

# Modern Rheumatology

VOLUME 32 SUPPLEMENT 2022



# JAPAN COLLEGE OF RHEUMATOLOGY ABSTRACT SUPPLEMENT

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## Presidential Lecture

### PL

#### **We shall overcome —beyond the age of division—**

Sakae Tanaka

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Conflict of interest: Yes

Since the establishment of the Japan Rheumatism Association, the predecessor of the Japanese College of Rheumatology, in 1957, the treatment of rheumatic diseases has been thus cross-disciplinary, and not only doctors but also nurses, pharmacists, physical therapists, and now even patients are expected to commit to the decision of treatment policy. However, the new coronavirus pandemic that began in 2020 has changed the face of the medical field. The characteristic of this infectious disease, which is the spread of infection from asymptomatic and unaffected individuals, has caused society to fear many times more than the danger of the disease and has torn apart human relationships. The title of the column by journalist Kai Kupferschmidt, “A divisive disease”, does not overstate the characteristics of this new coronavirus infection (Science 18 Dec 2020: Vol. 370, Issue 6523, pp. 1395-1397). “We shall overcome” is the title of a protest song, which was used effectively in the civil rights movement in the United States. I chose this phrase as the theme of this year’s meeting of the Japanese Society of Rheumatology because I believe that in this age of division, many people must work together to overcome the current difficulties. What we need to overcome are the new coronavirus infections, rheumatic diseases, and the division of people. In this lecture, I would like to discuss how rheumatology should be practiced across departments in the era of pandemics.

## Symposium

### S1-1

#### **How a joint surgeon is involved in patients with rheumatoid arthritis**

Asami Abe, Hajime Ishikawa, Kei Funamura, Masanori Sudo, Sayuri Takamura, Hiroshi Otani, Satoshi Ito, Kiyoshi Nakazono, Akira Murasawa  
Department of Rheumatology, Niigata Rheumatic Center

Conflict of interest: None

I have been working for 16 years at the only public rheumatism hospital in Japan and have been devoting myself to patient care every day. Over 4000 outpatients visit our hospital each year, managed by over 800 of our doctors, and 1400 inpatients are managed by 60 of our doctors. Patients are hospitalized for joint surgery, control of high disease activity, and management of infectious diseases. Outpatient clinics are held every day. The annual number of operations at our hospital is 236, and I myself have performed 54 surgeries. I mainly perform small joint surgery and am in charge of surgeries involving the fingers, wrist joints, elbow joints, shoulder joints, toes, and ankle joints. Our clinic focuses on finger and wrist joint surgery, subsequent rehabilitation, head-preserving toe formation, and subsequent rehabilitation. Our hospital focuses on rheumatism treatment, surgery and rehabilitation in Niigata Prefecture. Of course, even surgeons consider surgical treatment while controlling disease activity using biopharmacy and Janus kinase inhibitors. Ideally, you should be referred by your practitioner if treatment with methotrexate (MTX) or csDMARDs is not normally controllable. However, due to the circumstances surrounding MTX (HBV, HCV, Tbc), it is difficult to prescribe it so many patients are overseen by our hospital. As a joint surgeon and a female one at that, there are many issues that men fail to notice in RA, where the majority of patients are women. I encourage patients to note any dysfunctions or issues that they aren’t familiar with and bring these up with their physician. RA is a disease loathed by general orthopedists. The treatment is long-term, and complications and side effects are a nuisance, creating issues such as difficulty medicating patients. However, some patients wish to receive treatment at their local hospital, so please be open to cooperating with other physicians to develop treatment strategies.

