old and consulted gastrointestinal medicine. By colonoscopy, we found erosion, edema, loss of visible vascular pattern from the sigmoid colon to the rectal lower part. In addition, we accepted a cryptitis, a lacunar abscess in the pathology. Therefore we made a diagnosis of active UC. And oral mesalazine was started. And the intestinal symptom was improved and had a diagnosis of the remission UC by colonoscopy after eight months. [Conclusion] The report for the coexistence of RA and UC is rare.We could have no report in Japanese RA patient with UC during ADA therapy as far as we were able to confirm it. When diarrhea, bloody

stool continued to RA patient, we thought that the close inspections such as a medical examination or colonoscopy by the specialist were necessary.

P3-247

Three Cases of pyothorax under treatment with tocilizumab for rheumatoid arthritis

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Conflict of interest: None

We report three cases of pyothorax under treatment with tocilizumab (TCZ) for rheumatoid arthritis (RA). Case 1 is a 37-year-old man who has 8 year history of RA. He received intravenous (IV) TCZ with MTX for 2 years. After 17 days of last TCZ, he felt general malaise. After 24 day, he hospitalized with right chest pain and dyspnea. After drainage, meropenem and levofloxacin were administrated. Because of inadequate response of antibiotics, surgical treatment was performed. Case 2 is a 78-year-old man who has 7 year history of RA with ACOS (Asthma-COPD Overlap Syndrome**)**. He received TCZ-IV monotherapy for 5 years. After 14 days of last TCZ, he felt exertional dyspnea, increased sputum, and left chest pain. After 18 days of last TCZ, he hospitalized. MSSA was detected. He was improved by drainage and antibiotic. Case 3 is a 79-year-old woman who has 20 year history of RA with bronchodilation and bronchiolitis. She received subcutaneous TCZ for 3 years. Although she felt damp coughing and the right chest pain, she received TCZ routinely. After 7 days of last TCZ, he visited family doctor and hospitalized our hospital with fever. Pseudomonas aeruginosa was detected. She was improved by chest drainage and antibiotics. We discussed the pyothorax during TCZ with literatures.

P3-248

A case of severe invasive streptococcal disease with rheumatoid arthritis undergoing Certolizmab

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Conflict of interest: None

We report a case of severe invasive streptococcal disease with rheumatoid arthritis undergoing Certolizmab. 67-yr woman developed rheumatoid arthritis in 2006. The treatment of Infliximab was started in January 2014, but was switched to Certolizmab in April 2015 for the second failure. DAS28 improved from 5.81 to 3.61. Left second toes changed color suddenly on August 15. On the next day there was the change of color of first toes and fever, severe polyarthralgia, and she was transported to our hospital on August 17. There was no blood flow, and the change of color department, we made a decision of the amputation. From the same night, hypotension, tachypnoea, a DIC sign appeared, and it was performed left leg amputation in emergency and an endotoxin adsorption therapy. Streptococcous equisimllis (SDSE) was detected in blood cultures subsequently, and severe invasive streptococcal disease was diagnosed. She was improved by treatment such as Penicillin G. SDSE disease has reported a lot to late years, comparative elderly people with the underlying disease, and there are no difference between A-group hemolytic streptococcus and SDSE. Because delay of the start of therapy is connected directly with prognosis, prompt diagnosis and start of therapy are essential.

P3-249

Case of GPA with multiple lung nodule complicated by invasive pulmonary aspergillosis(IPA) that we were struggling to differentiate granulomatous lesions of vasculitis or IPA or others

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Conflict of interest: None

【Case】80-year-old man【CC】Fever. Bloody sputum【History】February one year, he was admitted our hospital with fever and bloody sputum. Thickening of bronchi and lung nodule were observed on chest CT, and sinusitis was observed. Mild renal impairment were observed and PR3-ANCA rise in 219U / ml, so it was diagnosed GPA. PSL60mg was started but after dose reduction titer of ANCA was ceasing to fall, then IVCY was stared on March 17.3times IVCY was conducted but CRP held up positive and ANCA elevated and multiple lung nodule was observed in CT on April 13.We considered it worsening of GPA because B-D glucan was negative and no symptom of respiratory infection, RTX was started on May 12.Then ANCA reduced but lesions were worsen. So considering the possibility of malignancy or infection, TBLB was done. Multiple erosions seen in the bronchi and fungus body of Aspergillus was confirmed in bronchial lavage fluid. Although Aspergillus lesions were not observed in the tissue, granulomatous lesions and malignancy were not recognized. We diagnosed it IPA and after start of oral voriconazole the lesions were improved.【Conclusion】We report a case of GPA that was struggling to differential diagnosis on whether worsening of vasculitis or complications of infection.

P3-250

Maintenance immunosuppressive therapy in MCTD-, SLE-PAH patient in our facility

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Conflict of interest: None

(Objectives) CTD-PAH had a lower survival rate compared with IPAH before. However, the prognosis in CTD-PAH is improving by changed strategy of diagnosis and treatment. CTD-PAH is categorized in one of the PAH in *Nice* classification and we treat under 2015 ESC guidelines. Some report suggests that the immunosuppressive therapy in CTD-PAH patient is effective, especially MCTD, SLE patient. However, maintenance therapy in MCTD-, SLE-PAH is not established. We propose induction and maintenance therapy strategy in MCTD-, SLE-PAH by examining treatment in CTD-PAH patient in our facility. (Methods) We investigated 3 MCTD and 4 SLE patients treated in our facility. We surveyed induction and maintenance therapy retrospectively. (Results) All patients were treated with high dose corticosteroid or corticosteroid pulse. IVCY was used for 4 patients as induction therapy. Azathioprine, Tacrolimus, Mycophenolate mofetil and Tocilizumab were used for patients as maintenance therapy. It is suggested that IVCY induction and maintenance therapy are effective for PAH recurrence. The agent used for maintenance therapy is not fixed, we need to devise appropriate maintenance therapy.

P3-251

A case of pulmonary hypertension with Lc-SSc patient treated under appropriate hemodynamic evaluation

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Conflict of interest: None

【Patient】76-year-old female 【Case presentation】The patient was followed-up in some outpatient clinic because of limited cutaneous systemic scleroderma which was diagnosed more than 15 years ago. She was admitted to our hospital because of traumatic subarachnoid hemorrhage due to falling down in faint.After that she had high fever and developed type1 respiratory failure, neurosurgeon doctor suspected the association of systemic sclerosis and consulted us. We initiated antibiotics and diuretics as hospital acquired pneumonia with acute heart failure. Cardiac echography showed the tricuspid regurgitation pressure gradient (TRPG) up to 62mmHg.Right heart catheterization revealed elevation of mean pulmonary arterial pressure (37mmHg) and pulmonary wedge pressure

(19mmHg). We considered pulmonary arterial hypertension with SSc and initiated phosphodiesterase 5 inhibitor, but were struggled with dyspnea and hypotension. We reconsidered the hemodynamic status and noticed her Diastolic pressure difference (DPD) was enough low to suggest the diagnosis of pulmonary hypertension with left heart failure.We stopped phosphodiesterase 5 inhibitor and changed the treatment with mainly diuretics as heart failure. Her symptoms were gradually improved and she discharged our hospital.

P3-252

Clinical features in dermatomyositis-associated interstitial pneumonia (DM-IP) with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] We evaluated the clinical features in RA patients under treatment complicated by DM-IP. [Methods] We retrospectively identified all RA patients with DM-IP followed in the Division of Rheumatology at Osaka medical college from 2005 through 2015. We assessed clinical features, treatment, and clinical course. [Results] 14 RA patients diagnosed with DM-IP. The median age (IQR) and disease duration of RA at diagnosis with DM-IP was 62.5 yrs (54-68.5), 1095 days (577-1580). All patients were female, and 4 patients (28%) had a smoking history. The anti-CCP levels divided into 3 groups; high (>100) / middle (15~100) / low (<15), were 7 cases (54%) / 3 cases (23%) / 3 cased (23%), respectively. The KL-6, Aldolase, CK, Ferritin values at the diagnosis with DM-IP were 769 U/ml (368-1215), 7.2 U/l (5.8-11.2), 83 U/l (40-331), 119 ng/ml (91-253), respectively. Concerning HRCT images, 7 patients showed NSIP pattern, 7 showed OP pattern, and no patients had honeycomb lung. PSL was administered to all patients. In 12, it was combined with immunosuppressive drugs (IVCY was used in 3, CsA was 9, TAC was 3). With respect to the prognosis, all patients was alive. [Conclusion] RA patients with DM-IP had higher levels of anti-CCP antibody, and further attention will be necessary.

P3-253

CD28 null T cells are increased in the lung of connective tissue disease(CTD) associated interstitial pneumonia(IP)

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Conflict of interest: None

Objective: CD28 null T cells are terminal differentiated effector cells with cytotoxity and profound cytokine production. It has been reported that these T cells were expanded in peripheral blood and muscles in PM/DM. However, it is unknown CD28 null T cells are increased in the lung of PM/DM-IP. The aim of this study is to answer the question. **Methods:** Subjects were 13 of PM/DM-IP (PM/DM/ADM; 5/3/5, anti-MDA5Ab positive case;5, fatal case;2), 6 of Sjogren-IP and 5 of RA-IP. CD28 expression on CD4/CD8 T cells from bronchoalveolar lavage fluid obtained before starting therapy. **Results:** Total cell numbers and lymphocyte % were increased in PM-DM-IP and non-myositis-IP. CD4/8 were 0.57 (median) in PM/DM-IP and 1.65 in non-myositis-IP. Percentage of CD28 null cells in CD4 and CD8 cells were 58% and 84% in PM/DM-IP and 43% and 79% in non-myositis-IP. No relation was found percentage of CD28 null cells and clinical features of PM/DM-ILD including autoantibodies, response to therapy, prognosis. **Conclusion;** CD28 null T cells were increased in pulmonary lesions of CTD-IP, including not only PM/DM.

P3-254

Examination of lung cancer complicated with connective tissue diseases in our hospital

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Conflict of interest: None

[Background] It is reported that the patients with connective tissue diseases have more risks of the lung cancer. However, there are few reports about clinical features of the lung cancer complicated with connective tissue diseases. We performed the clinical examination of the cases with lung cancer complicated with connective tissue diseases. [Method] We examined retrospectively 24 CTD cases that had a diagnosis of lung cancer during the period of from January, 2010 to December, 2014. [Conclusion] The patients with lung cancer complicated with CTD had interstitial pneumonia at higher rate, and it was suggested that interstitial pneumonia restricted the treatment options of lung cancer.

P3-255

Analysis of pleural effusion due to rheumatic disease

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Conflict of interest: None

Background: In the case of patients with rheumatic disease under immunosuppression, it is necessary to differentiate between rheumatic and infectious pleural effusion.We analyzed ADA activity in pleural effusion of rheumatic disease patients. Method: We extracted all the patients with rheumatic disease (SLE, RA, SSc, Vasculitis, myositis) who had pleural effusion ADA examination from our electronic medical record from 2007 and October 2015.We selected the case of pleural effusion associated with rheumatic diseases by exclusion of other cause of pleurisy in rheumatic disease patients.We analyzed the chemistry profile and pleural fluid ADA activity. Results: The number of rheumatic pleural fluidwas 57 patient. Pleural effusion ADA value, mean, median, range) was SLE (42.4, 32.9, 3.3-98.0), RA (27.8, 23.15, 4.7-75.5), SSc (15.8, 10.9, 6.6-29.9) and Vasculitis (14.9, 15.2, 2.9-29.3). The number of the case which exceed ADA cut-off value of tuberculous pleural effusion (>50 U / L) cases were 5 / 15 cases in SLE, 3 /3 0 in RA, 0 / 3 in SSc and 0 / 7 in Vasculitis. Conclusion: History taking, cultivation test and histopathological examination is important when interpreting pleural effusion ADA values.

P3-256

Rheumatoid arthritis in patients who admitted pulmonary diseases

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Conflict of interest: None

Objective: Pulmonary diseases are frequently developed in RA, which was based on observation of RA patients. However, it is unknown what proportion of patients with pulmonary diseases has RA. To answer this question, we examined the patient profile who admitted our department because of pulmonary diseases. **Methods:** Subjects were 808 patients who admitted Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University Hospital from Oct 2014 to Oct 2015 because of pulmonary symptoms or abnormalities. Medical records were reviewed retrospectively. **Results:** Among 808 patients who admitted by pulmonary diseases, 28 patients had RA (3.3 %, (95% CI: 2.1-4.5%)). In interstitial pneumonia (IP), organizing pneumonia, respiratory infection and neoplasms, RA cases were 9 (20% in indicated (IP) cases, (95% CI; 8.3-31.6%), 2 (16.6%(0-37%)), 9 (3.7%(1.3-6.0%)) and 5 (1.5%, (0.002-2.8%), respectively. **Conclusion:**The proportion was significantly high in IP and infectious diseases, which confirms previous findings that RA is

a risk factor for pulmonary diseases, particularly for IP and infection.

P3-257

Comparison of cryptogenic organizing pneumonia and organizing pneumonia preceding or simultaneous onset rheumatoid arthritis

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Conflict of interest: None

[Background] Organizing pneumonia (OP) associated with rheumatoid arthritis (RA) is less common, especially preceding or simultaneous onset RA. In this study, we compare the background of patients with cryptogenic organizing pneumonia (COP) and OP preceding or simultaneous onset RA (OP-RA). [Method] Twenty-four patients were diagnosed as COP by transbronchial lung biopsy between Nov.2012 and Oct.2015 in our hospital. We used the 2010 ACR-EULAR classification criteria to make diagnosis of RA. [Results] Two patients developed RA six month after onset of OP, and six patients RA and OP simultaneously. Sixteen patients were not associated with RA 19.4 months on average after onset of OP. The average age at onset was 58.5 and 70.6 years in OP-RA and COP, respectively, and significantly younger in OP-RA patients ($p=0.0106$). The positivity of RF or CCP was higher in OP-RA patients (8 of 8 patients) than in COP (2 of 11 patients) ($p<0.0001$). Serum complement titer was low in three of five patients of OP-RA, but high in all of COP. [Discussion] Younger onset of OP with positive RF or CCP could be developed with RA. And we should follow up our two COP patients carefully for long time because a case of RA 32 months after onset of OP was reported.

P3-258

Four cases of malignancy and elevated serum KL-6 in patients with connective tissue disease

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Conflict of interest: None

[Case 1] A 55-year-old woman with a history of Sjogren's sydrome was admitted for fever. Her KL-6 level was 2,100 U/mL. She was diagnosed with lung squamous cell carcinoma. [Case 2] A 74-year-old woman with a history of rheumatoid arthritis was admitted for purpura and general malaise. CT scanning showed mediastinal tumor. Laboratory data showed thrombocytopenia and KL-6 level was 5,300 U/mL. She was diagnosed with plasma cell leukemia. [Case 3] A 67-year-old man developed dyspnea and had elevated serum KL-6 level. He was diagnosed with dermatomyositis and interstitial pneumonia one year ago. Although he was treated with steroid pulse therapy, his KL-6 level was 4,500 U/mL. He was diagnosed with lung pleomorphic carcinoma. [Case 4] A 48-year-old woman was diagnosed with lupus nephritis. She had an mastectomy for invasive ductal carcinoma one year ago. Her KL-6 level was 1,235 U/mL. She was diagnosed with recurrent breast cancer and multiple bone metastases by FDG-PET. [Clinical significance] KL-6 is known as a biomarker of interstitial lung disease, but sometimes it indicates malignancy.

P3-259

Rheumatoid elbow and hand surgeries and functional improvement by the self-assessment of the patient

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Conflict of interest: None

[Objectives] To clarify the effect of the rheumatoid elbow and hand surgeries aiming at functional remission for the patients with rheumatoid arthritis, the self-assessment of the patient about the physical function was performed prospectively. [Patients and Methods] Primary surgical reconstruction of the elbow and the hand was scheduled to perform in 145 patients (M:20, F:125) with RA. The average age was 62 years old. The surgical site was wrist in 73 patinets, fingers in 46 and elbow in 26. The procedure was wrist arthroplasty, radiolunate arthrodesis, arthroplasty at the finger MP joint (Swanson), total elbow arthroplasty and others. DAS28-CRP (4), DASH (JSSH version), and J-HAQ was investigated just before surgery, 6 month and one year after surgery. [Results] DAS28-CRP (4) before surgery, 6 months and one year after surgery was 3.1, 2.2 and 2.3 ($p<0.01$, compared to before surgery) respectively, DASH was 43, 36, 36 ($p<0.01$), and J-HAQ was 1.10, 0.98, 0.93 ($p<0.01$). In the subgroup of unchanged medication (n=45), DAS28-CRP (4) was 2.8, 2.0, 2.1 ($p<0.01$) DASH was 44, 42 (n.s.), 39 ($p<0.05$), and J-HAQ was 1.1, 1.1, 1.0 (n.s.). [Conclusion] Disease activity and physical function were ameliorated by the surgical intervention to the structurally damaged elbow and hand.

P3-260

Surgery for the rheumatoid thumb-Reconstruction of the CM/ MP joints-

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Conflict of interest: None

[Objectives] To clarify the effect of the rheumatoid thumb reconstruction, clinical and radiological assessments were performed. [Patients and Methods] Surgical reconstruction of the rheumatoid thumb was performed on the 165 cases between 2006 and 2014. The average age was 64 yrs. old and the average follow-up period was 3 yrs. and 8 mos. MP joint arthroplasty (Swanson) was performed in 69 cases, CM joint arthroplasty in 38 cases, IP joint arthrodesis in 62 cases and so on. Clinical and radiological assessments were performed. [Results] A painless stability was provided to the thumb in most of the patients. In the MP joint arthroplasty, the pre- and the postoperative flexion angles at the MP joint were 58 and 18 degrees, and extension angles at the IP joint were 46 and 0 degree (s). In the CM joint arthroplasty, M1-M2 angles were 10 and 27 degrees, and extension angle at the MP joint were 8 and 0 degree (s). Joint stability and prehension pattern improved by arthrodesis or capsulodesis. [Conclusion] By the rheumatoid thumb surgery, deformity was corrected and hand function was improved.

P3-261

Rapidly destructive arthrosis of bilateral shoulder in chance of trauma; A case report

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Conflict of interest: None

【Case】Eighty one year old female【Present illness and courses】She presented left shoulder pain after falling down and right shoulder pain at 13 days after she fell down again. X-ray of the bilateral shoulders showed humeral head collapse without destruction of glenoid fossa. Blood exam showed neither inflammatory nor infectious findings. Neither RF nor anti-CCP antibody were positive. Synovial fluid punctured from glenoid joint showed no crystal and negative in bacterial culture exam. Her lumbar spine was low bone mineral density (0.56 g/cm^2 ,T-score; -4.1). She was diagnosed as shoulder rapidly destructive arthrosis (RDA) and bilateral hemiarthroplasty was performed. Intraoperative findings showed humeral head collapse and granulation tissue around collapse site. Pathological findings showed callus formation and osteoid tissue and the appearance of osteoclasts. No finding of osteonecrosis (empty lacuna) was detected. 【Clinical significance】Insufficiency fracture of bilateral humeral head was triggered by falling down twice, resulting in shoulder RDA. As its

risk factor, she had osteoporosis without treatment. For the diagnosis of RDA, it is important to differentiate various diseases which cause arthralgia and to examine pathological findings.

P3-262

Clinical short term outcome of humeral head replacement for highly destructive shoulder due to RA

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Conflict of interest: None

(Objective) To examine the clinical outcome of humeral head replacement in patients with destructive shoulder. (Methods) Seven RA patients (8 shoulders) with severe destructive shoulder were entried. Larsen Grade was III in 1 and IV in 7 shoulders. Age was 43 to 76 years old and 59 y.o. on average, RA duration was 5 to 39 years and 22 years on average. Physioshoulder system®(JMM, Osaka, Japan) was used. The follow up duration was 0.4 to 8.6 years (1.9 years on average). The pain scale before and after surgery, JOA shoulder score, range of motion of flexion, abduction, and external rotation before and after surgery, were evaluated. Paired t-test was used for statistical analysis. (Results) JOA shoulder score showed a remarkable improvement from 42 to 76. The item of pain showed the most remarkable improvement from 8.8 to 29.4. About range of motion, flexion was improved from 83˚ to 102˚, abduction was improved from 63˚ to 70˚, and external rotation was significantly improved 22˚ to 34˚ ($p<0.05$). No surgical site infection and no dislocation was detected except that wound healing was delayed in 1 case. (Coclusion) Humeral head replacement is a useful method for highly destructive shoulder due to RA because of remarkable improvement of pain.

P3-263

Coonrad-Morrey total elbow arthroplasty for Rheumatoid Patients

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Conflict of interest: None

We studied Fifteen Coonrad-Morrey total elbow arthroplasties (TEAs) for 15 rheumatoid patients (3 males and 12 females). In fifteen TEAs, there were two revision surgery and three fractures (one distal humeral fracture and two olecranon fractures) were included. The mean age at surgery was 71.3 years and mean follow-up period was 3 years and 10 months. Preoperatively, the mean JOA elbow score was 48 points. At last follow-up, the mean JOA elbow score was 72 points. There was no radiographic loosening, but nonunion was seen in one olecranon fracture. Coonrad-Morrey TEA provided short-term good results for rheumatoid patients.