### S1-2

#### **The necessity of a multidisciplinary approach in the treatment of rheumatoid arthritis**

Yutaka Kawahito

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Conflict of interest: Yes

The prognosis of rheumatoid arthritis (RA) has been greatly improved by the advent of molecular targeted drugs and by treatment strategies based on the concept of T2T. However, the current treatment of RA is still inadequate to achieve a better prognosis. Treatment strategies in the aspect of ADL are a major issue, especially in elderly RA patients due to inadequate approaches to improve joint function. There are many cases in which physical functions deteriorate and it becomes difficult for patients to return to daily life before achieving their targets with drug therapy. The RA clinical practice guideline 2020 was the first in the world to create an algorithm for non-drug and surgical treatment. This algorithm can be applied to any phase of the drug treatment algorithm and includes the four pillars of total RA management other than drug treatment: care, rehabilitation, and surgery. Daily life guidance, exercise therapy, occupational therapy, orthotic therapy, and even joint surgery at the appropriate time will not degrade ADL function and will also have a positive psychosocial impact. The background that made it possible to create this algorithm is the existence of orthopedist with rheumatologists in Japan. In addition, collaboration of medical and orthopedist in the treatment of RA enables early diagnosis by differentiating rheumatic and orthopedic diseases other than RA at the time of diagnosis, and allows multidisciplinary treatment that includes rehabilitation and surgery at the appropriate time. Thus, the optimal RA treatment is completed on the basis of a balance between the physician’s approach and the surgical approach. These two things are the two indispensable wheels of car. Thus, it is necessary to build an environment and relationship that allows bidirectional RA treatment. In this symposium, I would like to discuss the current status and future of orthopedist

through the necessity of a multidisciplinary approach in the treatment of RA.

### S1-3

#### Current Problems and Prospects in Rheumatoid Arthritis Treatment from the Perspective of Orthopaedic Surgeons

Yu Mori

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Conflict of interest: None

Drug treatment for rheumatoid arthritis has developed dramatically, and the situation of rheumatoid arthritis treatment has changed. We provide drug treatment for patients with rheumatoid arthritis in the same way as rheumatologists, and perform surgery, mainly joint replacement and arthroplasty for knee and toe lesions in patients with severe residual deformity, joint pain refractory to drug treatment, and functional disability. Although the number of surgeries for rheumatoid arthritis is decreasing due to the improvement of drug therapy, many patients who require surgery have severe deformity, bone destruction, and significant functional decline, and some of them are very difficult to operate. We collaborate with the department of rheumatology to treat cases of idiopathic osteonecrosis of the femoral head caused by steroid therapy, in addition to cases of rheumatoid arthritis for which surgery is indicated. We also focus on the treatment of osteoporosis, which is an important complication of autoimmune diseases including rheumatoid arthritis. Another issue is that due to the small number of orthopaedic rheumatologists, it is difficult to provide training in surgical treatment and drug treatment for rheumatic cases except in some core hospitals such as university hospitals. The perspective for orthopaedic rheumatologists is that even if the number of surgeries decreases, surgeries for load-bearing joints such as knee joints and toe deformities will continue. Even though the treatment of rheumatoid arthritis has improved, rheumatoid arthritis patients are still at risk for osteoporosis, so we consider that we must provide comprehensive treatment and contribute to maintaining the QOL of patients with rheumatoid arthritis.

### S1-4

#### Current status and future of orthopedic surgery for patients with rheumatoid arthritis

Kengo Harigane<sup>1</sup>, Yuichi Mochida<sup>1</sup>, Takayuki Shimazaki<sup>1</sup>, Naomi Kobayashi<sup>2</sup>, Taro Tezuka<sup>3</sup>, Ken Kumagai<sup>3</sup>, Hyonmin Choe<sup>3</sup>, Shunsuke Yamada<sup>3</sup>, Shuntaro Nejima<sup>3</sup>, Akiko Nagaoka<sup>1,3</sup>, Yutaka Inaba<sup>3</sup>

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Conflict of interest: None

Center for rheumatic diseases in our hospital have accepted 160-200 first visit referred patients annually. In approximately 20% of them, the referral purpose was orthopedic surgery for joint destruction due to rheumatoid arthritis (RA). The rate of the referral purpose for surgery has not changed in the last 10 years. Although in Japan the number of orthopedic surgeries for patients with RA has decreased in the last 10 years, we have performed 80-100 surgeries annually and the number of surgeries has not changed. Despite of dramatic improvement in medical treatment of RA including methotrexate or biologic agents, we sometimes experience the difficult-to-treat (D2T) cases which have some joint swellings with moderate to severe disease activity or case with severe joint destruction. In those cases, orthopedic joint surgery is sometimes needed to improve activities of daily living. Not only orthopedist but also internal physicians who participate in drug therapy of RA should recognize the importance of the appropriate timing for RA joint surgery.