P3-264

Short-time clinical results of the PROSNAP linked elbow prosthesis for the reconstruction of rheumatoid elbows

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Conflict of interest: None

Object: We aimed to evaluate the early clinical results of the reconstruction of severely damaged elbow joints due to rheumatoid arthritis (RA) using a PROSNAP linked elbow prosthesis (Kyocera Medical, Osaka, Japan). Methods: Twenty seven elbows in 25 RA patients were replaced by PROSNAP TEA. The mean follow-up period was 36 months (range, 12-90 months). The preoperative conditions of the elbows were arthritis mutilans (n.19), an ankylosed or stiff elbow (n.5), and loosening of a primary total elbow arthroplasty (n.3). The clinical outcome of the elbows was evaluated by the range of motion, the Japanese Orthopedic Association (JOA) score, the Mayo Elbow Performance Index score (MEPS) and complications. Results: The mean postoperative elbow and forearm range of motion improved significantly. The average postoperative JOA score improved from 48.9 points to 88.2points, and the mean postoperative MEPS improved from 50.2 points to 92.9 points. Complications were noted in 3 elbows (11%). Conclusions: The PROSNAP elbow prosthesis can be safely implanted and provides satisfactory short-term clinical outcomes for the reconstruction of severely damaged RA elbows.

P3-265

Short and mid-term clinical results of a total elbow replacement in rheumatoid arthritis

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Conflict of interest: None

Introduction: Total elbow replacement (TEA) is a reliable treatment for severe rheumatoid arthritis (RA) of the elbow. The purpose of this study was to assess the short and mid-term clinical results of TEA for RA patients. Material and methods: The objects were 18 RA patients (22 elbows) treated using TEA in our center between 2009 and 2014. The mean mean age and disease duration of them was 66.3 and 25.3 years respectively. The semi-constrained, cemented prosthesis was used for all case, Coonrad-Morrray (Zimmer) for 15 elbows and Discovery (Biomet) for 7. We undertook a retrospective study of medical records and assessed the range of motion (ROM), Mayo Elbow Performance score (MEPS) for clinical evaluation, complications and standard radiographs. Results: The post-operative ROM was progressed of almost all patients. MEPS elevated in all, associated with progression of the pain, ROM and the stability. Radiographic signs of loosening and sinking were not seen. The complications were seen in 7 patients (32%). Conclusion: Our study reveals that TEA provides pain relief and recovery of functional range of motion for severe RA of the elbow in short and mid term follow-up as reported previously. However, continuous efforts are needed to reduce complication rates.

P3-266

Total wrist arthrodesis by Feldon' s method for rheumatoid wrist

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Conflict of interest: None

Recently most of rheumatoid wrists are treated by arthroplasty or partial arthrodesis for the reservation of the wrist function,but total wrist arthrodesis still have been the gold standard for the wrists with sever instability or destruction. From 2007 to 2015, 5 wrists of rheumatoid arthritis patients were fused in our hospital by Feldon`s method using two Kirschner wires and fixing the wrist in slightly flexion, and their clinical outcome were investigated: They were all women, 56.8 years old on average, and followed up in 44.2 months on average. All wrists were fused in 5.6˚ volar flexion and 4.7˚ ulnar deviation on average, range of motion in supination and pronation were 86˚and 81˚on average, ratio of grip strength and pinch strength were 72 % and 93% of the contralateral wrist on average, VAS of pain was 2.2 on average, DASH score was 43.1 and PRWE score was 28.5. They were satisfied with wrist arthrodesis and they would accept wrist arthrodesis if they had the same disability of their wrist. Arthrodesis by Feldon`s method were the good surgery for rheumatoid wrists because of acquirement of fusion in slight flexion, re-

movement of pain, and satisfaction of patients.

P3-267

Disabilities in the rheumatoid hand; thumb deformity and ulnar deviation of the digits

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Conflict of interest: None

[Objective] The finger deformities in RA impair finger function such as grasp or pinch. The hands with thumb deformity and ulnar deviation of the digits are commonly seen and lead serious problems. We assessed the functional impairment in these cases. [Materials and Methods] We enrolled 31 in this study cases 50 hands who had any finger deformity. Thumb deformity was classified by Nalebuff classification into 'A'(type I, II) and 'B'(type III, IV) groups. Ulnar deviation was classified into 'a' and 'b' groups by the degree of MP joint destruction. Finally there were 4 groups (Aa, Ab, Ba and Bb). Finger mobility, grip strength, and ADL were compared between the groups. [Results] All the subjects were female, and an average age was 72.2 years, and an average affected period was 23.4 years. Aa group was the most frequent (56%). Aa group had worst finger mobility and Ba group had worst grip strength. There was no significance in the ADL field. [Discussion] Recent development in the drug therapy and surgical treatment in RA enables us to have better prognosis in treating rheumatoid hand. From the result of this study, deformities impair the finger function accompanied by progression. An early intervention like an orthosis and rehabilitation may have important role.

P3-268

Evaluation of simultaneous surgery for hand and forefoot in rheumatoid arthritis

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Conflict of interest: None

Objective When rheumatoid arthritis (RA) patients need several surgeries, we perform simultaneous surgery for both upper and lower extremities to reduce hospitalization and anesthesia. We aimed to evaluate the simultaneous surgery. Method We evaluated 22 cases who underwent simultaneous surgery for both hand and forefoot (S group). Control group (C group, N=22) underwent only forefoot surgery, matched to the S group at age, sex, surgical method and classification. We compared operative time, bleeding, hospitalization, blood test (AST, ALT, eGFR, CRP, Hb), and complication between two groups. For the S group, we asked a degree of satisfaction for the surgery (4 grade) and asked if they wound undergo simultaneous surgery again when they need both hand and forefoot surgery again. Result The S group had significantly longer operative time. There were no statistical differences in bleeding, hospitalization and in blood test pre and postoperatively. In the S group, 2 forefeet wound infections and 1 bronchitis occurred and in the C group, 2 wound infections and 1 cystitis occurred. 71% answered satisfaction and 79% chose the simultaneous surgery again. Conclusion Simultaneous surgery for both hand and forefoot is an effective procedure for RA patients who need several surgeries.

P3-269

Total Shoulder Arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

Conventional total shoulder arthroplasty (TSA) or reverse total shoulder arthroplasty (RSA) was performed for the shoulder of the patients with rheumatoid arthritis (RA). A female patient aged 78 years received RSA for retear of rotator cuff of the shoulder classified in Larsen grade 2, and the other female patient aged 68 years had TSA against destructed RA shoulder classified in Larsen grade 4 after arthroscopic synovectomy. After a surgery, patients in whom TSA or RSA performed got the similar clinical result (86 points after RSA and 83 points after TSA in shoulder clinical score of Japanese Orthopaedic Association) at the final visit. However, there was difference of the period until attainment of 90-degree elevation. Less than 4 weeks had passed in the RSA patient, whereas about 3 months was needed in the TSA patient. Although both TSA and RSA are useful operative methods for the shoulder of the patient with RA, RSA may be more adaptive to restore the function of the shoulder in RA patient due to impairment of soft tissue such as rotator cuff around the RA shoulder as well as early restoration of the shoulder function after surgery.

P3-270

A case study: Difficulties in diagnosing rheumatoid arthritis in a patient with a history of tuberculosis

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Conflict of interest: None

[Objectives] We present a case study of a patient with RA. He had severe elbow arthritis with a history of tuberculosis.Establishing an accurate diagnosis was difficult.. [Results] The patient was a 65-year-old man with RA (stage IV, class II). He had severe left elbow arthritis and synovitis. He was diagnosed with RA in 2003 and had been treated with MTX. In 2006, he developed tuberculosis and was treated with antituberculosis agent. In April of 2015, he visited our department and complained of swelling in the left elbow. His MRI detected many rice bodies in his elbow and synovitis. The examination of T-spot, arthrocentesis, and sputum culture tested negative. The drugs administered for treatment were changed from SASP to IGU. In August of 2015, he complained of a discharge from his elbow, and then we performed biopsy. The culture tested negative. The tissues were necrosis of fibrin. The discharge was continuous, therefore we performed synovectomy. The tissues were pathologically comparable to RA. After synovectomy, his conditions improved. [conclusion] The important thing is that in diagnosing a patient with RA with a history of tuberculosis, tuberculosis's arthritis should be taken into account. Decisions in the course of treatment should be made in a very careful manner.

P3-271

Revision total elbow arthroplasty using allograft for extensive loosening after linked type total elbow arthroplasty in a patients with rheumatoid arthritis - a case report

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Conflict of interest: None

Total elbow arthroplasty (TEA) has been widely performed in patients with rheumatoid arthritis (RA) for relief of pain or improvement of elbow function. There are several reports of good long-term results of linked type TEA, however the higher complication rate were reported including loosening of the implants or extensive periprosthetic osteolysis after TEA compared with other joint arthroplasties. We report a revision TEA using allograft for extensive loosening after linked type TEA in a patients with RA. A 69-year-old man was diagnosed with RA at 34 years old, and underwent right TEA using GSBIII(Zimmer) seven years ago. Revision TEA using long-stemmed Coonrad-Morrey system was performed five years ago because of dislocation of implants and extensive loosening around the humeral implant. Five months after revision TEA, elbow radiograph showed loosening at the top of the humeral stem, and osteolysis around the humeral implant was gradually appeared. Re-revision TEA using tibial allograft was performed five years after revision

TEA. Radiographic showed a well-fixed implants after re-revision surgery.

P3-272

A case of arthroscopic resection arthroplasty for basal joint osteoarthritis of the thumb in patient with rheumatoid arthritis

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Conflict of interest: None

We report our experience with arthroscopic resection arthroplasty in a patient with rheumatoid arthritis (RA), accompanied by both tenderness at the base of the thumb and swelling in both basal joints. A 52-year-old female was diagnosed with RA six years ago. She was treated with etanercept and methotrexate (8 mg/week), and her disease was controlled well. However, because of the persistent bilateral basal joint osteoarthritis of the thumb, she visited our orthopedic department by referral. Her both basal joints of the thumb had swelling and pain, but she had no evidence of inflammation in any other joints, and her inflammatory response was negative. The range of motion of the joint was not limited, but her X-rays showed narrowing of joint space and subluxation. Her pain was not improved in spite of treatment with brace; therefore, we performed arthroscopic resection arthroplasty of the left trapeziometacarpal joint one year ago and performed the same operation of the contralateral joint six months later. A half year after the operation, although the instability of joint remained, the swelling and the pain were gone, and she was satisfied. We produced a good short-term outcome. This operation is acceptable in terms of minimal invasion.

English Poster Session Clinical

P2-263

The validity of three-dimensional leg alignment assessment system for total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

[Object] To investigate the validity of three-dimensional leg alignment assessment system for total knee arthroplasty in patients with rheumatoid arthritis. [Methods] 40 patients (47 knees) who received primary total knee arthroplasty for the treatment of rheumatoid arthritis between June 2006 and September 2010 were included in this study. The average age at time of surgery was 59.2. The average follow-up period was about 2.4-year. For the component, Bi-surface (JMM) was selected in all patients. For three-dimensional leg alignment assessment system, KneeCAS (LEXI) was used. The evaluation tool included the JOA score that was taken in preoperatively and the latest follow-up, the agreement late for the size of the components between pre-operative planning and at the operation, the case reports. [Results] In the JOA score, the pre-operative score was 37.5 and the post-operative score improved significantly to 87.3 at the latest follow-up period. The agreement late for the size of the components between preoperative planning and at the operation was 93.6%. It was possible to choice the right size for the components more exactly even in severe deformity and/or contracture cases by investigating the position of components three-dimensionally and checking the bony erosion and defect preoperatively. [Conclusions] It was useful to plan the total knee arthroplasty preoperatively with three-dimensional leg alignment assessment system in patients with rheumatoid arthritis.

P2-264

Ten-year survival rate of total hip arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Total hip arthroplasty (THA) is a useful treatment for RA patients with hip disorder. However, several complications associated with this treatment result in poor outcome. The purpose of this study was to investigate the 10-year survival rate of THA in RA patients. Method: 51 RA patients (60 hips) who underwent THA between 1989 and 2005 in our institution were enrolled in this study. 10-year survival rate for aseptic loosening in radiographic evaluation or revision surgery was investigated. DAS-28 (CRP) was measured at the latest follow-up. 10-year mortality rate in this population was also assessed. Result: 25 RA patients (33 hips) followed-up longer than 10 years (mean: 15 years). 10-year survival rate for aseptic loosening was 97%. 5 hips with complications that include dislocation (2 hips), infection (1 hip), periprosthetic fracture (2 hips) required revision THA. 10-year survival rate for revision surgery was 82.0%. Mean DAS-28 (CRP) at the latest follow-up was 3.05. In 51 patients, 7 died during 10-year follow-up period and 10-year mortality rate was 13.8%. Conclusion: THA was successful treatment that ensures good long-term clinical outcome for RA patients. However, indication of THA requires consideration of relatively high complications and mortality rate.

P2-265

Systemic Lupus Erythematosus presenting as macrophage activation syndrome in a 20 year old female patient

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Conflict of interest: None

Introduction: Macrophage activation syndrome (MAS) is a potentially life threatening condition brought about by disproportionate activation and proliferation of T lymphocytes and macrophages with hypersecretion of inflammatory cytokines causing persistent febrile illness with pancytopenia. MAS is a rare complication of several autoimmune conditions including Systemic Lupus Erythematosus (SLE), occurring in 0.9-4.6% of cases. Case reports on the description of presenting symptoms and course of illness of MAS is significant to aid clinicians in prompt disease detection. ***Case report:*** The patient is a 22 year old female who was admitted due to fever of 5 days. Physical examination revealed pallor, diffusedly thinned hair, cervical lympadenopathies and non-pruritic salmon-colored patches on both upper and lower extremities. Initial laboratory work up revealed bicytopenia, hyponatremia, transaminitis, conjugated hyperbilirubinemia and unremarkable urinalysis, chest xray and creatinine levels. During the course of admission, patient developed persistently high fever spikes, shortness of breath, oral ulcers and arthralgias. Further workup showed pancytopenia, pleural effusion on chest xray, positive ANA and a low complement hence meeting the criteria for diagnosis of SLE. Other tests revealed low ESR and fibrinogen level, high CRP, elevated triglyceride, hyperferritinemia and bone marrow aspirate showing hypercellular bone marrow, negative for TB PCR. Patient was given 1 mkd prednisone which then resulted to fever lysis. There was persistent pancytopenia hence steroid dose was increased to pulse IV methylprednisolone 1gm/day for 3 days which resulted to improvement of blood counts. Patient was discharged with hydroxychloroquine and oral corticosteroid. ***Conclusion:*** Patients with MAS often succumb to hematologic complications if not corrected. The key to better disease outcome is primarily early detection and prompt and appropriate immunosuppression.

P2-266

Granulomatosis with polyangiitis presenting as chronic rhinosinusitis in a 37 year old female patient

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Conflict of interest: None

Introduction: Granulomatosis with Polyangiitis (GPA) belongs to the group of antineutrophil cytoplasmic antibody-associated vasculitis (AAVs), commonly describe as fibrinoid necrotizing vasculitis involving small and medium-sized vessels. The prevalence of GPA in the United States is estimated to be 3 cases per 100,000. Due to the rarity of this condition, case reports to describe the presentation and course of this illness are significant. ***Case report:*** The patient is a 37 year old female who started having left maxillary pain and fever of 4 months duration, later associated with vague toothpain, prompting dental consult, eventual tooth extraction and antibiotic treatment without relief of symptoms. Patient then manifested with facial swelling, erythema, anosmia, decreased hearing on the left ear, nasal congestion, left eye pain and depression on the nose bridge. Persistence of symptoms prompted admission where patient was initially managed as Chronic Sinusitis with cholesteatoma formation. Despite mastoidectomy and empiric antimicrobial treatment, patient had persistent fever hence referral to Rheumatology. Physical examination revealed prominence of saddle-nose deformity with mild proptosis of the left eye. Initial laboratory tests revealed leukocytosis, normal urinalysis, elevated ESR an CRP, negative TB PCR and fungal culture of the maxillary tissue revealing *Candida dubliniensis*, negative ANCA and radiologic imaging studies showing subglottic stenosis and pulmonary nodules. Histopathology of the left maxillary tissue showed Chronic Granulomatous Inflammation. Antifungal treatment and prednisone were given. Patient was then discharged, afebrile and improved with oral corticosteroid. ***Conclusion:*** ANCA associated vasculitis involve small and medium sized vessels. Cyclophosphamide with glucocorticoids is considered the "standard of care" as induction therapy for those with generalized disease, continued for 3 to 6 months.

P2-267

Bamboo Nodes: An Unusual Cause Of Dysphonia In A Filipino Patient With Mixed Connective Tissue Disease

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Conflict of interest: None

Background Bamboo node is a rare vocal cord pathology causing dysphonia usually among patients with autoimmune disorders. This "bamboo-joint-like" transverse vocal cord lesion interferes with the vibratory cycle during phonation leading to voice hoarseness. The worldwide prevalence rate of bamboo node is unknown. A review of Schwemmle from 1993- 2009, showed seven cases of bamboo node among patients with Mixed Connective Tissue Disease (MCTD). **Setting** University of the Philippines-Philippine General Hospital (UP-PGH), a tertiary training government hospital and the national referral center in the Philippines. **The Case** A 36-year-old Filipino female developed voice hoarseness one year after she was diagnosed with MCTD. Videostroboscopic findings revealed bilateral bamboo nodes, vibratory defects, and amplitude abnormalities. Treatment with prednisone, methotrexate, hydroxychloroquine, along with voice rest and speech therapy resulted in normalization of amplitude, mucosal wave and vibratory behavior during repeat videostroboscopy. **Significance** To date, this is the first known case of bamboo nodes associated with Mixed Connective Tissue Disease (MCTD) in a Filipino patient. This case highlights the importance of properly investigating the symptom of hoarseness among patients with rheumatologic diseases. A multidisciplinary approach involving the rheumatologist, otorhinolaryngologist, and speech therapist plays an important role in the complete care for this patient.

P2-268

Utility of Positron Emission Tomography (PET) -CT Scan in the Screening of Malignancy-Associated Dermatomyositis: A Case Report and Review of Literature

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Conflict of interest: None

Introduction: Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by proximal muscle weakness, muscle inflammation and characteristic cutaneous manifestations. Among the IIMs, DM is strongly associated with malignancy based on earlier case reports. With the clinical implications of these associations, screening is therefore imperative for patients with DM at the time of diagnosis and at relapse particularly if symptoms fail to respond to conventional immunosuppressive treatment. A previous study by O'Callaghan et al showed that FDG-PET/CT for diagnosing occult malignant disease in patients with myositis was comparable to that of broad conventional screening. In this case report with a review of literature, we aim to establish the utility of PET-CT Scan in the screening of malignancy-associated DM compared to conventional cancer screening. ***Case report:*** This is a case of a 51 year old female who presented with a 2 month history of bilateral proximal muscle weakness with subsequent appearance of Heliotrope rash, Gottron's and Holster signs. CKTotal was elevated at 5,067. The EMG findings were compatible with a myopathic process involving the proximal muscles and affecting both the upper and lower extremities, hence meeting the criteria for DM. She was given pulse Methylprednisolone 125mg -250mg/IV for 3 days with improvement in muscle strength and rashes.Instead of the conventional age-appropriate cancer screening tests, she underwent a whole body PET CT scan which revealed amild diffuse metabolic activity involving the muscles of the upper extremities, chest, abdomen and thighs suggestive of an inflammatory process and compatible with DM. There wasno evident hypermetabolic lesion suggestive of malignant disease. ***Conclusion:*** PET CT scan is one of the most sensitive techniques in the detection of malignant lesions. For patients with DM, it seems to be useful, cost-effective yet comparable to multiple con-

ventional cancer screening tests.

P2-269

Use of tocilizumab in a patient with pyoderma gangrenosum and rheumatoid arthritis: a case report

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Conflict of interest: None

Introduction: Pyoderma gangrenosum (PG) is a rare and painful skin condition characterized by one or more areas of chronic ulceration with well demarcated and undermined borders. We report a patient with severe superficial PG on rheumatoid arthritis (RA), which responded to tocilizumab therapy after failure of high-dose steroid therapy. **Case report:** A 51-year-old woman who was diagnosed with RA 3 years previously at local clinic was referred to our department with ulcerative skin lesion on left lower leg. Multiple biopsies were obtained from the edge of the ulcer to confirm its nature. Histology showed granulation tissue with nonspecific inflammation. On this basis, a diagnosis of PG was made. Treatment with oral corticosteroids (prednisolone 30mg once daily) was started. There was a rapid initial response with marked reduction in the size of the wound and marked relief of pain. However, when the dose of steroid was lowered the wound and the symptoms deteriorated rapidly. A maintenance dose of 20mg once daily was required and this was continued for 3 weeks. Despite this dose, the wound failed to heal and the patient continued to experience pain. Our decision was made to begin treatment of the anti-interleukin (IL) 6 drug - Tocilizumab. Treatment was started at a dose of 162mg subcutaneously biweekly. Simultaneously, the dose of oral prednisone was reduced to 10mg once daily over a period of 4 weeks, after which steroids were stopped completely. Despite complete withdrawal of prednisolone, the ulcer continued to heal. The patient currently remains on tocilizumab with no recurrence of PG with significant improvement of her joint symptoms. **Conclusion:** Our cases represent the first report of the use of tocilizumab for treatment of PG in patients with RA. Treatment with tocilizumab has advantages over TNF agent. We therefore suggest the use of this drug for PG associated with RA resistant to conventional therapies. Further studies are need to confirm this finding.

P2-272

Poncet's disease in tuberculous mastitis, a case report

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Conflict of interest: None

Poncet's disease, named after a French surgeon, Antonin Poncet, is a rare form of polyarthritis occurring in patients with tuberculous infection. It is an immunological reaction to tuberculoprotein wherein CD4+ cells together with bacterial antigens migrate into the joints after infection thus causing symmetric polyarthritis. Patients would clinically present with fever, malaise, polyarthritis of the large joints such as the knees, ankles and wrists. Around 6% of patients with Poncet's disease would have erythema nodosum, which is a tender red nodule or lump that is usually seen on both shins produced by inflammation of fat cells under the skin (panniculitis) spontaneously resolving after 3-6 weeks. It is more often associated with extrapulmonary TB infection than pulmonary TB. The diagnosis is largely clinical and is made by excluding other causes of polyarthirits. We report a case of a 39 year old female newly diagnosed with Tuberculous Mastitis via core biopsy, presenting with acute symmetric polyarthritis and erythema nodosum. Polyarthritis workup was unremarkable and symptoms were not relieved by non- steroidal anti-inflammatory drugs and steroids, but had complete resolution of symptoms after 6 weeks of anti-koch's therapy. To our knowledge, this is the first case report of Poncet's disease associated with Tuberculous mastitis. Poncet's disease is a form of polyarthritis affecting patients with tuberculous infection. It is a diagnosis of exclusion but must be included in differential diagnosis especially in countries/regions where prevalence of M. tuberculosis infection is high. Early initiation of anti-Koch's therapy is the treatment thus in patients with a background or exposure to tuberculosis with polyarthritis refractory to NSAIDs and steroids, a high index of suspicion for Poncet's disease is advantageous.

English Poster Session Basic

P1-258

Immunomodulatory activity of Phyllanthus niruri: An Indian Medicinal plant used to treat Rheumatoid Arthritis

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Conflict of interest: None

Objective: The present study was carried out to study immunomodulatory activity of petroleum ether, chloroform and alcoholic extracts of Phyllanthus niruri in albino mice at the dose levels of 150 and 300 mg/kg orally. Methods: Immunomodulatory activity on specific and non-specific immunity was assessed by carbon clearance test, delayed type hypersensitivity and cyclophosphamide induced myelosuppression methods. Cyclophosphamide (30 mg/kg) was used to induce immunosuppresion in mice and levamisole (50 mg/kg) was used as immunostimulating agent. Results: The results revealed that alcoholic extract showed most significant immunomodulatory activity. In carbon clearance test, alcoholic extract exhibited significantly ($p<0.01$) high phagocytic index against control group, indicating stimulation of the reticulo-endothelial system. It also increased significant ($P<0.01$) delayed-type hypersensitivity response Significant increase in WBC ($p<0.01$) count was seen on administration of both the doses of alcoholic extract. Conclusion: Thus the study demonstrates that Phyllanthus niruri is an important medicinal plant having immunomodulatory activity for treatment of an autoimmune disease, rheumatoid arthritis.

P1-259

Histomorphometric analysis on femoral heads of acute hip joint destruction in six cases with rheumatoid arthritis

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Conflict of interest: None

Purpose: We have often experienced the patients with rheumatoid arthritis (RA) who take acute hip joint destruction (AHD) in the clinical course. The purpose of this study is to analyze the histomorphometric findings of femoral head in RA to clarify the underlying acute destruction mechanisms. **Subjects and Methods:** Seven femoral heads from six cases with RA were collected when we underwent total hip arthroplasty (THA) for affected hip joint. Written informed consent was obtained from each case, in accordance with the ethics committee of Niigata University Medical and Dental Hospital. After femoral head was excised, 1 cm× 2 cm in size of bone sample block was made from central part, and subjected to histomorphometric study. The average age of patients was 71 years old (from 57 to 87). There were one male, and 5 female. These cases were divided into the two groups; AHD or chronic hip joint destruction (CHD) group. AHD was defined as fulfilled the following clinical and radiological criteria:(1) severe hip pain with a history of less than 1 year, (2) severe destruction and collapse of the femoral head within several months or at longest 1 year. Cases without fulfilling this criteria were defined as CHD group. **Results:** The values of osteoid volume and osteoid surface were significantly increased in AHD group compared with CHD group (OV/BV 3.22±1.79% vs. 0.70±0.48%, OS/BS 33.03 ±17.99 vs. 8.26±3.39, $p < 0.05$). The values of trabecular bone volume, trabecular thickness, osteoid thickness and Eroded surface didn't differ between CHD and AHD group (BV/TV 24.8±2.78% vs. 32.80±11.48; Tb. Th 172.4±28.31μm vs. 182.9±44.62 μm; O. Th 6.42±1.10 μm vs. 8.62±1.76 μm; ES/BS 1.98±1.24% vs. 2.87±1.76%). **Conclusions:** In the cases that possesses high values of osteoid in bone histomorphometry in femoral head tend to show the AHD group. We consider the possibility that AHD leads to the vigorous bone formation in the femoral head to endure the weight-bearing.

P1-260

T cell cytokine production in patients with rheumatoid arthritis: *invitro* effect of methotrexate and correlation with disease activity and response

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Conflict of interest: None

Objectives: Methotrexate (MTX) is the most widely used DMARD in rheumatoid arthritis (RA) despite its incompletely understood effects on immune cells. We studied its effect on *invitro* cytokine production by T cells in patients with RA **Methods:** Data on disease variables and blood samples were collected from steroids and DMARDs naïve RA patients. Whole blood cultures with anti-CD3 and anti-CD28 antibodies were done to stimulate T cells. MTX was added to the cultures in doubling dilutions. Culture supernatant was stored after 72 hrs for TNF-α, IFN-γ and IL-10 estimation by ELISA. Variables are expressed as median (IQR) and non-parametric tests were used. **Results:** Fifty seven patients (F:M=41:16) were enrolled. Median Disease Activity Score (DAS28ESR) and HAQ scores were 6.5 (5.8-7.1) and 1 (0.6-1.6) respectively. Unstimulated cultures had undetectable cytokine levels. In stimulated cultures, median TNF-α, IFN-γ and IL-10 levels were 180 (96-412.5), 3300 (1575-8750) and 120 (55.7-220) pg/ml respectively. Cytokine production correlated significantly with each other (TNF-α with IFN-γ $r=0.3, p<0.01$; IL-10 with IFN-γ $r=0.5, p<0.001$). Culturing with MTX suppressed cytokine production. Median MTX concentration that inhibited 50% cytokine production for TNF-α, IFN-γ and IL-10 was 27 (11.4-38), 31.9 (13.8-54.4) and 48.4 (18.8-93.8) ng/ml respectively with significant inter-individual variability. Paradoxically, in 17 of 57 (33%) patients, cytokine production increased at lower MTX concentrations. Baseline IFN-γ production correlated with DAS28ESR and EULAR response ($r=-0.3$ and $-0.4, p<0.05$). Similarly, baseline IL-10 production correlated with DAS28ESR ($r=-0.3, p<0.01$) and EULAR response ($r=-0.3, p<0.05$). **Conclusions**: Higher disease activity is associated with less T cell stimulated cytokine production probably due to pre-activation of T cells in vivo. MTX usually inhibits but may stimulate cytokine production in 33% patients at low dose which may account for its inefficacy at low dose

P1-261

IL-1β Promotes Differentiation of Human Osteoclast-like Cells Induced by a Combination of TNFα and IL-6 from $CD14^+$ Monocytes

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Conflict of interest: None

[Object] Since local bone destruction associated with RA is partially controllable by biological agents targeting TNFα or IL-6, inflammatory cytokines play an important role in the differentiation of bone-resorbing cells. We previously reported that the combination of TNFα and IL-6 induced the differentiation of mouse and human osteoclast-like cells (OLCs) from osteoclast precursors with bone resorption activity *in vitro* and/or *in vivo*. The objective of this study was to analyze the inflammatory cytokine gene expression patterns in human OLCs and conventional osteoclasts induced by RANKL, and to investigate the molecule mechanisms underlying the differentiation of OLCs. **[Methods]** Human $CD14^+$ monocytes were obtained from peripheral blood mononuclear cells in healthy volunteers. $CD14^+$ monocytes were stimulated by the combination of TNFα and IL-6, or RANKL. Expression levels of inflammatory cytokine mRNA and protein were measured by real-time PCR, ELISA, and immunofluorescent staining. **[Results]** Expression levels of IL-1β mRNA were significantly up-regulated in OLCs compared to osteoclasts, whereas other inflammatory cytokines mRNA levels were unchanged. The expression levels of IL-1β protein in OLCs culture supernatants were significantly up-regulated. Immunofluorescent staining photomicrography for IL-1β protein clearly expressed in OLCs. Stimulation with IL-1β on osteoclast precursors and OLCs significantly induced the expression levels of TNFα and IL-6 protein. Stimulation with IL-1β also promoted the

differentiation of OLCs in the presence of a lower concentration of TNFα and IL-6. **[Conclusions**] Our results demonstrate that a combination of the inflammatory cytokines TNFα and IL-6 can induce the expression of IL-1β, which promotes the differentiation of OCLs from $CD14^+$ monocytes. It indicates that inhibition of several combinations of inflammatory cytokines could more efficient in preventing bone destruction on inflammatory arthritis such as RA.

P1-262

MicroRNA-34a: Role in the development of Osteoarthritis during Obesity

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Conflict of interest: None

BACKGROUND: The prevalence of obesity is increasing at an alarming rate and is one of the major risk factors of osteoarthritis (OA). Previous studies in our lab show that mice fed a high-fat diet (HFD) exhibited an accelerated surgically-induced OA phenotype compared to lean diet fed mice. MicroRNAs (miRNA) are endogenous short non-coding RNA segments that are negative regulators of gene expression. Recent studies have shown that miR-34a is elevated in obesity; however, the functional role of elevated miR-34a in obesity is unknown. Despite the strong association between obesity and OA pathogenesis, no studies have examined the role of miR-34a in the development of OA during obesity. We hypothesize that during obesity expression of miR-34a is elevated and contributes to OA pathophysiology. **METHODS:** Mouse blood was collected via saphenous vein at 9 weeks of age (baseline) and at the end of a high-fat or lean diet course. Human plasma was taken at preadmission from end-stage OA patients undergoing total knee replacement (TKR) surgery. Patients with no co-morbidities were segregated according to body mass index (BMI) into normal weight (BMI= 18.5-24.9 kg/m^2) and overweight groups (BMI≥ 25 kg/m^2). **RESULTS:** Mir-34a was detectable in plasma of both human and mice. Plasma miR-34a levels were significantly up-regulated in mice fed a HFD for 18 weeks compared to baseline controls. This up-regulation correlated with percent body fat, body weight, and fasting blood glucose levels. Similarly, human plasma miR-34a levels were up-regulated in overweight end-stage OA patients compared to normal weight end-stage OA patients. **CONCLUSIONS:** Future studies will examine the differential miR-34a expression in joints of HFD mice compared to lean diet mice as well as markers of cell death and dysregulation of chondrocyte metabolism. This study will be the first to elucidate a mechanistic role for miR-34a in the development of OA during obesity and its potential as a therapeutic target.

P1-263

Functional analysis of macrophages in Behçet's disease

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Conflict of interest: None

[Introduction] The recent GWAS and subsequent studies have identified susceptible genes such as *CCR1* and *IL10* genes, suggesting pathological roles of macrophages in Behçet's disease (BD). [Objectives] To compare features of *in vitro* differentiated M1 and M2 macrophages from peripheral blood between BD and healthy controls (HC). [Methods] Differentiation into M1 or M2 macrophages (Mφ) was induced *in vitro* from peripheral monocytes in presence of GM-CSF or M-CSF, respectively. Expressions of CD68, CD163, and CCR1 were determined by realtime PCR and flow cytometric analyses. For the Mφ that were treated with LPS for 24 hours, the supernatants were analyzed for cytokine profiles using beads assay. [Results] Differentiated M1 Mφ produced higher amounts of IL-6 whereas, M2 Mφ secreted higher volume of IL-10. M2 Mφ has increased expression of CD163 protein and mRNA compared to M1 Mφ. CCR1 expression is increased in M2 Mφ compared to M1 Mφ. CCR1 in M1 Mφ showed trend toward higher expression in BD patients. [Conclusion] The data suggest that both susceptible *CCR1* and *IL10* genes are implicated in pathogenesis of BD. Further experiments including functional analyses are required to elucidate mechanisms how M1 or M2 Mφ are involved in pathogenesis of BD.

P1-264

Cyclic phosphatidic asid suppresses fibroblast activity in systemic sclerosis

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Conflict of interest: None

[Objectives] Skin fibrosis is one of the most obvious manifestations in systemic sclerosis (SSc) and is relevant to quality of life and prognosis; however, conventional therapy often fails to control the disease progression. Cyclic phosphatidic acid (cPA) is a naturally occuring lysophospholipid having pleiotropic biological activities such as anti-inflammatory effects. Here, we sought to determine whether cPA has the anti-fibrotic effects on SSc skin fibroblasts *in vitro* using its chemically stable derivative, 2-carba-cPA (2ccPA). **[Methods]** Primary human skin fibroblasts obtained from SSc patients or healthy individuals were incubated with 2ccPA in the presence or absence of TGF-β1. To determine the anti-fibrotic effects of 2ccPA, mRNA and protein levels of fibrotic markers were assessed using qPCR, Western blotting and ELISA. Intracellular cyclic AMP (cAMP) levels were evaluated using a commercially available ELISA kit. [Results] 2ccPA significantly decreased the expression of *COL1A1, COL1A2, CTGF* and *ACTA2* mRNA in SSc skin fibroblasts and healthy skin fibroblasts stimulated by TGF-*β1* in a concentration dependent manner. The protein levels of type I collagen, CTGF and αSMA were also significantly reduced in SSc fibroblasts treated with 2ccPA. In addition, the levels of hepatocyte growth factor (HGF) and prostaglandin E2 (PGE2) were significantly higher in the supernatant of 2ccPA-treated group. 2ccPA increased the intracellular cAMP levels and forscolin (which increases endogenous cAMP levels) similarly suppressed fibroblast activation. An adenylate cyclase (AC) inhibitor dideoxyadenosine antagonized the anti-fibrotic effects of 2ccPA, indicating that 2ccPA directly stimulates AC. [Conclusion] These findings support the hypothesis that 2ccPA attenuated the fibroblast activation in SSc by stimulating AC and therefore increasing intracellular cAMP levels. 2ccPA may be a promising agent for the treatment of skin fibrosis in SSc.

P1-265

Role of CaMK4 in the pathogenesis of rheumatoid arthritis

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Conflict of interest: None

Objectives: Aberrant Calcium/calmodulin-dependent protein kinase IV (CaMK4) activation has been implicated in the development of Th17 driven autoimmune diseases. We have previously reported that the blockage of CaMK4 ameliorates experimental autoimmune encephalomyelitis (EAE) and autoimmunity in lupus-prone mice. However the roles of CaMK4 activation in CD4+ T cells in the development and the pathogenesis of rheumatoid arthritis (RA) remain to be elucidated. Methods: To determine the role of CaMK4 in the development of RA, we examined the gene expression of *Camk4* in CD4+ T cells from healthy controls (HC: n=20) and patients with bio-naive active RA (n=21; median of DAS-

ESR:5.14). We evaluated the correlation among CaMK4 expression, disease activity, PDUS score and memory T helper (Th) subsets including (Th1, Th2, Th17, regulatory T cells; Treg and follicular helper T cells; Tfh) in the peripheral blood from RA patients. Results: The expression of *Camk4* mRNA in CD4+ T cells displayed significantly higher in RA patients than HC. Of note, the percentage of memory Th17 cells (CD4+CD45RA-CCR6+CXCR3-) was significantly positively correlated with *Camk4* mRNA expression in CD4+ T cells. Conclusion: Our results indicate that CaMK4 expression associates with RA development and its inhibition represents a novel therapeutic strategy for the treatment of RA.

Luncheon Seminar

LS1

Rheumatoid arthritis and bone

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Conflict of interest: None

In the pathogenesis of RA, two phases have been recognised:(1) an autoimmune phase, induced by environmental factors such as smoking, acting in a certain genetic background that imparts susceptibility. During this autoimmune phase, patients may develop rheumatoid factor and anti-citrullinated protein antibodies (ACPA) over 10 years before the clinical manifestations of the disease. (2) an inflammatory phase, possibly induced by an infection or other environmental triggers, which leads to a chronic inflammatory state, which can ultimately affect multiple organs, including the bone. There are many examples of an increased fracture, including vertebral and non-vertebral and, hip. Bone structure alterations, including reduced bone volume and bone mineral density (BMD), cortical bone thickness and increased fenestration have been seen in ACPA positive non-arthritic individuals compared to ACPA-negative controls. ACPAs isolated from sera of patients with RA have been shown to induce osteoclastogenesis and bone resorption in vitro. The synovial inflammation induces bone loss triggering an imbalance between bone resorption and formation. The synovial inflammatory tissue instruct T cells to produce M-CSF and RANKL which induce osteoclastogenesis. Moreover, use of glucocorticoid induced severe osteoporosis. RANKL is highly expressed in the synovial membrane of patients with RA leading to osteoclast differentiation and activation. Treatment with denosumab, a human RANKL monoclonal antibody, increases lumbar spine BMD and reduces vertebral and non-vertebral fracture rates in postmenopausal women with osteoporosis, but also protects patients with RA from bone erosions, by arresting osteoclast formation and activation. Nevertheless denosumab does not have an effect on inflammation and its use would need to be combined with an anti-inflammatory strategy. The management and treatment of glucocorticoid-induced osteoporosis have to be done according to the guidelines.

LS2-1

Systemic lupus erythematosus and pregnancy morbidity

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Conflict of interest: Yes

A number of immunosuppressants have been used for the treatment of systemic lupus erythematosus in daily practice, and they contribute to improve the prognosis of the affected patients. Among them, azatioprim and cyclophosphamide are conventional drugs with some evidence. Nowadays two recommendations for the management of lupus nephritis were published; one from ACR and the other from EULAR/ERA-EDTA. Both are evidence-based and practical for the daily practice. In those guideline, Mycophenolate mofetil (MMF) is described for the treatment. Apart from those recommendations, tacrolimus has been proven usuful as well in Japanese patients. Lupus and antiphospholipid syndrome are two major causes of pregnancy morbidity. Lupus flare during pregnancy should be managed under a collaboration between rheumatologists and obstetricians. In addition, MMF is well recognised by its teratogenicity. In this seminar, those issues will be discussed and the better management will be explored in the evidence based fashion in the next future.

LS2-2

Lupus pregnancy

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Conflict of interest: None

Systemic lupus erythematosus (SLE) is a chronic and complex autoimmune inflammatory disease of unknown cause, but linked to genetic, environmental, and hormonal factors. The main basis of SLE is the hyperactivity of the innate and adaptive immune response, including T and B cell abnormalities, and overproduction of cytokines and autoantibodies. The clinical course is characterized by relapse and remission with involvement of a variety of organ damages. Lupus nephritis (LN) occurs in about 50% of SLE patients, and SLE patients with LN have a poor prognosis. Mortality due to renal failure in SLE patients is currently diminished by the contribution of progresses in immunosuppressive and renal replacement therapy, such as hemodialysis, although a large contribution to mortality in SLE patients was renal failure in the past. However, SLE patients are still suffering from renal failure in severe cases. Thus, there is still a considerable unmet therapeutic need in SLE. Controlling disease activity of SLE is an important challenge, and this is particularly so in relation to pregnancies in SLE patients, because SLE mostly occurs in women of childbearing age. Pregnancies in SLE patients result in higher rates of spontaneous abortions, intrauterine fetal deaths, preeclampsia, intrauterine growth restriction, preterm birth, and low birth-weight infants than in healthy women. Thus, particular care must be taken regarding the treatment with glucocorticoids and immunosuppressive agents in terms of safety and toxicity during pregnancy. Several recommendations for SLE have been published using an evidence-based approach and expert opinion in order to standardize and develop better approaches to managing SLE, including LN. This will be discussed in detail in this seminar.

LS3

Control of the infection in the treatment of rheumatoid arthritis

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Conflict of interest: Yes

The use of antibody preparation, in particular biological preparation used for the immune inflammatory diseases such as rheumatoid arthritis (RA), has been increased, and it occupies the top four in sales rank on the global pharmaceutical market in 2013. However, complications of infections as adverse events are increasing. In this seminar, the countermeasure for these infection risks will be discussed focusing on tuberculosis and non-tuberculosis mycobacterial disease (NTM disease) and pneumocystis pneumonia (PCP). In 2014, the numbers of people suffered from tuberculosis in Japan went down to 20000 for the first time, but along with the aging of the patients, the number of patients with various kinds of underlying disease/complications due to endogenous reheat is increased. It becomes latent tuberculosis infection (LTBI) after the infection at an early age, and not only the immunodeficiency and a variety of underlying disease/complications associated with aging, but also immunosuppressive therapies against them develop tuberculosis. Most medicines used for immunosuppressive therapies are biological preparation, and fatal cases are founded due to the use of them. In 2014, the Japanese Respiratory Society published “Practical Guideline for Biological Preparation and Respiratory Disease.” Close cooperation of each department is necessary, and also, in the case of LTBI, prophylactic administration of anti-tuberculosis drugs is very important. For NTM disease, administration of biological preparation has been relative contraindicated. In 2014, a guideline showing that *Mycobacterium avium* compex (MAC) shedding patient is capable of administration under certain conditions has been proposed from Respiratory Society, Tuberculosis Disease Society, Infectious Diseases Society and the College of Rheumatology. It is because of the fact that the fatal case at the time of administration of biological preparation has not been reported.