### S1-5

#### The Role of Rheumatology Surgeons in Achieving Treat to Target in Japan

Shigeki Momohara

Hakkeikai Incorporated Medical Institution / Keio University

Conflict of interest: None

Rheumatoid arthritis (RA) is a disease in which the pathogenesis the disease is still not completely understood, and the joints are damaged and dysfunctional due to immune abnormalities. Since glucocorticoids were first used in 1948, drug therapy has been the mainstay of treatment. There are conventional synthetic DMARDs, which are low-molecular-weight compounds such as methotrexate, and biological DMARDs (bDMARDs), which are high-molecular-weight protein drugs, such as TNF inhibitors, IL-6 receptor antibody drugs, and T-cell selective co-stimulation modulators. These drugs have expanded the range of options for drug therapy, resulting in a dramatic paradigm shift in treatment. Under these circumstances, new oral molecularly targeted DMARDs, JAK inhibitors, were also introduced. With the introduction of these various DMARDs, remission is becoming a realistic goal for treatment. However, the existence of a refractory population (D2T-RA) has also been revealed, and many patients who meet the criteria for remission but still have unmet needs are actually experienced in clinical practice. In Japan, orthopaedic surgeons have been actively involved in the treatment of RA since before the development of DMARDs, and while the importance of early diagnosis and treatment has been called for, orthopaedic surgeons are often consulted before and after the onset of RA in this country, and their presence still plays a significant role. It is very important to diagnose and treat D2T-RA as early as possible to prevent the development of refractory RA. In this sense, the involvement of orthopedic surgeons in this field will continue to be very important. In addition, it has been pointed out that even if inflammation is subdued, there are cases where patient satisfaction is not met, such as pain, fatigue, depression, and sleep disturbance, and how to improve so-called Patient Reported Outcomes (PROs) is becoming an issue. In this regard, the participation of orthopedic surgeons who are familiar with physical therapy and exercise therapy other than drug therapy is essential in the treatment of RA. Moreover, the presence of an orthopedic surgeon with a good understanding of RA is also very important when surgical treatment is considered as necessary. The future of RA treatment requires total management that aims to go one or two steps higher by improving lifestyle with medication, physical therapy, surgical treatment, and paying attention to infectious diseases such as COVID-19.

### S1-6

#### The best treatment for rheumatoid arthritis by a collaboration between orthopedic surgeons and collagen disease rheumatologists

Kensuke Oryoji

Center for Rheumatic Diseases, Matsuyama Red Cross Hospital

Conflict of interest: None

Rheumatoid arthritis is a chronic inflammatory disease that affects the synovium of the joints, but it is also a systemic disease with many medical complications, such as pulmonary complications. The management of patients with complications is mainly performed by collagen disease rheumatologists, but if physicians focus too much on complications, they may neglect to control the progression of joint destruction and to intervene orthopedically at appropriate times. In addition, many patients with complications are referred to the department of collagen disease rheumatologists, and there is less opportunity to see patients with rheumatoid arthritis who have not been treated for the first time or have not yet developed complications from the initial treatment than the department of rheumatology, which is mainly composed of orthopedist. Fortunately, the orthopedists and the collagen disease rheumatologists are in the same department at our center, so that we collagen disease rheumatologists have many opportunities to treat patients with rheumatoid arthritis who have not yet been treated. In addition, collagen disease rheumatologists have many opportunities to receive feedback from orthopedic surgeons on imaging interpretations such as joint x-rays and ultrasounds, and to share surgical findings. In addition, orthopedists will be able to provide medical care at ease with the presence of us collagen disease rheumatologists. In this lecture, I would like to outline the advantages of collaboration between orthopedists and collagen disease rheumatologists without barriers.