LS4

The role of interferon gamma release assay for the diagnosis of Latent Tuberculosis Infection in immunocompromised host

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Conflict of interest: None

Latent tuberculosis infection (LTBI) World health organization defined Latent tuberculosis infection (LTBI) as follows, “Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB.” The lifetime risk of reactivation for a person with documented LTBI is estimated to be 5-10%, with the majority developing TB disease within the first five years after initial infection. However, the risk is considerably higher in the presence of predisposing factors. (http://www.who.int/tb/challenges/ltbi/en/) Interferon gamma release assay Interferon-Gamma Release Assays (IGRAs) (QuantiFERON® TB Gold:QFT and Tspot®.TB:TSPOT) are currently available for the diagnosis of LTBI. We conducted a prospective study for comparing two IGRAs for LTBI in rheumatoid arthritis patients. The result was as follows, the percentages of positive and indeterminate in QFT were higher than in TSPOT. QFT positive was associated with age and chest X-ray of suspected TB, reflecting the TB risk factors in Japan. The risk of developing active tuberculosis (TB) The risk of developing active TB has been analyzed. (Landry J, Menzies D. IJTLD. 2008;12:1352) AIDS and HIV infection was very high risk, and relative risk (RR) was 110-170, and 50-110, respectively. Diabetes mellitus, hemodialysis and steroid therapy had been known as a kind of compromised host, and its RR is 2.0-3.6, 10-25, and 4.9, respectively. The RR of TNFαblocker, biological agents, was estimated to be1.5-4. The role of IGRAs The Japanese Society for Tuberculosis published two guideline associated with LTBI and IGRA. One is “Treatment Guidelines for Latent Tuberculosis Infection” in 2014 and the other is “GUIDELINES FOR USING QuantiFERON® TB Gold In-Tube” in 2013, and revised in 2014 after TSPOT was available in JAPAN. The role of IGRAs was described in both guidelines for practical use. There is not “Gold standard for the diagnosis of LTBI”, however we can use many evidences associated with LTBI and IGRA. Especially, Sensitivity, specificity, positive predictive value and negative predictive value are very useful information. There are many difficulties for the estimation of compromised host. The physician for compromised host need to understand the characteristics of IGRAs, and make final diagnosis.

LS5-1

Autoinflammatory diseases in non-pediatric rheumatology

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Conflict of interest: None

Unexplained bouts of fever with a certain frequency and constellation of manifestations fall under the term ”recurrent” or ”periodic fever syndrome” when immunodeficiency or organ malformations ca n be excluded. The term “autoinflammatory” appeared in the pages of Cell in the spring of 1999 to denote an emerging family of clinical disorders characterized by episodes of seemingly unprovoked inflammation without high-titer autoantibodies or antigen specific T lymphocytes. The hereditary periodic syndromes were the first illnesses to be classified as autoinflammatory diseases, which are mainly caused by the overproduction of cytokines due to disorders of the innate immune system. As the majority of the cases were observed during childhood, they were treated as the “Sickness for Pediatricians”. However, there are cases where each of the syndromes emerged during adulthood. According to Italy’s report, the breakdown of cases of autoinflammatory diseases for age 18 and above are: Familial Mediterranean Fever 39%, Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) 36%, Cryopyrin-Associated Periodic Syndromes (CAPS) 22%. On the premise that infections, malignancy, and autoimmune disorders are excluded, you should confirm the correspondence of the characteristic symptoms for each diseases, and gene analysis should be applied. For late diagnosis or untreated cases, the complication of amyloidosis and function disorders caused by lesions will be the point at issue. Furthermore, due to the change in the medical subsidy system in 2015, the three diseases mentioned above has been newly approved. Therefore, I believe there will be more opportunities to take part in the new diagnosis for adult onsets. Here, I would like to present several cases focusing on the three diseases and explain about differential diagnosis and the features the diseases.

LS5-2

Diagnostic and therapeutic points for autoinflammatory syndrome

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Conflict of interest: None

Autoinflammatory syndrome is a syndrome that causes systemic inflammation. Main symptom is fever, accompanied by inflammation of the site, such as joint, skin, intestine, eye, and bone. As symptom is similar to that of infectious diseases and collagen diseases; however, pathogenic microorganisms cannot be identified, and autoantibodies or antigen specific T cells is also not detected. Recently, it is known that there are many patients with autoinflammatory syndrome in Japan, and has been fairly recognized to clinicians. Diagnosis of autoinflammatory syndromes is performed mainly by clinical symptoms and genetic testing. In particular, the hereditary periodic fever syndrome, the disease genetic mutation is important for diagnosis. It is desirable that it is used the Japanese genetic diagnosis guidelines and flowchart ("autoinflammatory disease site" http://aid.kazusa.or.jp/2013/) as a reference. Treatments of autoinflammatory syndromes are different for each syndrome. In FMF, colchicine is the first drug of choice. If colchicine is not effective or unable to use for side effects, such as diarrhea, biologics are administered in FMF patients. In CAPS, Canakinumab (anti-IL-1 drugs) is remarkably effective; it is first drug of choice. In TRAPS, Blau/EOS, PAPA syndrome, non-steroidal anti-inflammatory drug (NSAID) and steroids is the first drug of choice. Effect of anti-IL-1 drugs have been reported in a number of autoinflammatory syndromes. In this meeting, I focus the diagnostic and therapeutic points for autoinflammatory syndrome.

LS6

Tacrolimus in the treatment of interstitial pneumonitis associated with polymyositis and dermatomyositis

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Conflict of interest: Yes

The guideline for treatment of polymyositis and dermatomyositis (PM/DM) has been established by research group for PM/DM in Dr. Sumida's research team, which is founded by the Ministry of Health, Labour and Welfare, Japan. Treatment options depend on the involved organs. If the skin is the only organ involved, local treatment is recommended. If the patients have rapidly progressive interstitial pneumonitis, high dose glucocorticoids (GC) together with immunosuppressants such as calcineurin inhibitors and cyclophosphamide (CPA) should be started immediately. Since immunosuppressants that were initiated more than two weeks after GC initiation exerted poor therapeutic effects, we should not wait for the effect of GC before starting immunosuppressants. We performed physician-led clinical trial of tacrolimus for treating rapidly progressive interstitial pneumonitis associated with PM/DM. Of note, the approved dose is different from those in rheumatoid arthritis and lupus nephritis. The same treatment should be initiated for the patients who have poor prognostic markers of pneumonitis, which are low muscle involvement, positive anti-MDA-5 autoantibody, and high serum ferritin. Although the patients who do not respond to GC and tacrolimus are often treated with additional CPA, the effects of CPA addition are unclear. Tacrolimus is surely effective for skin and muscle involvement, implying that T cell hyperactivity is involved in all aspects of PM/DM. The myositis can be treated not only with high-dose GC but also with intermediate dose of GC together with immunosuppressants. However, in use of calcineurin inhibitors like tacrolimus, nephrotoxicity should be monitored carefully to avoid irreversible renal damage. The proper use of tacrolimus as well as the treatment guideline should be published from Japan, which is the motherland of tacrolimus.

LS7

Reactivation of hepatitis B virus in patients with rheumatic diseases

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Conflict of interest: Yes

Hepatitis B virus (HBV) prevails in Japan: more than 20% of the Japanese population have previously resolved infection. Amplification of HBV is usually inhibited by immune system in vivo in individuals with previously resolved infection, but they have increased risk for developing liver injuries (i.e., *de novo* hepatitis B) because of HBV reactivation during and after immunosuppressive therapies or antineoplastic chemotherapies. In recent years, risk for reactivation of HBV and *de novo* hepatitis B in patients with rheumatic diseases has come under the spotlight with the accumulation of cases with HBV reactivation in RA patients given biologics. The MHLW study group implemented two cohort studies. Cohort #1 invited 289 patients with previously resolved HBV infection who newly start immunosuppressive therapy from specialists with rheumatology, nephrology, oncology and hematology. Cohort #2 included 289 patients (200 with RA, 28 with skin diseases, 28 with bowel diseases, and 17 with ophthalmic diseases) with previously resolved HBV infection who newly started or were receiving immunosuppressive therapy. Accumulated rates of HBV reactivation defined by HBV-DNA >1.3 log IU/ml in patients from rheumatology or nephrology specialists in cohort #1 at 3, 6, 12, 24, 36, and 48 months were 3.2, 3.2, 3.2, 3.2, 4.2, and 4.2%, respectively. Accumulated rates of HBV reactivation by the same definition in patients from rheumatology or nephrology specialists in cohort #1 and all patients in cohort #2 at 3, 6, 12, 24, 36, and 48 months were 1.0, 1.0, 1.0, 1.5, 2.5, and 2.5%, respectively. As the number of immunosuppressive drugs and biologics used for patients with rheumatic diseases are on the increase, risk for reactivation of HBV in these patients may change further down the road. Current status and perspectives on this issue will be discussed in this seminar.

LS8

A novel potent therapy for the treatment of CTD-PAH

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Conflict of interest: Yes

Connective tissue disease-associated pulmonary hypertension (CTD-PH) is an intractable disease although many kinds of vasodilation drugs have been established. Due to improving the prognosis of CTD-PH, it is very important to detect an early phase of PH using an adequate screening method. In patients with CTD, the diseases that frequently are complicated with PH are systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and systemic lupus erythematosus (SLE). In MCTD and SLE, it would not be necessary to regularly examine the PH screening if patients were checked for the screening of PH once at their onset. However, in SSc, we recommend PH screening was repeatedly performed every year. The big difference of SLE- and MCTD-PH versus SSc-PH is a progressive speed of PH, especially PAH. Riociguat is a soluble guanyl cyclase stimulator that can exert a strong effect of vasodilation for pulmonary artery as well as systemic artery. Immunosuppressants can respond to PH associated with MCTD and SLE. In contrast, the pathophysiology of SSc-PH is very complicated and immunosuppressants are invalid. In SSc-PH, it is very important for us to initially discriminate a proper group of SSc patient from 5 WHO groups of PH. If PH of SSc patients was categorized to PAH (group 1), upfront therapy using endothelin receptor antagonist and cGMP-enhancing drugs could be recommended. In cGMP-enhancing drugs, PDE5 inhibitors were frequently used so far. However, riociguat has been approved in 2015 and we can use it for the treatment of PAH in SSc. Riociguat does not has only a vasocilation effect but may also have an anti-fibrotic effect, suggesting that it is suitable for the treatment of SSc-PH.

LS9

Precision Medicine in the Treatment of Rheumatoid Arthritis

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Conflict of interest: Yes

More than 10 years have passed since infliximab (IFX) was ap-

proved as the first bDMARDs for the treatment of rheumatoid arthritis (RA) in Japan. In the past decade, the level of treatment satisfaction with RA has improved dramatically. The wide availability of bDMARDs provides rheumatologists with more options and patients with a greater opportunity. Three classes of bDMARDs are available for RA: TNFα inhibitors and IL-6 receptor inhibitor, and T-cell costimulation inhibitor. These agents differ not only in their MOA but also in their administration route and potential for dose adjustment. However, previous clinical studies have shown no major differences between bDMARDs in the rate of clinical remission in patients who had inadequate response to methotrexate (MTX) (approx. 30-40%). The ACR 2015 guideline outline positioning of bDMARDs, however, the Japanese evidence-based positioning of bDMARDs is still not clear. Individual variations in patient background mean that the outcomes with a "one-size-fits-all" treatment can be unsatisfactory, and not lead to an ideal clinical response. Rheumatologists must therefore consider factors which underpin the pathophysiological condition of each patient and implement a more elaborate treatment strategy-Precision Medicine-based on the characteristics of each bDMARDs. In the RISING study, we evaluated disease activity and trough serum concentrations of IFX, and confirmed that EULAR responses improved with an increase in the trough serum concentration of IFX. In addition, we also found that EULAR responses significantly improved when the dose was increased among patients in whom baseline plasma TNFα concentrations were high. The next step in refining the treatment strategy of "Precision Medicine" is to explore factors that can influence the concentration of TNF-α. In this seminar, I will discuss further potential uses of Precision Medicine, based on the latest findings and reports.

LS10

Management of rheumatoid arthritis in "Bio Era" - Beyond the relief of inflammation

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Conflict of interest: None

Recent advances in the medications of rheumatoid arthritis (RA) have delivered not only the relief of clinical symptoms as joint pain and swelling caused by inflammation, but also avoidance or reservation of joint destruction. Also, presumably due to improvement of bone metabolism, such radiographic findings as bony erosion and ankylosis seem decreasing, but those often recognized in osteoarthritis (OA) as subchondral sclerosis and osteophyte are increasing. As a result, the number of joint surgeries exhibits declining tendency not only in synovectomies but also in total joint replacements. There is also a tendency that surgeries are performed in elderly patients after long duration. Fragile bone is more or less damaged during joint surgeries of RA. Since subchondral bone is often firm after modern medications, however, intra-operative special care should not always be taken as it was before. Also, such cases that surgeons should beforehand prepare specialized implant or augmentation materials for bone defect tend to decrease today. Overall, it can be said that surgeons can now operate RA joints almost in the same manner and attitude as they operate OA joints. Moreover, it has been reported that even OA like findings could be avoided, when biologics are introduced before the appearance of any joint deformities. On the other hand, disease activity of RA is measured in many ways in which patients' self-evaluation including subjective, often resulting in the failure in achievement of treatment goals. As aforementioned, today joint deformities can be avoided or reserved by proper medications, but there are still many patients with persisting pain, urging us to consider the pain beyond the relief of inflammation. These pain sometimes include neuropathic pain, in which the efficacy of NSAIDs are limited, and are often modified by psychosocial factors, suggesting that physicians should make efforts in total management of RA, including patient education and rehabilitation.

LS11-1

Swiching of biologics in the treatment of rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease mainly affecting the synovial membrane of joints and is characterized by lymphocyte activation, synovial proliferation, and bone/cartilage destruction. In 2010, ACR/EULAR proposed rheumatoid arthritis classification criteria to classify patients with progressive arthritis and introduce methotrexate-based therapy in early stage disease. With early therapeutic intervention using biologics, RA treatment with clinical, structural, and functional remission has become a reality. So far now, three different kinds of mode of action of biologics are available in japan. Thus we can choose one among five TNF inhibitors including infliximab, etanercept, adalimumab, golimumab, certolizumab pegol and anti-IL6 receptor antibody; tocilizumab and abatacept; an inhibitor of T-cell activation. In terms of efficacy of these agents to biologics naïve RA patients, it has been shown there is no difference among 8 biologics in the recent report. However, the evidence is based on the clinical trials and it is a very important issue how to select biologics in daily clinical practice. The factors should be considered regarding choice of biologics are mechanism of action, pharmaceutical properties such as structure, half life time, tolerance to MTX, safety, methods of administration, the possibility of treatment holiday after achieving clinical remission, medical economics and so on. Among these factors, immunogenicity is an important factor which restrict the second failure due to development of anti-drug antibody and the possibility of withdrawal of MTX without lack of effecasy. In the lecture, I will report the clinical results of eight biologics in Japanese PMS data together with the latest overseas findings and discuss where each biologics fits into RA treatment based on its pharmaceutical proper.Continue reading below...

LS11-2

Are TNF inhibitors different from non-TNF inhibitors as second biologics?

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Conflict of interest: Yes

Multiple large cohort studies with outcomes of patients with rheumatoid arthritis (RA) treated with biologics have been conducted. There are some data on discontinuation rates of biologics over the long-term, where patients were not selected based on randomized controlled trial eligibility criteria. However, most of the studies focused on the rates of the three earliest tumor necrosis factor inhibitors (TNFi) as first or second biologics. Recently eight biologics including three non-TNF inhibitors are available for the treatment of RA in Japan. The most important question that remains for us is whether there are differences in the discontinuation rate of TNFi compared to agents with other mode of action and whether the difference is the same when they are used for first versus second line. Recent some analyses reported a higher discontinuation rate of TNFi as a second line. On the other hand, the report based on the large cohort in the USA revealed that discontinuation rates were lower in patients using TNFi as first biologics, but tehere were no significant differences for second biologics adjusted using propensity score analyses, and all rates increased after the time when the number of biologics available increased. Furthermore, they reported that predictors of discontinuation of the first biologics were smoking, higher comorbidity index, worse overall health and not using concomitant methotrexate. Those results suggested that we should not regret an effort to continue biologics for a long time regardless of the mode of action of biologics. In this talk, the speaker will set up the argument by comparison of past reports.

LS12

Treatment strategies for early rheumatoid arthritis with anti-TNF agents

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Conflict of interest: Yes

According the 2014-JCR-guideline, MTX should be considered as the first DMARD right after the diagnosis of RA. If MTX is not applicable, other synthetic DMARD may be used for the treatment of early RA.

Biologic agents (BIO) should be the second-line therapy for non-responders to the first synthetic DMARD therapy. However, 2013-EULAR-recommendation says that the term "synthetic" before DMARDs was omitted, and it just emphasizes to treat it appropriately as soon as a diagnosis is presumed. That may mean treatment strategies for early RA include not only synthetic DMARD but other options such as MTX plus BIO. Actually, many clinical trials for early RA have demonstrated that combination of MTX plus BIO is more effective than MTX alone and has similar safety profiles. The C-OPERA trial in Japan, one of these studies, have also demonstrated that adding certolizumab pegol (CZP) on intensive MTX therapy was more effective than intensive MTX alone. CZP is a unique BIO in that polyethylene glycol is conjugated to Fab fragment of humanized anti-TNF alpha antibody molecule. This enables rapid increase of serum concentration after subcutaneous injection leading to rapid clinical response in addition to the loading method. So CZP may be one of the most appropriate DMARD for active early RA. However, the newest 2015-ACR-guideline recommends synthetic DMARD (mainly MTX) monotherapy as the first-line DMARD for the treatment of early RA and BIO should be the second-line. This may be based on the several trials such as TEAR tiral (Moreland LW, et al. Arthritis Rheum 2012) and the socio-economical perspective. In fact, intensive MTX mono-therapy in the C-OPERA trial demonstrated both clinical and radiographical efficacy. But there were still some patients who did not response well to intensive MTX therapy and should have been treated with BIO as the first-line therapy. We have to try to make sure which early RA patients may need BIO as the first-line DMARD.

LS13

Risk factors in rheumatoid arthritis: What is the role of biologic agents in patients with poor prognosis?

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Conflict of interest: None

In the last years, the etiopathogenesis of rheumatoid arthritis (RA) is starting to be better understood. RA is believed to result from a multi-step process, whereby in genetically susceptible individuals, environmental factors induce specific post-translational modifications, which in turn initiate a pathologic activation of the immune system that eventually leads to the clinical onset of the disease 1. Several environmental risk factors of the disease have been identified: Apart from established risk factors of RA, such as smoking, other airborne environmental factors have been recently recognized, such as air pollution or occupational pollutants (silica or textile dusts). Further, nutritional habits, obesity or chronic periodontal infections have also been associated with the development of the disease,2-4 but these findings still needs confirmation. Whether these risk factors may also constitute prognostic factors for more severe forms of RA has been less studied. We will review the evidence for environmental factors, such as smoking, alcohol consumption or obesity, as prognostic tools to identify patients less likely to respond to therapy. We will further examine other conventional prognostic factors of poor prognosis, such as seropositivity to rheumatoid factor or anti-CCP antibodies and elevated disease activity. We will show evidence for the effectiveness of biologic antirheumatic therapies in poor prognosis RA patients. REFERENCES: 1. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38-46. 2. Hart JE, Laden F, Puett RC, Costenbader KH, Karlson EW. Exposure to traffic pollution and increased risk of rheumatoid arthritis. Environ Health Perspect 2009;117:1065-9. 3. Lu B, Solomon DH, Costenbader KH, Keenan BT, Chibnik LB, Karlson EW. Alcohol consumption and markers of inflammation in women with preclinical rheumatoid arthritis. Arthritis Rheum 2010;62:3554-9. 4. Kallberg H, Jacobsen S, Bengtsson C, et al. Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case-control studies. Ann Rheum Dis 2009;68:222-7.

LS14

Impact of anti-drug antibodies on biologic treatment success in rheumatoid arthritis

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Conflict of interest: Yes

Treatment strategy of rheumatoid arthritis (RA) has evolved remarkably in the past 13 years. Updated recommendations for achieving optimal therapeutic outcomes in RA include clinical remission as the primary target for treatment, and frequent adjustment of drug therapy is required until completion of the desired treatment target. Introduction of biologics has contributed significantly to this progress. In clinical setting, it is important to sustain clinical remission for a long period to halt progression of joint damage and impaired activity of daily living. The most frequent cause of attenuation of efficacy during biologic treatment is production of anti-drug antibodies, which recognize complementarity-determining region, mouse-derived portion, or neo-epitopes produced by fusion with unrelated proteins. Anti-drug antibodies are capable of reducing efficacy of biologics, by competitively binding to antigen-recognition site and/or by facilitating clearance of biologics. In addition, immune complexes formed by biologics and anti-drug antibodies often induce skin and systemic immune reaction. Factors affecting production of anti-drug antibodies include disease activity; genetic predisposition; history of anti-drug antibody production; molecular structure of biologics; dosage, interval, and route of biologic administration; and concomitant use of immunosuppressants such as methotrexate. Multidisciplinary approach considering these factors are essential to achieve long-term remission in RA patients.

LS15

Diagnosis and Treatment of Pulmonary Hypertension Associated with Connective Tissue Disease

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Conflict of interest: Yes

Prognosis of pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH) is poorer than other causes of PAH and 5-year survival rate in patients with CTD-PAH is approximately 40%. On the other hand, patients with CTD-PAH are able to be detected early by programmed screening unlike patients with idiopathic PAH (IPAH) usually diagnosed in advanced stage and early detection may lead to improvement of prognosis. In the treatment of CTD-PAH, it is important to assess the indication of immnosuppressive therapy precisely. PAH associated with systemic lupus erythematosus and mix connective tissue disease can expect to respond to immnosuppressive therapy. PAH with Sjogren's syndrome (SS-PAH) also well respond to immnosuppressive therapy. However, some patients with SS-PAH, particularly with primary SS, might be misdiagnosed as IPAH because some patients with primary SS don't show distinctive symptoms of SS. SS-PAH should be considered the differential diagnosis of PAH. On the other hand, PAH associated with scleroderma (SSc-PAH) is not considered an indication for immnosuppressive therapy. Patients with SSc-PAH is usually treated with PAH specific agents as patients with IPAH. Recently, upfront combination therapy is efficacious for the treatment PAH. However, the causes of pulmonary hypertension (PH) associated with scleroderma are not only PAH, but also pulmonary veno-occlusive disease (PVOD) and PH associated with left heart disease (PVH). Recent report revealed that some patients with PVH showed normal pulmonary capillary wedge pressure and were diagnosed as PVH only after measurement of left ventricular end-diastolic pressure or fluid challenge. The correct differential diagnosis is important for patients with PH associated with scleroderma because easy introduction of PAH specific agents to patients with PVOD or PVH may result in clinical deterioration. In this seminar, we will discuss overarching points of diagnosis and treatment of CTD-PAH.

LS16

Treatment of osteoporosis

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Conflict of interest: Yes

Japan is one of the most aging countries in the world, and the proportion of people aged over 65 years old in the total population is highest in the world. By 2030, one in every three people will be over 65 years old and one in five people over 75. The aging of the society results in the increase in the number of osteoporosis patients, and more than 12 million osteoporosis patients exist in Japan. For aged people, to maintain mobility is critical for keeping independence, and osteoporotic fractures such as vertebral fractures and hip fractures are major causes of disability, morbidity and mortality in older people. The treatment of osteoporosis by anti-resorptive agents such as second and third generation bisphosphonates and denosumab successfully reduces the osteoporotic fractures. However, the fracture prevention using these agents is not sufficient and several adverse events have been recognized.

LS17

Immunosuppressive therapy and early diagnosis of CTD-PAH — Evidence review and our approach

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Conflict of interest: None

Connective tissue disease (CTD)-associated pulmonary hypertension (PH) is a category mainly consisted of pulmonary arterial hypertension (PAH, group 1) due to vascular lesions of CTD, along with other PH groups such as lung lesions (group 3), heart lesions (group 2), and venous lesions complicated with CTD. CTD-PAH is divided into systemic sclerosis (SSc)-associated PAH and non-SSc-assocaited PAH. Non-SSc-PAH tends to emerge acutely with activity of underlying diseases so that it requires intensive immunosuppressive therapy (IIT) besides pulmonary vasodilators. SSc-PAH tends to emerge silently so that it requires early diagnosis and intervention with pulmonary vasodilators. I will review the evidence of IIT in the treatment of non-SSc-PAH and present our 3 patients with SLE-PAH treated with glucocorticoids (GCs). Sanchez et al. treated SLE/MCTD-PAH and SSc-PAH patients with only IIT without pulmonary vasodilators, and the response rates were 38% and 0%, respectively. As to the efficacy of IVCY in the treatment of non-SSc-PAH, several studies support the predominance of GC+IVCY combination to GC monotherapy. Next, I will introduce our approach to early diagnosis of SSc-PH. We performed right heart catheterization (RHC) in 26 SSc patients who were suspected of having PH, and proved 12 of them had PH. From known predictive factors of PH, we picked 1) diameter of rtPA in X-ray, 2) diameter of PA trunk in CT, 3) plasma BNP level, 4) %DLCO, and 5) TR-PG in echocardiography. In the 26 SSc patients, the correlation coefficients (R^2) of the 5 factors with mean PA pressure in RHC were 0.22, 0.38, 0.33, 0.41, and 0.56, respectively, showing TR-PG correlates most strongly. If the cases were stratified by more or less than 40 mmHg of TR-PG, sensitivity was 91% and specificity was 83% in prediction of PH. Collaboration of specialists such as cardiologists and rheumatologists is important in the treatment of CTD-PH.

LS18

Role of oral conventional synthetic DMARDs in T2T strategies

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Conflict of interest: None

It is broadly understood that if remission cannot be achieved with methotrexate (MTX), introduction of biologic therapy should be considered for RA patients, and can result in significantly better clinical and radiographic outcomes compared to routine care. However, biologic therapy continues to involve substantial barriers preventing all patients from receiving these benefits, including high costs, co-morbidity (ie, interstitial lung disease, renal and liver dysfunction, advanced age), adverse drug reactions including infection, and incomplete safety data in long-term administration. Outside of Japan, several comparisons between non-biologics and biologics in patients with early RA have been reported in recent years; in the US (TEAR Study/RACATStudy) and Sweden (Swefot trial), multi-center controlled clinical trials comparing triple drug therapy (MTX plus salazosulfapyridine (SASP) plus hydroxychloroquine) and biologics have been conducted, showing equivalent disease activity outcomes in both groups. However, a substantial number of patients do not tolerate methotrexate or biologics, in which case an alternative DMARDs should be given. Iguratimod (IGR) is a small-molecule anti-rheumatic drug with unique mechanisms of action, and has been suggested to be a clinically useful DMARD for which ACR20 rate was non-inferior compared to SASP in Japanese patients with active RA. Another study suggested that the combination of MTX and IGR may have synergic efficacy for RA treatment. Furthermore, according to the recently published APLAR RA treatment recommendations, IGR was listed as an alternative DMARD and first line therapy in patients who do not tolerate or are contraindicated to use MTX. In treatment of RA, especially in the elderly or those with co-morbidity, therapeutic strategies of how to set the treatment target should be determined through shared decision-making between physician and patient after considering disease activity and clinical characteristics (presence or absence of complications). I will present a clinical significance of oral DMARDs, including IGR in treatment of RA, in light of trends in current treatment in both Japan and overseas.

LS19-1

The evaluation of recent disease control, and future surgical therapy for rheumatoid knees and hips

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Conflict of interest: None

The orthopaedic surgeries for rheumatoid arthritis (RA) are performed for pain relief, restoration of joint destruction, functional recovery, and improvement of quality of life. MTX and other DMARDs come to be used widely for RA in Japan for approximately 15 years, additionally, the uses of the biologics are on the increase. As benefits of these changes of medication, the case which indicates the thinning of cortical bone, decreased bone mineral density at medullary bone, significant abnormality of joint alignment, and the giant geode or bone defect are remarkably decreasing. With the recent changes of joint destruction, there are many reports for the change of the number of the surgery of RA. In TKA, increased cases of relatively low inflammatory joints with spur formation were observed. On the other hand, the cases of severe destruction with high levels of inflammation are decreasing. In THA, we also found that the cases which indicate the thinning of cortical bone, or decreased bone mineral density at medullary bone, are decreasing. These changes may lead to differences of surgical technique that may influence the postoperative results and complication rates. Whereas most of patients for RA surgery still have multiple organ complications with relatively long-term duration of disease. These cases are usually inhibited their immune system by updated medical treatment. It is very important to confirm the condition of each patient and we notice small abnormality and prevent complications. In this session, the reported change of the number of the surgery for RA and the recent changes of TKA and THA cases will be discussed. Then the expected changes of surgical procedure, preoperative preparations, and the actual methods of prevention of perioperative complication in "the biologics era" will be debated.

LS19-2

Orthopedic surgical intervention aiming at improved QOL and mental remission

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Conflict of interest: None

With the use of methotrexate and bDMARD or a recently appeared tsDMARD, uncontrollable synovitis in the past has been soothed. In the real clinical practice, more than 50% of the patients are in remission. However, some patients are still difficult to reach remission due to problems such as infection including tuberculosis, hepatitis B etc., respiratory disease, diabetes mellitus, aging and economic burden. In the patient in remission, smoldering synovitis is often detected by ultrasonograpy or by synovial histology in the small joints of the hand and the foot. Improved control of the disease activity is not always commensurate physical function and quality of life (QOL), because of the comorbidity such as locomotive syndrome including osteoporosis, sarcopenia, osteoarthrosis and dementia. In our rheumatic center, the number of large joint surgery is decreasing and the number of small joint surgery for the hand and the foot is increasing. A prospective cohort study was performed on 276 patients for the purpose of knowing whether surgical intervention affects the patient's QOL and mentality as well as physical function. They had a scheduled primary RA surgery for the damaged joint. As a result, J-HAQ (physical function & QOL), EQ-5D (QOL), Beck Depression Inventory-II (BDI-II: depression,mentality) at 6 months and at 12 months after surgery improved significantly compared to those just before surgery ($p<0.01$). Especially, J-HAQ in the elbow, the wrist and the knee surgeries, EQ-5D in the elbow, the wrist, the knee and the toe surgeries, and BDI-II in the wrist and the toe surgeries improved markedly 6 months after surgery. DAS28-CRP (4) decreased significantly in surgeries in all sites other than the toe ($p<0.01$). Surgical intervention on the tight medical control is possible to raise QOL and to lead mental remission for the patient with RA.

LS20

Optimization of RA treatment: Aiming at solving medical economic problems

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Conflict of interest: None

The introduction of biologics has resulted in significant advances in the treatment of rheumatoid arthritis (RA). Analyses of the IORRA, a prospective cohort study of Japanese patients with RA that has been ongoing at our Institute since 2000, have also provided evidence for improvement in the outcomes of patients with RA over time. However, one problem is the soaring cost of RA treatment. We have investigated the direct costs and loss of work in Japanese patients with RA based on the IORRA cohort. These studies revealed that the financial burden on patients with RA has grown year by year, and that direct and indirect costs relating to RA tend to increase with the progression of functional disability and a reduction in QOL. Our findings thus suggest that, if disease activity can be suppressed by actively controlling RA from the early stages of disease onset, physical dysfunction will not advance, potentially decreasing both direct and indirect lifetime medical costs. A pharmacoeconomic study evaluates both the clinical benefits and the economic efficiency of a drug to determine whether it is worth the cost. A simulation analysis based on the IORRA has demonstrated that cost-effectiveness in patients receiving biologics is well within the acceptable range compared with that in patients receiving the "anchor drug" methotrexate. Optimizing the use of high-cost biological preparations must also be considered from economic perspective. This refers to therapeutic strategies such as dose reduction and drug discontinuation of biologics in patients who have achieved remission. Etanercept has been shown to be amenable to dose reduction and drug discontinuation. Because of its low immunogenicity, moreover, it can be readministered in the event of recurrence, making it a drug that allows exceptional treatment flexibility. I wish to use this seminar as an opportunity to describe the medical economic usefulness of etanercept and to study its potential for optimizing RA treatment.

LS21

The Best Treatment Decisions for Medical Treatment of RA - Consideration of csDMARDs Combination Therapy -

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Conflict of interest: Yes

For medical treatment of rheumatoid arthritis (RA), methotrexate (MTX) is regarded as mainstay drug in guidelines of many countries. Additional combination with biological agents or conventional synthetic DMARDs (csDMARDs) is recommended in a case of insufficient effect with MTX. Depending on how csDMARDs is used, the range of choices for RA treatment can considerably vary as a low-cost therapeutic option. The effectiveness of triple therapy with MTX + salazosulfapyridine + hydroxychloroquine was shown, and the role of csDMARDs has been reviewed in foreign countries. In Japan, newly appeared csDMARDs include iguratimod and tacrolimus. For treatment of RA patients with various clinical / social backgrounds and variables, medical decisions of which to choose or how to combine with csDMARDs, MTX, biological agents, or steroids are required in clinical practice. In this lecture, recent findings of fundamental studies for pathology of RA will be introduced, and association with investigational drugs, rationalities of combination therapy and the best treatment decisions will be considered.

LS22

Treatment Strategies for Lupus Nephritis

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Conflict of interest: Yes

Lupus nephritis (LN) is a major organ complication of systemic lupus erythematosus (SLE). Inflammation of the glomerular basement membrane by immune complex deposition and subsequest impairment of renal function is postaldid to be the main mechanism of LN. The prognosis for LN patients is by no means favorable, and long-term management, including measures for dealing with flare-ups and complications, is essential. The treatment of LN is based on steroids combined with a variety of immunosuppressants. Therapies are currently divided into remission induction therapy, which is intended to control/inflammation immunological activity and stabilize renal function, and subsequent maintenance therapy. This seminar will introduce methods for evaluating disease activity in the treatment of lupus nephritis, and discuss the limitations of such methods. We will discuss immunosuppressants used for LN and the current evidence for a multi-target therapy using a combination of calcineurin inhibitor, metabolite immunosuppressant and a steroid, dividing them into remission induction therapy and maintenance therapy. And we will consider the future challenges regarding LN.

LS23-1

New Era in Spondyloarthropathy therapy - IL-17A inhibition

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Conflict of interest: None

Interleukin-17A (IL-17A), one of IL-17 family, is a cytokine which plays important roles in chronic inflammation. Accumulating evidence has revealed critical involvement of IL-17 pathway in both psoriasis and psoriatic arthritis (PsA). The contributions of IL-17A to the diseases will be discussed with detailed clinical results of novel medication by secukinumab, a fully human anti-IL-17A monoclonal antibody. The efficacy and safety of secukinumab were evaluated in patients (pts) with PsA in 2 randomized, double-blind, placebo (PBO)-controlled, phase 3 trials (FUTURE 1, FUTURE 2). In the FUTURE 1 study, 606 pts with active PsA were randomized to secukinumab 10 mg/kg i.v. or PBO, treated at baseline, Wk 2 and Wk 4, then 75 mg s.c.,150 mg s.c. or PBO every 4 weeks, starting at Wk 8. In the FUTURE 2 study, 397 pts with active PsA were randomized to s.c. secukinumab (300, 150, 75 mg) or PBO and treated at baseline, Wks 1, 2, 3 and 4, then every 4 wks. Primary endpoint was ACR20 response at Wk 24, and ~70% of pts were naïve to TNF inhibitors and ~30% exposed. In FUTURE 1, secukinumab 75 and 150 mg significantly increased ACR20 responses compared with PBO at Wk 24, and inhibited radiographic progression of joint structural damage. Also in FUTURE 2, ACR20 responses at Wk 24 were significantly greater with secukinumab 300,150 and 75 mg than PBO: 54.0%, 51.0% and 29.3%

versus 15.3%, (P<0.0001 300 and 150 mg; P<0.05 75 mg vs. PBO). Secukinumab 300 and 150 mg but not 75mg showed significant improvements in PASI75/90, DAS-28CRP and SF-36 PCS vs. PBO. Treatment-emergent AEs in PBO-controlled period (until Wk 16) were 58.9% and 58.3% in secukinumab (pooled from FUTURE 1 and 2) and PBO-treated pts, respectively, with serious AEs of 3.4% and 4.0%. Secukinumab 300 and 150 mg s.c. showed sustained improvements in PsA signs/symptoms and function, and inhibition of radiographic progression of joint structural damage. Secukinumab was well tolerated, with no unexpected safety findings

LS23-2

New Era in Spondyloarthropathy therapy - pathogenesis and emerging treatments

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Conflict of interest: Yes

Seronegative spondyloarthritis (SpA) has a close link to the presence of HLA-B27 epitope and is a group of inflammatory rheumatic diseases with common clinical and etiological features, including sacroiliitis, axial and peripheral inflammatory arthritis, enthesitis, extra-articular manifestations, which provide a significant impact on patient functional status and quality of life. SpA includes psoriatic arthritis (PsA), ankylosing spondylitis (AS), reactive arthritis (ReA), SpA associated with inflammatory bowel disease, juvenile SpA and undifferentiated SpA. The prevalence of PsA ranges from 0.02% to 0.2%, but the incidence in Japan is 1/30-100 of Caucasians. In patients with existing psoriasis, the prevalence of PsA rises to 10-40%. PsA is an aggressive disease that often leads to peripheral joint damage as well as spine involvement that are associated with functional decline and impaired quality of life. Thus, the importance of early diagnosis and initiation of aggressive treatment has been emphasized PsA and RA are inflammatory joint diseases, but they have different genetic associations and different immunopathologic. Most studies of T cell cytokine expression in PsA have focused on IL-17, IL-12/IL-23, IFN-g and TNF-a. IL-17 is of particular interest because of its potent osteoclastogenic activity and its ability to up-regulate MMP and proinflammatory cytokines such as IL-1, IL-8 and TNF. Recent data derived from a combination of clinical trials and registries have resulted in a better understanding of the efficacy and durability of methotrexate (MTX) and biological DMARD targeting TNF, IL-17, IL-12/23 (p40) in PsA. However, many patients with PsA experience a delay between onset of symptoms and diagnosis and appropriate treatments. I here review the latest studies regarding the efficacy of MTX and biologic DMARDs for patients with PsA and provides a brief overview of new agents in the pipeline.

LS24

Pain management in patients with rheumatoid arthritis

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Conflict of interest: Yes

In recent years, newly-launched anti-rheumatic drugs including biologic agents together with evidence-based treatment algorithms for induction and maintenance of remission have brought about a paradigm shift in the treatment outcome of rheumatoid arthritis (RA). We entered an era in which it became feasible to make preventing joint destruction, maintaining physical function and improving life expectancy. However, it is never acceptable to neglect attempting to improve patients' short-term QOL. Discrepancies between patients and physicians in their perceptions of global disease activity have been pointed out, but they have also been said to be attributable to physicians' attaching importance to the number of swollen joints when making global evaluations, as opposed to patients' putting greater emphasis on their pain level. Since RA is an inflammatory autoimmune disease, and controlling the autoimmune response and suppressing the excessive inflammation is the optimal way to control the pain. However, if the treatment provide insufficient pain relief for the patients, there are several treatment options to manage pain in RA, such as surgical intervention, analgesic agents, rehab and psychiatric therapeutic procedures. In this luncheon seminar, we would discuss about the pain in RA.

LS25-1

Tactics after achieving the clinical remission by biologic disease modifying anti rheumatic drugs in patients with rheumatoid arthritis

Satoshi Ito
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Conflict of interest: Yes

By the introduction of biologic disease modifying anti rheumatic drugs (bDMARDs), it became possible to achieve clinical remission (CR) in patients with rheumatoid arthritis (RA). Since bDMARDs is expensive, it is important to maintain CR with reduced cost for both patients and the national health expenditure. We tried to induce and maintain CR with adequate amount of the anchor drug, methotrexate (MTX) combined with anti-TNF antibody, and tried to stop bDMARDs (Bio-free condition: Takai C and Ito S will present about infliximab and adalimumab, respectively at JCR2016). In case of etanercept (ETN), soluble TNF receptor, we started 50mg/week and after achieving CR, we tapered to 25mg/week according to the PRESERVE study and the PRECEPT study considering the prevention of joint destruction. Tocilizmab (TCZ) is an antibody to IL-6 receptor. Although the incidence of the infection is not higher than TNF inhibitors, the masking of the signs and symptoms of the infection is a problem. We avoided using TCZ in very old patients and reduced the infection (Ito S et al. Rheumatology 2015). But the efficacy of TCZ is very strong even without MTX and loss of efficacy is rare. TCZ also works in the patients who did not respond to TNF inhibitors. Therefore, we use TCZ as a first line bDMARDs in patients not so old, without severe complications but have high disease activity. We also use TCZ as early as possible in patients with TNF inhibitor failure. TCZ is the most inexpensive bDMARDs in Japan. With the spacing, we can reduce more cost after achieving CR. In JCR 2016, we will report the spacing of TCZ. Enrolled were 63 patients (M 11, F 52) who were administrated iv TCZ for more than 1 year. TCZ significantly reduced disease activity, prednisolone and MTX. Spacing was done in 71.4 % of the patients. With Bio-free tactics, tapering or spacing of bDMARDs, we can reduce the medical cost with CR.

LS25-2

The treatment in and after achieving remission in rheumatoid arthritis

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Conflict of interest: Yes

The advent of intermittent methotrexate and various biologic agents has had such an impact on the treatment of RA that a paradigm shift has emerged toward earlier and more aggressive intervention with the goal of remission. The clinical remission is now a realistic goal to reach for. There are several recommendations and guidelines from EULAR, ACR, T2T committee and JCR for aiming to remission for patients with active disease. Many evidences from high-quality clinical trials and studies support those guidelines showing the effective and safe usage of DMARDs including biologic agents to achieve remission as quick as possible. Meanwhile, now that remission is a realistic goal, there has been great debate regarding withdrawal, dose reduction or spacing or DMARDs. Whereas the simple way to sustain remission is to continue the treatment that has attained remission, the treatment to sustain remission is not necessarily the same as the one to achieve remission. The treatment beyond remission is a challenge to work for from the standpoint of medical economics and possible side effects caused by treatment. However, drug withdrawal can be at risk of disease flare or irreversible joint destruction. In this seminar, the optimum treatment to achieve remission and to sustain remission will be discussed in light of the latest evidences.