## S2-1

### Consideration of Reproductive Challenges in Patients with Rheumatoid Arthritis Based on 20 Years of Experience

Atsuko Murashima<sup>1,2</sup>, Kayoko Kaneko<sup>3</sup>, Mikako Goto<sup>2</sup>, Chinatsu Takai<sup>3</sup>, Chie Kono<sup>3</sup>, Sawako Abe<sup>3</sup>, Eiko Miyagawa<sup>3</sup>

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Conflict of interest: None

We are pleased that advances in medicine and medical technology have made it commonplace to talk about the pregnancy of patients with rheumatic diseases. However, pregnancy in patients with rheumatic diseases must be at high risk for both mothers and infants. Recently, clinical practice guidelines for the relevant field have been published in Japan and overseas. Although the contents written in Japan are not significantly different from those of EULAR and ACR, they lack themes of contraceptive methods and fertility treatment. We expect that it will be improved in future updates. The creation of evidence on an “all-Japan” basis is a top priority issue that should be tackled by academic societies. Evidence in this field is not sufficient, and it is undeniable that domestic and international guidelines are based on consensus among experts rather than evidence. It is expected that evidence will be generated in this field by various methods which are registry studies such as the PLEASURE-J study started in 2019 studies based on real-world data. One of the issues in this area is the development of a team medical system. There is a need to collaborate with specialists in reproductive medicine to deal with cases requiring infertility treatment and to preserve fertility in cyclophosphamide treatment. In addition, collaboration with obstetricians and neonatologists is essential because SLE is associated with many perinatal complications such as hypertensive disorders of pregnancy and early preterm rupture of membranes. Furthermore, collaboration with medical staff such as pharmacists, nurses, and midwives is also important from the perspective of preconception care. A guide for supporting RA patients has just been published, and it is hoped that this approach will spread to the entire field of rheumatic diseases in the future. In this session, I would like to summarize our experiences over the past 20 years, including my own data, and mention future issues.

## S2-2

### Current status and issues of Oncofertility in Japan-How does it relate to rheumatology?

Nao Suzuki

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Conflict of interest: None

Oncofertility is a multidisciplinary field of medicine that bridges the biomedical and social sciences to examine issues related to the reproductive options, intentions, and goals of individual patients in light of their diagnosis, treatment, and survival. In clinical practice, it aims to bring physical, mental, and social enrichment to cancer patients of reproductive age and before by providing biomedical and social science assistance to patients and their families to have children and to rethink their meaning (Japan Society for Fertility Preservation). In Japan, the Japan Society for Fertility Preservation was established in 2012, and in 2014, the Japanese Society of Obstetrics and Gynecology issued an opinion on cryopreservation for medical indications for cancer patients. In addition, in 2017, the Japanese Society of Clinical Oncology published “Guidelines for Fertility Preservation in Childhood, Adolescent, and Young Adult Cancer Patients”, and this area is becoming established as a field in Japan. In April 2021, the government started to provide financial support for fertility preservation therapy for childhood and AYA cancer patients as part of a research project, and collagen disease was included as a target disease for this financial support. When providing decision support to patients and their families in cancer and reproductive medicine, it is important to ask whether or not they wish to preserve their fertility, but it is also important to build a decision support system that can provide reliable information at the right time

so that patients can choose not to preserve their fertility. To provide decision support to cancer patients and their families, who are anxious and fearful in the face of an uncertain future, while giving priority to cancer treatment above all else, there is an urgent need to develop human resources among medical professionals in charge of Oncofertility. In this lecture, I will give an overview of the recent findings in this field.