LS26-1

Hydroxychloroquine (Rheumatology)

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Conflict of interest: Yes

Hydroxychloroquine is an important part of standard treatment of systemic lupus erythematous regardless of organs involved in this systemic autoimmune disease. Unless there is a specific contraindication, hydroxychloroquine should be considered in all patients with systemic lupus erythematous. The toxicity is limited especially in comparison to other medications utilized in the care of patients with systemic lupus erythematosus, such as glucocorticoid and immunosuppressants. Shared information on the efficacy and the side effects between physicians and patients is crucial to secure the superb risk benefit ratio. The simple once a day administration of the oral medication is expected to lead to a good adherence with most of patients, and all the rheumatologists who take care of patients with systemic lupus erythematosus are required to be well versed in the use of this medication and should consider its introduction to patients according to major domestic and international guidelines.

LS26-2

The effectiveness of Hydroxychloroquine (HCQ) in cutaneous manifestations of SLE

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Conflict of interest: None

The antimalarials hydroxychloroquine (HCQ), has been used to treat systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE) for decades. Lupus erythematosus mainly affects young women, the refractory cutaneous manifestations usually located on the face that always generate great negative influences on patient's quality of life (QoL). Although HCQ is the first-line therapy in the management of SLE and CLE around the world, it is not available in Japan since 1972. In 2012, a multicenter, double-blind, randomized trial was undertaken, the safety and efficacy of the drug has been proved in Japanese CLE patients with and without SLE. In July 2015, HCQ has been approved for use in Japan. The standard therapeutic option for treating mild lupus and CLE in Japan alternative to HCQ, is NSAIDS, topical therapy followed by low dose prednisolone (PSL) only or in combination with an immunosuppressant. The recurrence of lesions when only low doses of PSL are administered leads to long-term use of corticosteroids and a host of concomitant adverse events. The new approval of HCQ in Japan suggests that we are step into a new stage of managing SLE and CLE, HCQ will be the first-line therapy to treat mild and moderate SLE and CLE alternative to low does of PSL in the near future. In this lecture, we summarize our cases of HCQ from our clinical experience, and discuss the safety, efficacy, and side effects of the drug using clinical images.

LS26-3

The basics of hydroxychloroquine retinopathy and coordinating care with ophthalmologists

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Conflict of interest: None

Since hydroxychloroquine sulfate (HCQ) was first approved for use in the US, studies over a period of 60 years have examined its proper use in clinical settings. Overseas, HCQ is frequently used as a standard treatment for cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE). The most concerning adverse reaction to HCQ is retinal damage in the form of HCQ retinopathy. HCQ retinopathy rarely develops, but it is an adverse effect that is noted in a certain proportion of patients receiving HCQ. Ophthalmologists needs to be involved in patient care in order for HCQ to be used safely. Once HCQ retinopathy develops, restoring visual function is difficult even if HCQ is discontinued. Thus, the most important steps are to detect signs of HCQ retinopathy developing early and to promptly discontinue the drug. In this lecture, I will describe the basics of HCQ retinopathy that clinicians should be familiar with so that HCQ can be used properly, and I will also describe ideal patient care in which internists and a dermatologists coordinate with ophthalmologists.

LS27-1

Current and Novel Therapies for Lupus Nephritis: Induction Therapy

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Conflict of interest: Yes

Treatment of lupus nephritis (LN) consists of 2 phases; induction therapy and maintenance therapy. In induction therapy, patients with high activity of LN are treated with high dose corticosteroids and potent immunosuppressants to achieve normalization of proteinuria, urinary sediments and renal function. In the first half of this seminar, I would like to talk about the recommendations for the induction therapy in the current guidelines of LN and the situation of clinical trials of novel therapies for LN. Based on the RCTs of LN in 2000s, which compared intravenous cyclophosphamide pulse therapy (IVCY) and mycophenolate mofetil (MMF), some guidelines of LN were published in 2012 and all of them recommended the use of MMF or IVCY as the first-line immunosuppressants for active proliferative LN. However, even in the ALMS trial, which was a representative RCT of LN, responder rates (complete remission + partial remission) at 6 months were between 50 to 60% in both MMF and IVCY group. To achieve higher response rate, several clinical trials were undertaken, in which the efficacy of the combination therapy of biologics with MMF or IVCY were studied. Namely, RCTs using B-cell targeting agents (rituximab, ocrelizumab, atacicept, belimumab) or T-cell targeting agents (abatacept) were undertaken (or are undertaking). However, except post-hoc analysis, until now, no agents could show superiority over MMF or IVCY. In contrast, multitarget therapy using MMF and tacrolimus (TAC) showed a significant higher response rate than IVCY and is attracting increasing attention. In the recent multicenter RCT in China, in which 362 patients with Class III, IV, V active LN were enrolled, complete remission rate at 24 weeks was significantly higher in the multitarget therapy group compared to the IVCY group. We are also using the multitarget therapy in our department and getting good results. We believe this therapy could be a novel treatment option in active LN.

LS27-2

Efficacy of tacrolimus for maintenance therapy in patients with lupus nephritis

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Conflict of interest: None

Systemic lupus erythematosus (SLE) is clinically and serologically diverse multisystem autoimmune disease. Renal involvement is the most important risk factor associated with the poor prognosis of SLE. Lupus nephritis (LN) may occur in approximately 50-60% of patients of SLE. LN plays a key role in the prognosis of SLE and nearly 10% of patients with LN develop end-stage renal failure requiring dialysis or renal transplantation. LN and chronic use of corticosteroids and immunosuppressive agents contribute significantly to mortality. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN was published. The treatment of LN, especially class III and IV, mainly involves remission induction therapy in the acute stage and maintenance therapy thereafter. Remission induction and maintenance therapy includes steroids and immunosuppressant. Nowadays, we can use azathioprine, mizoribine, tacrolimus (Tac) and mycofenolate mofetil on remission therapy in Japan We subjected the cases at our hospital as we diagnosed LN, and used Tac for the maintenance treatment. We analyzed the clinical information retrospectively such as WHO pathological tissue classification, treatment, and outcome. Tac was administered for 47 cases

of maintenance therapy phase of lupus patients. Renal biopsy was performed at 24 cases, these were type II (5 cases), type III (2 case), type IV (15 cases), type V (2 cases), and type IV+V (2 cases). Traf level of Tac was 4.9 ng/ml (mean). Remission rate was 85.3% and above all of first nephritis cases were complete remission state. We did not recognize chronic kidney failure and artificial dialysis. In this session, to evaluate efficacy of Tac for maintenance therapy with LN.

LS28

Importance of pain management in the rheumatoid arthritis treatment

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Conflict of interest: Yes

Rheumatoid arthritis (RA) treatment has dramatically changed by biologics. It is the realistic goal of the treatment to achieve remission and to avoid the progress of the joint destruction. However, the patient who can achieve remission is around 30% and may not maintain it throughout the life. We could not provide enough treatment because of an escape phenomenon of DMARDs, second failure of biologics, or adverse events. We may use glucocorticoid to achieve LDA, at least, under such conditions. If the inflammation still remained, joint destruction would gradually progress. It is known that the progress becomes faster when there is osteoporosis. Even if the remission is maintained without joint destruction in several years, decades would produce degeneration like osteoarthritis or spondylosis. In the elderly onset case, pain caused by the existing joint destruction may affect the disease activity index. We treat young early patients who can receive enough treatment with biologics, and we also find the difficulty to treat old established patients. When we think about the life of RA patients, it seems not enough to focus on the control of inflammation only. We should treat from various aspects for decades. Especially, it is important to manage pain which can directly affect the ADL of RA patients.

LS29-1

Treatment strategy for psoriatic arthritis

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Conflict of interest: None

Psoriatic arthritis may not be common form of inflammatory arthritis in Japan because the prevalence of psoriasis in Japan is much lower than those in Western countries. However, the impact on functional ability or quality of life of psoriatic arthritis is comparable to that of rheumatoid arthritis. Moreover, the efficacy of TNF inhibitors on disease activity and radiological progression has been shown. Recently, recommendations for the treatment of psoriatic arthritis have been published by some international groups. Recent evidences show that early treatment and treat to target strategy is important for psoriatic arthritis. Minimal disease activity criteria that has been developed originally for psoriatic arthritis and consists of seven categories, i.e. tender joint count, swollen joint count, Psoriasis Activity and Severity Index (PASI), patient pain visual analogue score (VAS), patient global disease activity (VAS), health assessment questionnaire and tender entheseal points. MDA criteria may be a useful index for treat to target strategy in the treatment of psoriatic arthritis. NSAIDs, csDMARD and biological DMARD form the mainstay of treatment of psoriatic arthritis. However, NSAID should not be used as a monotherapy in patients with active psoriatic arthritis. In csDMARD, methotrexate (MTX) is the first-line drug although sulfasalazine, leflunomide or cyclosporine A can be considered as a monotherapy instead of MTX or concomitant use with MTX. In patients with an inadequate response to at least one csDMARD, biological DMARD should be used. TNF inhibitors should be the first choice because of the many evidence of the efficacy on joint inflammation, radiographic progression and skin disease. Patients with predominant enthesitis, dactylitis or spondylitis, biological DMARD should be considered when response to NSAID is inadequate.

LS29-2

Axial disease and its treatment in ankylosing spondylitis

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Conflict of interest: Yes

Ankylosing spondylitis (AS) is a prototypic disease of axial spondyloarthritis (axSpA) classified by a classification criteria proposed by Assessment of SpondyloArthritis international Society (ASAS). AS was specified to an intractable disease determined by the Japanese government in July, 2015. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line drug in axSpA, and TNF inhibitors are started for active AS patients in spite of NSAIDs. In general, oral glucocorticoid and conventional anti-rheumatic drugs, including methotrexate, are not used because of lacking clinical evidence. Clinical efficacy of infliximab and adalimumab, anti-TNFa monoclonal antibody agents approved for AS in Japan, has been well accepted. Since ASAS criteria for axSpA was established to diagnose early stage of AS, cases without radiographic change in X-ray can be also classified as SpA (non-radiographic axSpA (nr-axSpA)). However, the TNF inhibitors are not approved for nr-axSpA in Japan. In addition, it should be cautious to manage nr-axSpA since it is a term for classification and not always progresses to AS. The mechanism of new bone formation in AS is still unclear. The imaging has demonstrated that erosive lesions caused by inflammatory process are repaired with fat metaplasia and backfill, and subsequent new bone formation is likely to be observed following this step. It is also controversial whether medication can prevent the radiographic changes as seen in rheumatoid arthritis. It has been reported that TNF inhibitors failed to inhibit the radiographic change at 2 years, however, more recently, new bone formation has assumed to be reduced by TNF inhibitors with longer observation period. In this seminar, as presenting our cases, pathophysiology and treatment of axial disease in AS will be discussed.

LS30-1

Tuberculosis (TB) in Japanese patients with rheumatoid arthritis (RA)

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Conflict of interest: None

We demonstrated that the number of RA patients among all TB patients was approximately three times as high as the prevalence of RA in the entire population in Japan. We calculated the standardized incidence ratio (SIR) of TB from the clinical data on National Database of Rheumatic Disease by iR-net in Japan (***NinJa***). Among 7,832 RA patients without biological agents, 7 patients developed TB. The SIR of TB in RA patients without anti-TNF therapy was 3.98 (95%CI:1.22-6.74). According to the post-marketing survey of infliximab and etanercept, the SIR of TB were 21.5 and 5.5, respectively. The incidence of TB in patients with RA was higher than general population, and was incresed more by the anti-TNF therapy. But the SIR of TB in RA patients treated with biologic agents was 2.76 (0.96-4.57), and the SIR of TB in patients treated without biologic agents was 3.05 (2.25-3.85). Among 95,421 RA patients registered from 2003-14, 65 patients developed TB and the SIR of TB was 2.97 (95%CI:2.25-3.39). 9 patients (13.8%) were treated with biologic agents: Looking at the trends of every two years, the SIR of TB was on a downward trend after peaking at 4.76 in the 2007-08. The SIR of TB in Japanese patients with RA is in decline by this prospective study, but the problems have been left behind, such as the following in the TB treatment for RA patients who were treated biological agents:1)Extrapulmonary TB is a high rate, often leading to delays in diagnosis.2)Since the immunosuppressive agent such as biological agents also MTX, is also discontinued, that the activity of RA increases in many cases, the RA treatment of these cases are limited.3)Corticosteroids effect is reduced by the rifampicin administration.4)After stop the biological agents, cellmediated immune function is restored may TB is worsening, so called "immune reconstitution syndrome", recently, some case reports have been reported.

LS30-2

Rheumatoid arthritis and non-tuberculous mycobacteriosis

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Conflict of interest: None

As remedy for rheumatoid arthritis (RA) has made remarkable progression and been established, especially with biological agents, non-tuberculous mycobacteriosis (NTM) has become as important complication as tuberculosis. But the epidemiologic data about NTM in RA patients (pts) are scarce. We investigated NTM prevalence rate and clinical features and risk factors associated with NTM in RA pts registered in *NinJa* (National Database of Rheumatic Diseases by iR-net in Japan) database in 2012 to 2014. We surveyed the reasons of diagnosis of NTM, associated other diseases, detecting bacterial species, chest radiographic findings, patient profiles and so on in the 2 year. Diagnosis of NTM was made by Japan respiratory society diagnostic criteria. By the reason of hospitalized diagnosis prevalence of the pts associated with NTM by *NinJa* 2014 was 12/15,023 (79.9 cases/100,000 persons) and those by *NinJa* 2013 and 2012 were 12/13,285 (90.3) and 9/11920 (75.4), respectively. Of 12 by *NinJa* 2014, 3 pts died, 2 cause from pneumonia, 1 from interstitial pneumonitis. Prevalence in NTM surveyed by questionnaire was 751.2 cases/100,000 persons in 2012 and 971.1 cases/100,000 persons in 2013, both of which were remarkably high. Incidence rates of RA pts enrolled in *NinJa* 2012 in the fiscal year of 2013 was 58.5 cases/100,000 persons year and is considered to be remarkably high. By analyzing *NinJa* 2012, RA pts with NTM showed higher age and high disease activity and a higher class of functional impairment than in non-NTM pts. Considering with treatment, RA pts with NTM were less frequently used with MTX and more glucocorticoids compared with non-NTM pts. And biologics, especially TNF inhibitors were less frequently used and the reason is presumed to be difficulty of those remedy to use for NTM pts. It is suggested that NTM prevalence rate in RA pts was remarkably high compared to prevalence rate in the general population. We also report the efficacy of mycobacterium avium complex (MAC) antibody.

LS31

Rheumatoid Arthritis and Social Insurance in Japan: Issues and Strategies

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Conflict of interest: None

Japan's universal health insurance system covering all citizens by public medical insurance is highly regarded throughout the world, yet the system has numerous challenges including expensive biological agents (BA). In Japan, patients must pay 30% of their medical cost out of their pocket. This ratio is much higher than other OECD countries where patients can receive specified medical care for free or at low cost. The U.S. lacks universal healthcare, yet the patients bear just a low cost, as drug companies often take some measures for them. In Korea, the ratio is 30% basically, but 10% is applied to those with RF positive as an exemption. With these facts in mind, Japan needs to ease high burden of healthcare cost on patients. In 2014, all 7 BAs ranked among the top 50 most expensive drugs and the 3 BAs are within top 4. Rheumatologists should always examine treatments for patients and also comply with regulated fee schedule and guidance. The guidance on costly medicine sometimes hinder effective treatment. In 2015, questionnaire survey to the councilors of the Japan College of Rheumatology (JCR) revealed re-examination cases of medical remuneration issues, including the cases out of scope of the guidelines and recommendations. The medical remuneration has been drastically reduced since 2013. The fact that the remuneration amount varies based on BA types has been regarded as problematic since long ago. It would be a big issue if the BA with higher remuneration are prioritized in medical practice. JCR will discuss the issues with the Ministry of Health, Labour and Welfare. JCR is also working on to cover new intactable deceases such as SLE by subsidies. National health expenditure has reached 40 trillion yen level and the government policy of reducing cost has recently become apparent. Rheumatologists need to examine treatment options in line with the policy as far as possible. I will discuss combination DMARD therapies besides costly BA in this session.

LS32

Total Joint Arthroplasty for the Elderly or Rheumatoid Arthritis Patients; from Implant Selection to Pharmacological Intervention

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Conflict of interest: None

Life expectancy has progressively increased, and we are experiencing considerable growth in its older population. Patients undergoing total joint arthroplasty are also getting older, and surgeries could be challenging especially in cases of very elderly patients > 85 years old with various comorbidities. As for patients with rheumatoid arthritis, total joint arthroplasty procedures are decreasing due to advances in biological DMARDs, however, difficult cases with severe osteoporosis or massive bone defect still exist. In order to prevent intra- and post-operative fractures, osteoporosis treatment should be taken into account. Also appropriate implant selection and thorough preoperative planning is necessary.In this lecture mainly on total hip and total knee arthroplasty, with regard to hardware, I will touch on the recent trends in total joint replacement surgery in Japan, newly developed trabecular metal augmentation blocks, and constrained liner or dual mobility articulation to prevent dislocation of the hip. Regarding the pharmacological intervention, various antiresorptives and osteoanabolic agents for osteoporosis, intraoperative hemostatic agents, pain management, hypnotic pills, deep venous thrombosis prophylaxis will be discussed.

LS33

JAKinibs in treatment of rheumatoid arthritis

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Conflict of interest: Yes

Cytokine inhibition has been proven as an inevitable treatment tool for rheumatoid arthritis (RA). However, the amount of patients that cannot earn privilege of biologics is not negligible. Janus kinase (JAK) inhibitors (JAKinibs) possess a different mechanism of action from biologics by targeting JAKs in the cytoplasm. JAK family (JAK1, JAK2, JAK3, Tyk2) activates the downstream molecules. Cytokine signaling cascade is wide spreading toward the downstream, like a flow of a river. Thus, inhibition of the upstream can result in inhibiting wide range of signaling. In addition, because JAKs can be activated by multiple cytokines, JAKinibs are considered as a multiple cytokine inhibitor. Tofacitinib, the only JAKinib approved for RA has demonstrated similar efficacy to a TNF inhibitor. Multiple JAKinibs with different specificity are on their way. Due to the mechanism of kinase activation, specific inhibition of a single kinase has been considered difficult. Needless to say, inhibiting a specific JAK from others *in vivo* is extremely difficult. Therefore, it has been speculated that inhibitory specificity would not necessarily reflect on efficacy and side effects. By contrast, Baricitinib a JAK1/2 inhibitor has demonstrated exceed efficacy compared to a TNF inhibitor with possible difference in side effects compared to tofacitinib. Therefore, it is possible that specificity could result in different efficacy and side effects. Interest on JAKinibs is focused on its side effects even more than its clinical efficacy. Rate of herpes zoster in Japan is clearly increased and malignancy is numerically higher although not clearly increased compared to western countries. Hence, we should carefully observe the subsequent clinical trials and post marketing studies. JAkinibs are a new class of anti-rheumatic drug facing a host of challenges, it is important to consider their positioning in RA treatment as a post-biologic new treatment tool.

LS34

Mechanisms of osteoarthritis development and conservative treatment for the disease

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Conflict of interest: None

Articular cartilage is the highly specialized connective tissue of diarthrodial joints and maintains its morphological properties for a long period of time. Its principal function is to provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient. Because articular cartilage has limited potential for regeneration, cartilage destruction are progressive in osteoarthritis (OA), resulting in impairment of joint function. Currently, it remains uncertain what develops cartilage destruction in OA. Accumulating evidence indicates that OA development involves alterations in cartilage with aging and mechanical stress on cartilage. This talk focuses on the mechanisms of cartilage destruction in OA development by aging and mechanical stress. Enhanced proteolysis leads to generation of proteolytic products of cartilage matrix in OA joints. Of the proteolytic products of extracellular matrix, some fragments have catalytic activities, and are called matrikine, Matrikine may act as damage-associated molecular pattern molecules (DAMPs) and drive further cartilage destruction in OA. This talk demonstrates such matrikine activities of fibronectin fragments and type II collagen peptide. Conservative treatments for OA include drug therapy, rehabilitation, and orthosis. Hyaluronan of high molecular weight is clinically used for treatment of OA. There is evidence that HA may work as a suppressor of cartilage destruction in OA. The inhibitory effects of hyaluronan on proinflammatory cytokine and matrikine are shown in this talk.

LS35-1

Treat my RA! Treat-to-target (T2T) and treat-for-patient (T4P) approach

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Conflict of interest: None

A treat-to-target strategy (T2T), measuring disease activity (cf. DAS28) and treating patients to remission, is strongly recommended in the management of rheumatoid arthritis (RA) worldwide. Recent advances in the development of medications make this approach feasible in clinical practice. The 2014 Japan College of Rheumatology guidelines for the management of rheumatoid arthritis contribute to introducing these evidence-based strategies in the management of RA in Japan. However, the clinical application of these approaches should be tailored to individual patients by physicians. The 2014 update of the T2T recommendation (Somlen J, et al. Ann Rheum Dis 2016;75:3-15) focus emphasized the individual patient factors such as comorbidity, work productivity, drug toxicities, or economical status. A cure, or drug-free remission, can be anticipated in almost hepatitis C patients thanks to advances in medicine. However, it is still difficult to achieve even low disease activity in all RA patients. As Mayeroff Milton stated, caring is “to help (the patient) grow and actualize himself (On caring,1971).” Rheumatologists who treat patients with this disabling chronic illness, regardless of their disease activity, have to make the best use of their knowledge and experience in addition to the evidence-based medicine in order to help their patients grow and actualize themselves: ‘treat-for-patient’(T4P). In this lecture, I will introduce the clinical practice of using the Multi-Dimensional Health Assessment Questionnaire (MDHAQ), which is designed for use in a busy clinical setting. Furthermore, by presenting measurements of self-efficacy and SOC (sense of coherence) obtained from participants in this seminar, I would like to discuss how even the sickest RA patients can grow and actualize themselves.

LS35-2

QOL evaluation as outcome and its significance

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Conflict of interest: None

Although an initial report of quality of life (QOL) as a healthcare outcome was in 1940s, the role as its outcome has increased dramatically in recent years. In 1980s, a study of QOL as a healthcare outcome, also called health-related quality of life (HRQL), was actively conducted in the United Kingdom, Canada, and other countries. In these nations, the development of a new assessment scale for HRQL was mainly promoted by research methods used in computational psychology, but to date several standard scales, along with various disease-specific scales, have been published regardless of target diseases. The reason why QOL or HRQL has emerged as a healthcare outcome is not because they have considered their livelihood and lifespan simply as quantity, but because their interest has shifted to a subjective aspect of how they can obtain their good quality of livelihood and life, while people’s lifespan is extended by the development of various health technologies. In this manner, QOL as a healthcare outcome became recognized as a crucial part in terms of the evaluation. On the other hand, in health-technology-assessment bodies that include the NICE in the United Kingdom, cost-effectiveness evaluation of various healthcare technologies has been conducted in order to improve efficiency in healthcare. In these assessment bodies, quality-adjusted life years (QALYs) are used as an index in many cases. This index shows not only lifespan extension of patients, but also HRQL which shows the value of health rather than patient satisfaction. Our nation also plans to introduce cost-effectiveness evaluation of various healthcare technologies experimentally from the fiscal year 2016; therefore, the importance of measuring HRQL will grow increasingly in the future. In this seminar, we would like to summarize the current situation which is using QOL as a healthcare outcome and its significance.

Evening Seminar

ES1-1

Role of poor prognosis factors for rheumatoid arthritis in pathogenesis and treatment

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Conflict of interest: Yes

Bone destruction develops in the first two years after onset of rheumatoid arthritis (RA). Therefore, the ACR/EULAR RA classification criteria have been revised in 2010 in order to classify early RA patients and initiate early intervention with disease modifying anti-rheumatic drugs (DMARDs). Among the items included in the classification criteria, serology (anti-citrullinated protein antibody; ACPA and rheumatoid factor; RF) is emphasized in addition to joint involvement. Both are considered to turn positive within 5 years prior to onset of the disease. Severe synovitis and bone destruction is observed in ACPA positive compared to negative patients and is listed as a poor prognosis factor in guidelines and recommendations. Rather severe bone destruction is observed in patients with higher ACPA titer. When combined with RF, ACPA+/RF+ double positive patients have severe and fast bone destruction compared to single positive patients (ACPA-/RF+ or ACPA+/RF-). Basic investigation shows that autoantibodies against mutated citrullinated vimentin, a type of ACPA, induce both osteoclast differentiation and osteolytic function. Therefore, an RA treatment that is able to act on autoantibody formation would be appreciated as a new mechanism for treatment. In this seminar, I would like to discuss the role of poor prognosis factors on pathogenesis and treatment strategy.

ES1-2

The possibility of personalized strategy with biological agents in patient with rheumatoid arthritis

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Conflict of interest: None

With the development of TNF inhibitors, clinical remission has become a primary goal in the treatment of rheumatoid arthritis (RA). In addition to TNF inhibitors, tocilizumab and abatacept were recently introduced. Abatacept and tocilizumab are regarded as standard treatments along with TNF inhibitors in patients with RA who are refractory to methotrexate (MTX). Current research focuses on how to use these biological products. Especially, no randomized controlled trials (RCTs) comparing the efficacies of abatacept and tocilizumab have been conducted, and there is limited evidence to guide drug selection. To overcome these issues, first, we compared between adalimumab and abatacept. This study showed that abatacept and adalimumab are similar in terms of clinical efficacy, especially in bio-naive patients. This result supports those of the AMPLE study (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate), an RCT directly comparing abatacept and adalimumab which showed that these drugs are comparable in terms of clinical effects. Second, we compared between tocilizumab and abatacept. This study employed propensity score matching and showed that abatacept and tocilizumab had comparable continuing efficacies. These studies revealed the similar efficacies among TNF inhibitors, anti-IL-6 receptor antibody and CTLA-4 Ig. On the other hand, our studies showed that the predictors of the response to treatment were a higher RF titer for abatacept and a lower HAQ-DI for tocilizumab and adalimumab. In recent years, selecting among different biologics has been recognized as an important issue for the treatment of RA. However, sufficient evidence to differentiate among these drugs is as yet lacking. We believe that statistical methods such as propensity score matching can contribute to the growing body of clinical evidence and might lead to the development of tailor-made medicine using biological products for patients with RA.

ES2-1

Abrogation of inflammation with effective treatment strategies for rheumatoid arthritis, and the possibility of optimized treatment options after the achievement of remission

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Conflict of interest: None

Rheumatoid arthritis (RA) is characterized by joint inflammation leading to damage and disability over time. As an incurable chronic autoimmune disease, treatment concepts such as T2T are very important. Risk factors for the progression of joint destruction in RA have been well established. Reducing inflammation that causes joint damage will interfere with the early destructive processes of RA or, if halted early enough, prevent joint damage from developing at all. Thus, more effective treatment strategies for RA not only halt the progression of damage but also improve physical function and reduce comorbidity, especially when achieving stringent remission. Meanwhile, despite early intervention with conventional DMARDs, joint damage and functional impairment are still seen, and even with biologics, if disease activity is not sufficiently controlled. Thus, the more stringent the remission criteria, the higher the opportunity for good structural and functional outcomes, as RA-related complications will develop. Once the target is reached, reduction of dose or an increase in the interval of administration are possible options to maintain the success of treatment. While induction therapy in early RA followed by withdrawal of biologic agents may be a feasible approach, drug-free remission is still far from reach even if in early RA patients, because current data suggest that this can only be attained in a very small proportion of patients, while most of them lose the good response and flare with all the consequences of the recurring inflammation. Taken together, I will summarize the importance of the stringent remission and the possibility of the optimal treatment option after the remission, in this symposium.

ES2-2

The optimization of RA treatment by IL-6 signaling inhibition learned from the translational research

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Conflict of interest: Yes

Disease Modifying Anti-Rheumatic Drugs (DMARDs) inhibit the progression of joint damage and improve the functional status in RA patients, and the treatment with DMARDs is widely conducted to achieve remission. Better development for diagnosis tools are expected and preventive care, pre-emptive therapy and personalized healthcare will be the next candidates of RA strategies for the future. However, at this stage, we need to take into account the maximization of RA treatment using approved DMARDs. Methotrexate (MTX), which is one of many synthetic DMARDs, is the most frequently used in Japan. To optimize MTX therapy, we believe it is more effective to measure erythrocyte-MTX-polyglutamate concentrations in RA patients. Meanwhile, we described that the efficacy of MTX in combination with TNF inhibitor was superior to that of TNF inhibitor monotherapy in the JESMR study. Additionally, the SURPRISE Study with Tocilizumab (TCZ) which inhibits IL-6 signal, is a multicenter, prospective, randomized, open-label study that compared the MTX plus TCZ with TCZ monotherapy for RA patients who have inadequate response to MTX. The remission rate of combination therapy was higher than that of TCZ monotherapy at 24 weeks, however, there was no significant difference among two groups at 52 weeks. Therefore, it suggests that TCZ might be able to taper the dose of MTX if remission is achieved with combination therapy after 24 weeks, in terms of the optimization for TCZ therapy. Also, we accumulated the data of translational research which used blood samples in our laboratories. Our research suggests that the changes of serum cytokine and several subsets of peripheral cells are not the same in RA patients treated with different biological DMARDs, even if the results of clinical efficacy are similar. In this seminar, we will discuss our studies by focusing on the optimization of RA treatment, including the significance of IL-6 inhibition.

ES3-1

Psoriatic arthritis update

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Conflict of interest: None

The terms spondyloarthritis, spondyloarthropathies, and seronegative spondyloarthropathy are used to refer to a family of diseases that share a group of clinical features. The preferred term for this family of arthritis is now "spondyloarthritis"(SpA). The group includes: ankylosing spondylitis (AS), reactive arthritis (formerly Reiter's syndrome), psoriatic arthritis (PsA), Juvenile SpA, enteropathic arthritis (spondylitis/arthritis associated with inflammatory bowel disease), and undifferentiated SpA. All display a variety of symptoms and signs, but they also share many features in common, including: inflammation of axial joints (especially the sacroiliac joints), asymmetric oligoarthritis (especially of the lower extremities), dactylitis (sausage digits), and enthesitis (inflammation at sites of ligamentous or tendon attachment to bone). Among SpA, the prevalence of PsA among Japanese psoriasis patients is thought be less than that of Westerners. However, in keeping with our clinical experience that the prevalence of PsA among Japanese patients may actually be higher, we reported prevalence rates of up to 20.4% among Japanese psoriasis patients (1). Further improvements in awareness of this disease entity is necessary to allow patients to receive early and appropriate care. In this session, we overview PsA and aim to guide the distinguishing clinical features of PsA in Japanese patients, which will allow us to improve both under-diagnosis and misdiagnosis of an increasingly treatable disease, and emphasize the need for early diagnosis and appropriate differential diagnosis.

ES3-2

Treatment of psoriatic arthritis

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Conflict of interest: None

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, and one of the Spondyloarthritis (SpA) group, together with ankylosing spondylitis. Most of the patients with PsA presents peripheral arthritis, but some has axial spondylitis. Some has enthesitis and dactylitis similar to that seen in other forms of SpA. The treatment of SpA had dramatic progression in recent years because of emergence of biological agent, such as TNF inhibitor. Particularly in the treatment of PsA, the efficacy of IL-17A inhibitor, which is failed in RA, and IL-12/23 p40 inhibitor as well as TNF inhibitor has been reported. In addition, apremilast have also used in overseas. It is very important to use these new drugs in any condition or any lesion. The guidelines in the treatment of PsA were published in 2009 from GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) and in 2015 from ASAS (Assesment of SpondyloArthritis international Society). In this seminar we will explain these guidelines that established the treatment of PsA.

ES3-3

How to diagnose PsA? ~About examination method: Interview, inspection, palpation~

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Conflict of interest: None

In 2014, Nature Review Rheumatology advocated that Psoriatic disease have many symptoms such as Skin, Nail, Joint involvements, metabolic changes, cardiovascular disease, therefore we should think that patients with psoriasis have many problems at baseline. Psoriatic arthritis was one of spondyloarthritis (SpA) with peripheral arthritis, ductility's, enthesis, and inflammatory back pain. Nowadays,Ohara reported prevalence of Psoriatic arthritis in Japan**(Ohara Y et al J Rheumatol. 2015)** . PsA was 14.3% of psoriasis patients. Now she described that PsA were not rare disease. Therefore, we should have a knowledge of diagnostic for PsA. Now, Contents of my talk are "Examination method, Differential diagnosis, Evaluation item of PsA and co-operation with the dermatology.

ES3-4

Psoriatic arthritis (PsA) - Psoriasis examination point

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Conflict of interest: None

Psoriasis is a common chronic inflammatory and complex immune-mediated disease. The IL-23/Il-17 pathway is deeply involved in the development of psoriasis. Mentally as well as physically quality of life diminish in psoriasis patients. In recent years psoriasis has been associated with multiple comorbidities. PsA is a form of inflammatory arthritis that may occur in up to 20 percent of patients with psoriasis in Japan. Psoriasis has also been associated with cardiovascular disease, uveitis and other systemic diseases. Arthritis appears after the onset of skin lesions in the majority of patients with PsA. However, the arthritis precedes the skin disease in a few patients. Sometimes skin lesions are present but have not been diagnosed. A significant proportion of patients with PsA may develop destructive and potentially disabling disease. Patients appear to benefit from evaluation and treatment early in the disease. There is a weak relationship between the severity of skin disease and arthritic involvement, although some studies have suggested that PsA occurs more commonly among patients with severe psoriasis There are five clinical subtypes of psoriasis. Psoriasis vulgaris, the most common type of psoriasis, most commonly presents with red papules and well-demarcated erythematous plaques topped by silvery scales. The scalp, extensor elbows, knees, and sacral region are common locations for psoriasis vulgaris. Characteristic features of psoriasis may affect the nail, including nail pits, onycholysis, nail bed hyperkeratosis and splinter hemorrhages. Nail lesions occur in 80 to 90 percent of patients with PsA. The psoriatic nail involvement is more common in those with DIP joint arthritis. A diagnosis of psoriasis can be made by history and physical examination in the majority of cases. A full skin examination that includes examination of the scalp nails, and anogenital skin should be performed in patients with suspected psoriasis. Other characteristics supportive of psoriasis include evidence of the Koebner phenomenon and the Auspitz sign. Differential diagnosis of psoriasis is nummular eczema, seborrheic dermatitis, fungal infection of the nails and cutaneous T cell lymphoma. Occasionally, a skin biopsy is needed to rule out other conditions including cutaneous T cell lymphoma.

ES4-1

MMP-3 in RA: Roles in cartilage destruction, usefulness as a diagnostic biomarker and future projects to be clarified

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Conflict of interest: Yes

Synovitis of rheumatoid arthritis (RA) is characterized by hyperplastic synovial lining cells and inflammatory cell infiltration and angiogenesis in the sub-lining layer, and contributes to the destruction of joint tissues by the action of many proteinases including MMPs (matrix metalloproteinases). RA synovial lining cells overproduce MMP-1, 3, 9 and MT1-MMP as well as TIMP-1 and 3 (tissue inhibitor of metalloproteinases-1 and 3) and sub-lining fibroblasts produce MMP-2 and TIMP-2. Polymorphonuclear leukocytes infiltrated in synovium and joint cavity secrete MMP-8 and 9, and macrophages produce MMP-1, 9, TIMP-1 and 2. MMP-1, 2, 3, 8, 9, TIMP-1 and 2 are present in RA synovial fluids, and metalloproteinase activity can be detectable in the synovial fluids. Among them, MMP-3 levels in RA synovial fluids are 50~100-fold higher than other MMPs. MMP-3 levels in serum samples reflect activity of synovitis and are useful for prediction of joint destruction and monitoring effectiveness of the therapies targeting synovitis such as biologicals in

RA patients. We isolated MMP-3 from culture media of RA synovial fibroblasts at the Ted Harris' laboratory in 1986, and focused on the aggrecan-degrading activity. However, next studies have disclosed that MMP-3 cleaves type IX collagen as well as the telopeptides of type II and type XI collagens, and acts as activator for proMMP-1, 7, 8, 9 and 13. Thus, MMP-3 is considered to play a key role in degradation of collagen fibrils in articular cartilage. In the present seminar, I will review the cartilage destruction mechanism in RA by MMP-3 and discuss several unresolved issues on MMP-3, which emerged after its clinical application as a diagnostic tool for RA. They may include increased serum levels of MMP-3 in non-RA diseases such as polymyalgia rheumatica and psoriatic arthritis, increase in serum MMP-3 after steroid therapy, different levels of MMP-3 between male and female, and metabolism of MMP-3 within our body.

ES4-2

How to reduce the lower of the threshold of MMP-3 for clinical value

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Conflict of interest: None

Matrix Metalloproteinase 3 (MMP-3) is a useful indicator of the joint destruction that occurs in rheumatoid arthritis (RA). Currently in the treatment of RA, achieving and maintaining clinical remission is the primary goal. However, even if clinical remission is achieved, MMP-3 levels remain high joint destruction will proceed. The question then arises to what level must we reduce MMP-3 in the treatment of RA to prevent this destruction? Factors which affect the measured level of MMP-3 include kidney failure and corticosteroids (CSs). Due to this, it is commonly held that in RA accompanied by kidney failure or in RA patients on CSs, the use of MMP-3 levels as a marker of joint damage becomes unreliable. But is this really the case? In the treatment of RA, if the level of kidney failure is extreme, attaining simple disease activity index (SDAI) remission is problematic. Herein, we show data that suggests that the chances of achieving an SDAI remission score are far lower than achieving a desirable MMP-3 level. We also suggest MMP-3 values that predict a change of <0.5 in the modified total sharp score (mTSS) in patients who have achieved SDAI remission, across various levels of kidney damage and steroid doses. In order to reduce the MMP-3 levels of RA patients an appropriate treatment strategy is indispensable. Furthermore, when it comes to reducing MMP-3 levels, the speed of that reduction is important. Unfortunately, there is no drug available that will reduce MMP-3 to desirable levels in all patients. Drugs that can reduce MMP-3 levels vary both by patient and depending on disease pathology. Herein we show the ability of biologics and Tofacitinib to reduce and normalize MMP-3 levels and hope to demonstrate a new model for the treatment of RA based on these data. Finally, we will address the usefulness of MMP-3 in a treatment strategy that reduces the dose of biologics and methotrexate, after achieving SDAI remission.

ES5-1

True remission achieved by "early intervention, intensive initial treatment" and "treatment holiday"

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized with inflammatory synovitis, progressive joint destruction and multiple organ manifestations that causes severe irreversible disability. The early diagnosis, early intervention and intensive initial treatment are important to protect joint destruction which causes severe irreversible disability with progress. Considering the above, the "treat-to-target"(T2T) strategy was advocated in 2010, and it became an international consensus. Moreover, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), have both individually and together, successively announced classification criteria, treatment recommendations and remission criteria. It is still fresh that the ACR revised the guidelines for the treatment of RA in 2015. In japan, the guidelines for the management of the rheumatoid arthritis of Japanese College of Rheumatology published in 2014 which has been applied to clinical daily practice. The treatment targets set out in the guidelines are not only improvement of clinical symptoms but also improvement in long-term prognosis, especially aiming for prevention of disability and improvement of mortality. In such circumstances, disease-modifying anti-rheumatic drugs and biologic agents has provided drastically improvement of treatment outcomes in recent RA daily practice. Appropriate use of methotrexate (MTX) and biologics, it may be said that clinical remission and inhibition of joints destruction become realistic targets or goals not a conventional symptomatically treatment. On the other hand, there are some issues such as increased medical costs and insufficient evidence for safety of long-term usage. In this seminar, I would like to reexamine how early intervention is important, with reference to the data obtained from clinical trials of biologics including adalimumab, based on current global trends in the treatment of RA. I will also have an in-depth discussion about treatment strategies after sustained long-term remission, especially possibility and significance of "treatment holidays" by biologics, looking at and reviewing clinical data from different perspectives which has been often discussed as the latest topics in recent years.

ES5-2

Optimizing the management of rheumatoid arthritis with musculoskeletal ultrasound

Kei Ikeda
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Conflict of interest: Yes

Musculoskeletal ultrasound visualizes synovial inflammation (i.e. synovitis, tenosynovitis, bursitis), enthesitis, crystal deposition, and bone surface abnormalities (i.e. erosion, osteophyte) and contributes to accurate diagnoses of rheumatic conditions such as rheumatoid arthritis, psoriatic arthritis, crystal-induced arthropathies, and osteoarthritis. In addition, ultrasound potentiates tight control of rheumatoid arthritis by accurate assessment of synovial inflammation and improves clinical outcomes. Furthermore, ultrasound helps rheumatologists understand the pathophysiology, improve skills, and establish optimal patient-physician communication, and thus contributes to improved quality of management of rheumatoid arthritis.

ES5-3

Importance of tight control and the value for RA patient after achieving the remission

Ferdinand C Breedveld
Department Rheumatology, Leiden University Medical Centre, The Netherlands

Conflict of interest: None

Since rheumatoid arthritis (RA) causes irreversible physical dysfunction, in particular joint destruction, it is important to provide proper treatment from an early stage. There is a worldwide consensus on "T2T: Treat-to-Target" as a treatment of rheumatism, proposed in 2010, and later revised in 2014 in light of new study results. The framework of T2T is also important for daily clinical practice. Not only we, specialized doctors in rheumatism, but also a wide range of medical practitioners should put it into practice. Based on the results of systematic literature review (SLR) and expert opinions, a task force team made revisions to the 2010 T2T, and compiled the recently-published T2T recommendations. The T2T recommendations, a worldwide consensus, suggest that the main goal of RA treatment is to improve the long-term quality of life (QOL) of patients to the maximum extent possible. In addition to participation in social activities, participation in work activities is also emphasized and newly integrated as part of the 2014 revision. In order to achieve the goal suggested by the T2T recommendations, it is important to ensure tight control through proper treatment intervention in early stages, as well as monitoring with comprehensive disease activity indexes. In this seminar, the importance of early treatment intervention and the long-term out-

comes produced by the early treatment intervention will be outlined, in light of the results of exemplary clinical studies for adalimumab, including the PREMIER Study, PROWD Study and DE032 Study, and other large-scale clinical studies for TNFi. Furthermore, the daily clinical practice of T2T in the Netherlands will be introduced, and the global trends of RA treatment will be discussed, while reviewing the clinical treatment approach in Japan.

ES6-1

Early intervention with anti-TNFs in rheumatoid arthritis

Daniel E Furst
University of California, Los Angeles (UCLA), USA

ES6-2

Treating early rheumatoid arthritis with anti-TNF biologics

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Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine

Conflict of interest: Yes

Over the past 10 years, treatment algorism of rheumatoid arthritis (RA) has made remarkable progress. Optimal therapeutic outcomes can be achievable in RA patients by early induction of clinical remission through frequent adjustment of drug therapy. Early diagnosis and therapeutic intervention as well as introduction of biologics have contributed significantly to this progress. According to updated recommendations for RA treatment, synthetic disease modifying anti-rheumatic drugs, including methotrexate, are the first-line therapeutic agents for early RA, and biologics are added if treatment goals have never been achieved within 6 months. However, in clinical setting, patients who have multiple prognostic factors are often treated with a combination of methotrexate and a biologic agent as an initial treatment regimen. On the other hand, biologic monotherapy is sometimes used to treat patients, in whom methotrexate is contraindicated because of renal insufficiency or severe interstitial lung disease. Upon treating these difficult cases with early RA, we have to decide which biologic agent is appropriate to use. For this purpose, two important features should be considered upon selection of anti-TNF biologics. Fist, since anti-TNF agents exert their efficacy through neutralization of soluble and membrane TNF at site of inflammation, increase of dosage and/or shortening of dose intervals of agents are required to achieve remission in patients with high concentration of TNF. Second, anti-TNF biologics with low immunogenicity should be used to treat patients with significant risk for production of anti-drug antibodies, which are capable of reducing efficacy of biologics, by competitively binding to antigen-recognition site and/or by facilitating clearance of biologics. In summary, appropriate selection of anti-TNF biologics is crucial for treating patients with early RA, who require prompt remission induction to obtain best clinical outcomes.

ES7-1

Discussion of quality evaluations for biologics and biosimilars: Quality and clinical evaluations to ensure comparability

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Conflict of interest: None

The introduction of biological drugs to rheumatoid arthritis (RA) treatment has allowed us to finally achieve remission. Guidelines for the management of RA from JCR consider biologics a valuable treatment option, with a recommendation level of "high." However, it is also pointed out that practical social considerations require evaluation of economic factors such as efficiency and cost-effectiveness (CE) as well, and that ongoing clinical research in Japan may significantly impact CE. MHLW has announced plans to cut at least JPY1 trillion by increasing rates of generics use to at least 80%. Further, most of the top 10 drugs worldwide in terms of sales are biologics, and going forward these will undergo patent or re-examination expiration. In such circumstances, the first infliximab (IFX) biosimilar was launched in Japan in Nov 2014. At about 70% of the price of the innovator IFX, this biosimilar is expected to help reduce social healthcare costs and individual burdens for treatment. Biosimilars are defined as equivalents to approved innovator biologics produced after the patent expiration. Although these are fundamentally the same as generics in terms of their cheaper cost, a key difference is the difficulty of proving equivalence between the innovator and biosimilar. MHLW provide a comprehensive framework for companies developing biosimilars to create their own production methodologies and evaluate comparability with the innovator drugs, including quality tests, non-clinical studies, clinical studies, and post-marketing surveillance. This seminar will touch upon fundamental concepts of biosimilars, basics of production processes, quality characteristics, physical/chemical characteristics in comparison with original drugs, and controlled clinical studies. Finally, I will give my thoughts on efficacy and safety observed in switching studies, as well as possibilities for the field going forward.

ES7-2

Recent advances and perspectives of bDMARDs for rheumatoid arthritis: Positioning and review of new agents including biosimilars

Atsushi Kawakami
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Conflict of interest: Yes

bDMARDs selectively inhibit the action of inflammatory cytokines and effector cell functions. Eight kinds of bDMARDs, including one biosimilars, are available in Japan toward patients with RA. In addition to the inhibitors of TNF, IL-6R and CD28, the clinical trials of several new class of bDMARDs such as anti-GM-CSF and anti-IL-6 are in progress. Furthermore, small molecule inhibitors including JAK inhibitors are being developed. EULAR (2013), JCR (2014) and ACR (2015) have published the recommendations/guidelines for the management of RA, and bDMARDs are considered to play a central role in these recommendations/guidelines. Each bDMARD is effective toward MTX-IR patients or previous bDMARD-IR patients, therefore, these recommendations/guidelines do not show the ranking of usage of bDMARDs. Establishment of the evidence of the choice of bDMARDs, based on the mode of actions, will be necessary in the future. In addition to bDMARDs reference products, the development of biosimilars is anticipated by economic considerations. Infliximab biosimilar became to be available in 2014 and the market is increasing. In the recommendation of EULAR (2013), infliximab biosimilar was considered to place alongside the other TNF inhibitors in the therapeutic cascade. JCR (2014) and ACR (2015) did not mention the biosimilars due to the lack of evidence at the time of systematic review of articles. However, several biosimilar products are being developed and the data of these clinical trials have been shown in the recent EULAR/ACR scientific meetings. The methods to achieve T2T will be expanding by the introduction of new class of bDMARDs/small molecule inhibitors and biosimilars in clinical practice. I am going to discuss the positioning and review these new anti-rheumatic agents in this seminar.

ES8-1

Update of psoriatic arthritis (PsA) diagnosis and treatment

Philip J Mease
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Conflict of interest: Yes

Psoriatic arthritis (PsA) is an immunologically-mediated inflammatory disease characterized by arthritis, enthesitis, dactylitis, spondylitis, and psoriasis. Recent epidemiologic studies suggest that PsA occurs in up to 30% of patients with psoriasis, but is often undiagnosed or misdiagnosed, partly because of its heterogeneous clinical presentation. Prior to the introduction of targeted biologic medications the ability to control disease activity was limited, with only modest effects noted with oral medications such as methotrexate and sulfasalazine. The introduction of TNF inhibitors substantially changed the outlook of PsA patients, yielding significant response in all relevant clinical domains, including the ability to inhibit progressive structural damage of joints. However, not all patients respond to these agents initially and many patients display initial re-

sponse which wanes over time, partly due to immunogenicity to the biologic protein, or tolerability/safety issues. Several medicines with a different mechanism of action (MOA) have been approved or are in development for the treatment of PsA, including an IL12/23 inhibitor, PDE4 inhibitor,, IL17A inhibitors, JAK inhibitor, and several IL23 inhibitors. Several of these medications specifically target the TH17 cell pathway of inflammation, in particular through inhibition of IL23 and IL17, which appears to have special significance in psoriasis, PsA and ankylosing spondylitis. The emergence of medicines with a different MOA than TNF inhibition has broadened and strengthened our ability to effectively treat PsA. We have also developed more accurate ways to measure therapeutic response in PsA, allowing us to quantitate achievement of low disease activity and remission in all relevant clinical domains of the disease. Updated international treatment recommendations from GRAPPA and EULAR emphasize striving for disease remission, now more achievable with a growing therapeutic armamentarium.

ES8-2

Importance of early diagnosis of psoriatic arthritis~Tips for differential diagnosis~

Mitsumasa Kishimoto
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Conflict of interest: None

The prevalence of psoriatic arthritis (PsA) among Japanese psoriasis patients is thought to be less than that of Westerners. However, in keeping with our clinical experience that the prevalence of PsA among Japanese patients may actually be higher, we reported prevalence rates of up to 20.4% among Japanese psoriasis patients (1). Further improvements in awareness of this disease entity is necessary to allow patients to receive early and appropriate care. Another potential problem is misdiagnosis as rheumatoid arthritis (RA) or another joint condition. A recent systematic literature review reported that the 2010 ACR/EULAR RA classification criteria have a moderate specificity of 61%(2). However, clinical application of these criteria is only valid after careful consideration of alternative diagnoses. Awareness of clinical characteristics of PsA, including both articular and extra-articular manifestations, is essential for this process, especially because clinical characteristics of PsA are highly variable across patients. In this session, we aim to characterize the distinguishing clinical features of PsA in Japanese patients, which will allow us to improve both under-diagnosis and misdiagnosis of the increasingly treatable disease, and emphasize the need for early diagnosis and appropriate differential diagnosis. References 1. Ohara Y, Kishimoto M, et al. J Rheumatol 2015;42:1439-42 2. Radner H, Neogi T, et al. Ann Rheum Dis 2014; 73: 114-23

ES8-3

Diagnosis of psoriatic arthritis (PsA) from a dermatologist's point of view

Akimichi Morita
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Conflict of interest: Yes

Psoriatic arthritis (PsA) is one of the most well-known comorbidities. PsA is characterized by various symptoms, such as peripheral arthritis, spondylitis, dactylitis, enthesitis, and nail lesions, and commonly occurs in psoriasis patients. Although the precise rate in Japan is unclear, the prevalence of PsA is ~10%. In many cases, skin symptoms precede other symptoms and joint symptoms begin to manifest after approximately 10 years. Careful follow-up of psoriasis patients is important, because patients with skin symptoms on the head, genital region, and/or nails are at increased risk of developing PsA. Therefore, dermatologists are in a position to detect the initial signs of the development of arthritis. PsA leads to joint destruction and limits the activities of daily living as the symptoms progress, severely affecting the patient's quality of life. PsA requires a definite diagnosis and treatment not only for the arthritis, but also for the skin lesions. The Moll and Wright criteria are the most well-known diagnostic method for PsA, but there are some other methods, such as the CASPAR criteria, that are highly regarded among rheumatologists and orthopedists. The CASPAR criteria are a very reliable and convenient diagnostic tool. The Psoriatic Arthritis Screening and Evaluation tool, which has been validated in many languages including Japanese, is a novel questionnaire to screen for PsA patients among individuals with psoriasis. The relationship between dermatologists and rheumatologists is important for providing PsA patients with the appropriate treatment to prevent joint deformity and a decrease in their quality of life. In this lecture, I will provide a comprehensive explanation of PsA from the point of view of a dermatologist.

ES9

Recent progress in management of Sjögren's syndrome: Update in 2016

Hiroto Tsuboi, Shinya Hagiwara, Hiroyuki Takahashi, Tomoya Hirota, Hiromitsu Asashima, Yuya Kondo, Isao Matsumoto, Takayuki Sumida
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Conflict of interest: Yes

Sjögren's syndrome (SS) is an autoimmune disease which affects salivary and lacrimal glands, accompanied with various extra-glandular manifestations (EGM). SS has been targeted for medical expenses subsidy as specify incurable disease from January 2015 in Japan, if patients satisfy the diagnostic and disease severity criteria. Standardized diagnosis and disease activity assessment as well as evidence based therapy are needed for SS. We introduce the recent progress in 1) comparison of different sets of criteria, 2) disease activity assessment by ESSDAI and ESSPRI, 3) new therapeutic strategy by immunosuppressant and biologics, and 4) practice guideline in the making by the research team of MHLW, in this seminar. 1) The research team of MHLW previously showed the superiority of the revised Japanese Ministry of Health criteria in the diagnosis of Japanese patients with SS compared with AECG and ACR criteria. Moreover, new ACR-EULAR classification criteria have been presented in ACR 2015. 2) ESSDAI was defined as the sum of [weight of each domain (1-6) X activity (0-3)] in 12 domains. ESSPRI was defined as the mean of 3 scales (0-10 for dryness, fatigue, and pain) assessed by patients. 3) No immunosuppressant has been confirmed as useful therapy for glandular and EGM. Although hydroxychloroquine (HCQ) is frequently used in overseas, a recent RCT (JOQUER trial) did not confirm the effectiveness of HCQ. Among biologics, rituximab has not been shown to be effective in a recent large RCT (TEARS trial) same as TNF inhibitors, while some previous trials revealed the usefulness of rituximab. Belimumab improved ESSDAI and ESSPRI, whereas not salivary and lacrimal secretion, in the pilot study. We showed effectiveness of abatacept for both RA and SS involvements including secretion of secondary SS with RA in multicenter prospective study (ROSE trial). 4) The research team of MHLW is working on the evidence based practice guideline for SS, according to the procedure of Minds.

ES10

Strategy of future treatment learned from overseas experience – What will be the best choice for RA treatment for?

Maurizio Cutolo
Department of Internal Medicine, University of Genova, Italy

Conflict of interest: None

Rheumatoid arthritis (RA), is a systemic multifactorial immune-mediated disease, with circadian clinical symptomatology and mainly characterized by synovial tissue proliferation and subintimal infiltration of inflammatory cells (macrophages, T and B cells, neutrophils), followed by progressive and symmetrical damage of the joints. Different cellular responses and epigenetic modulators are involved in the pathogenesis of RA, including activation of the immune-inflammatory cells and expression of various cytokines and local growth factors, as well as local angiogenesis. Since RA is also associated with multiple comorbidities and psychosocial impairments including CV disease, osteoporosis, infections, malignancies, nutritional defects (i.e. vitamin D deficiency), depression and work disability, all these conditions must be recognized in strategic approaches. The introduction in the 2000s of the novel targeted therapies

for RA such as biological disease-modifying antirheumatic drugs (bDMARDs), has facilitated considerably the approach to the "goal" of disease remission much faster and safely. Biological DMARDs may interact with sensitive targets such as circulating cytokines or their receptors (i.e. TNFalpha, IL-6, IL-1, IL-17), crucial surface markers of activated immune cells (i.e. CD20 on B cells) or costimulatory cell surface molecules (i.e. CD80/CD86 on antigen presenting cells, macrophages and other cells like osteoclasts). More recently, small molecule inhibitors of signaling mediators have been introduced which have intracellular targets such as the Janus kinase (Jak) family of tyrosine kinases, which are mediators of immunoreceptor signaling in T and B cells. Furthermore, as many bDMARDs are near to patent expiry, a number of 'biosimilar' drugs have been developed, however, validity of indication, extrapolation, 'switchability' and relative immunogenicity of biosimilars and their reference drugs still on debate. Finally, inadequate production of endogenous cortisol in relation to ongoing inflammation is recognized in chronic inflammatory conditions like RA, therefore, daily low-dose (<5mg/day) of exogenous glucocorticoids (GCs) are adminstered in RA with the intention to act as a "replacement" therapy. Indeed, recent EULAR recommendations* for the management of early RA include, as first step, the use of low-dose GCs in combination with conventional DMARDs (i.e. MTX, Leflunomide) and then bDMARDs. Very recent ACR guidelines** for RA therapy also include low-dose GCs (<10mg/day) for short-term at any time of the disease and/or in presence of RA flares. In any case, early diagnosis of RA, using safe diagnostic tools (i.e. power-doppler US) and specific serum biomarkers (i.e. ACPA), is confirmed the first strategic action before to act therapeutically and adopting individually tailored and targeted best treatments. *Smolen JS al. Ann Rheum Dis 2014;73:492 ** Singh JA al. A&R 2016;68:1

ES11-1

Up-to-date hand surgery for rheumatoid arthritis ~for the improvement of QOL~

Hajime Ishikawa
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Conflict of interest: None

The treatment of rheumatoid arthritis (RA) is coming in next phase to consider how we should manage it after remission. We need to acquire surgical technique and therapy to improve hand function and better cosmesis. Hand specialists will give lectures about the updated information. Dr. Ishikawa will describe that hand surgeries are usually performed after suppressing inflammation to less than low disease activity. Hand splint plays an important role not only to prevent progressive deformity in a corrected position, but also to utilize for therapy program after surgery. Dr.Nakagawa will give an overview of this hand splint. Dr. Iwamoto will state that this method is useful in the patients with RA, since Quick DASH correlates well with disease activity in IORRA cohort consisting of 5,000 patients. Dr.Akita will present surgical technique for swan-neck deformity of the fingers by presenting some clinical cases. Thumb deformity causes obvious disability in pinching and grasping. Dr. Kobata will state it is important to balance dexterity with pinch power, since the stable mobility is essential for the thumb. We invited Professor Kerschbaumer in this seminar. He will give a lecture about basic operative technique for prevention and reconstruction of tendon and joint malalignment in early and later stages of RA. I hope this seminar will contribute to improvement of patients' QOL.

ES11-2

Basic operative techniques for prevention and reconstruction of tendon and joint malalignement in early and later stages of RA

Fridun Kerschbaumer
Klinik Rotes Kreuz, Frankfurt, Germany

Conflict of interest: None

Regarding the natural history of a rheumatic wrist joint we differentiate three stages: Stage one begins with a ulno-carpal ligamental instability leading to a supination deformity of the wrist. Stage two is associated with a palmar-carpal capsular loosening and leading to a palmar subluxation of the whole carpus which may be manually reduced. Stage three refers to the fixed palmar dislocation of the carpus with radial deviation, shortening and non reducible. Therapy of stage one is done by reconstruction and shifting of the radio-luno-triquetral dorsal ligament using bone screws with reposition and reefing of the DRU capsule and relocation of ECU tendon. For the surgical treatment of stage two we have been using the Chamay-Delasanta procedure with radio-lunar fusion and reposition of the carpus. Stage three deformities are normally treated by reposition and radiocarpal fusion using Mannerfelts technique or AO-plating. In order to prevent extensor tendon ruptures we normally resect Listers tubercle, divide the extensor retinaculum and fix it over the dorsal wrist capsule. Prevention procedures against palmar dislocation of MP joints and swan neck deformities are early flexor tendon synovectomies. We perform less Total Joint Replacement for the wrist joint nowadays and perform instead more often wrist arthrodesis in later stages of destruction. Flexible Boutonierre deformities of the thumb are treated by extensor pollicis longus tenodesis in association with division of the oblique retinacular lig.We treat the rigid buttonhole deformity of the thumb by arthrodesis of the MP joint. Early swan neck deformities of long fingers are treated by intrinsic release (Littler),whereas in later stages the reconstruction of the oblique retinacular ligament according to Littler is performed. For Buttonhole deformities of long fingers we prefer a transosseous fixation of the intermedium tract with elongation of the oblique retinacular lig. or Dolphins procedure. We still use Swansons technique for destructed MP joints of long fingers and pyrocarbon implants for CMC lesions of the first ray.

ES12-1

Optimization of treatment with biologics for rheumatoid arthritis using musculoskeletal ultrasound

Kei Ikeda
Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

Conflict of interest: Yes

Biologics has revolutionized the treatment strategy of rheumatoid arthritis (RA) and improved the clinical outcome. On the other hand, the medication cost of biologics has become a substantial socioeconomic burden. Researchers have studied to optimize the use of biologics by selecting right patients, selecting right biologics, or dose reduction/discontinuation; however, strategies balancing the clinical outcome and the affordable cost have not been established. In most of these studies, synovitis is assessed by clinical measures such as subjective symptoms, physical examination, and acute inflammatory responses. The suboptimal accuracy of these measures is one of the limitations of these studies. Musculoskeletal ultrasound directly visualizes synovitis, which is the central pathophysiology of RA, and determines the severity of inflammation more accurately than does clinical assessment. For example, ultrasound detects synovitis in joints without apparent symptoms or findings and determines the absence of synovitis in joints with non-inflammatory pain or in patients with elevated inflammatory markers due to other reasons. Therefore, ultrasound can determine RA patients with residual synovitis that needs treatment escalation with biologics and also those in "deep remission" under treatment with biologics, for whom the dose reduction/discontinuation of biologics can be considered.

ES12-2

New insights for treating early rheumatoid arthritis intervention of pre-clinical RA

Paul Emery
Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK

Conflict of interest: None

A number of advances have allowed the concept of intervention in pre-clinical "at-risk" individuals to be realistic. These include:

- The realisation that inflammatory arthritis is a continuum
- The ability to see patients early even pre-clinically,
- A better understanding of aetiopathogenesis,
- New treatments, treatment approaches,

• Identification of biomarkers in at risk patients.

The first step is to identify at risk individuals; and a nation-wide population case-selection programme1 has proved the feasibility of this. Interestingly the localisation of non-specific pain was relevant for prediction of ACPA positivity. In the ACPA positive non-specific symptoms/arthralgia population a number of seminal studies have been undertaken identifying the risks that predict progression. Generally the risk of progression also predicts the increased speed of progression. The factors that have been relevant include high titre of rheumatoid factor and/or CCP, early morning stiffness, ultrasound, MRI and immunological abnormalities. These have now been included in risk algorithms.

Using the stratified approaches it is possible to identify patients with a risk of progression to arthritis of >50% within 12 months. These are therefore eligible for specific intervention interventions currently being undertaken. So far the major intervention studies that have been completed have been in undifferentiated arthritis where early use of abatacept has shown potential benefit 2.

1.J.L. Nam, L. Hunt, E.M.A. Hensor, Emery P. Enriching case selection for imminent RA – the use of anti-CCP antibodies in individuals with non-specific musculoskeletal symptoms: a cohort study. Ann Rheum Dis 2015.

2. Emery P, Burmester GR, Bykerk VP Combe BG, Furst DE, Barré E, Karyekar CS, Wong DA, Huizinga TWJ. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicenter, randomized, active controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015;74:19-26.

AUTHORS' INDEX

PL	Presidential Lecture
RS	Representative Session
S	Symposium
EL	Educational Lecture
MTE	Meet the Expert
JS	Joint Symposium (Research Group Joint Symposium on Intractable Vasculitis Syndromes)
EUS	EULAR Session
GEP	Gender Equality Committee Planning Program
ICW-C	International Concurrent Workshop Clinical
ICW-B	International Concurrent Workshop Basic
W	Workshop
P	Poster Session
EPSC	English Poster Session Clinical
EPSB	English Poster Session Basic
LS	Luncheon Seminar
ES	Evening Seminar

Bold Abstract No. ····· **Presenting Author**

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P

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