## S2-3

### Fertility preservation: clinical practice and the results of our nationwide survey

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Conflict of interest: None

The progress of assisted reproductive technology (ART) has been remarkable in recent years, and the number of ART treatment cycles in Japan has increased rapidly since around 2000 in combination with the aging of the child-bearing age. On the other hand, advances in cancer diagnosis and treatment have significantly improved the prognosis of young cancer patients, and QOL including post-treatment fertility has become more important. Cancer treatments such as chemotherapy and radiation therapy may lead to deterioration of gonad function and loss of fertility. Fertility preservation in cancer patients, in which oocytes, embryos, ovarian tissues, or sperms are frozen before treatment and attempts to become pregnant using these frozen products after cancer treatment is completed, is called oncofertility; it has been developing in the last 10 to 15 years, along with the progress of ART. The awareness of oncofertility has increased considerably in Japan recently. Not only in treatment for cancer but also for systemic autoimmune disease, treatments such as cyclophosphamide that may affect fertility may be performed, but regarding fertility preservation in this area, awareness is low even among medical professionals and knowledge is extremely limited. In this lecture, I will first explain the basic knowledge of ART and fertility-preserving treatment. Then, current situation of fertility preservation in the oncology field in Japan will be introduced. Finally, I will introduce the results of our two surveys on fertility preservation in the area of autoimmune diseases (a survey on fertility preservation for patients with autoimmune diseases at the certified ART institutions of the Japan Society of Obstetrics and Gynecology and a survey on the approach to fertility during the treatment at the certified educational facilities of the Japanese Society of Rheumatology). Future perspectives of fertility preservation for patients with autoimmune diseases will also be discussed.

## S2-4

### Perspectives on the kidney as the most important organ in complicated pregnancy

Keiko Uchida

Division of Nephrology, Department of Internal Medicine, Tokyo Women's Medical University

Conflict of interest: None

During pregnancy, the kidneys play significant physiological changes. In particular, the glomerular filtration rate (GFR) is 1.5 times higher than in non-pregnancy, which contributes to the maintenance of pregnancy. If this change occurs in a pregnant woman with renal disease, her serum creatinine (Cr) will be decreased and with proteinuria, her urine exam will be worsened. If these changes are clinically occurred in a patient with renal complications, the renal lesions are focal or segmental, and the area without lesions has physiological function. Nephroprotective treatment is always used with the treatment of renal disease activity, the main purpose of that is the suppression of hyperfiltration. But many drugs of nephroprotective treatment are contraindicated during pregnancy, and the patient is in a state of hyperfiltration. So even if the pregnancy is successful, there are cases where the renal function gradually deteriorates afterwards. Pregnant women with renal complications develop pregnancy complications more frequently than she without renal complications, even if they are in CKD1,2. The clinical manifestations of hypertensive disorder



of pregnancy (HDP) are hypertension, proteinuria and edema, which are caused by the cross-talk between placental insufficiency and the kidneys. In many rheumatic diseases, the age of childbearing is the preferred age of onset, and there are cases in which the disease must be controlled using drugs that are contraindicated during pregnancy. Furthermore, in cases of renal complications, it is necessary to perform a renal biopsy before pregnancy whenever possible to identify the renal lesion, assume the risk of pregnancy and childbirth, and share information with the patient about the treatment plan. In addition, more careful preconception care is necessary because pregnancy complications with renal complications are more likely to affect maternal renal function during and after pregnancy than those without.

### S3-1

#### Support for patients with rheumatoid arthritis according to their life stage

Toshihiro Matsui

Department of Rheumatology, National Hospital Organization Sagami-hara National Hospital

Conflict of interest: Yes

In recent years, remarkable progress has been made in the treatment of rheumatoid arthritis (RA), and joint destruction as well as disease activity have been suppressed. Under such circumstances, dealing with various issues according to the life stage, such as the transitional medical care system from childhood to adulthood, the support system for life at work and school, pregnancy and childbirth, and complications in the elderly age are required. RA treatment by life stage (elderly, transitional, and perinatal) is mentioned in the revised guidelines (“2020 Japan College of Rheumatology Clinical Practice Guidelines for the Management of Rheumatoid Arthritis”) and will be discussed further in the future. On the other hand, it is expected that the provision of correct information, knowledge enlightenment, and various support systems for RA patients and their families at various life stages will be further enhanced. These cannot be practiced by physicians alone, and a multidisciplinary medical team including nurses, pharmacists, rehabilitation staff (physical therapists, occupational therapists, etc.), nutritionists, social workers, and care managers is desired to be constructed. This time, we organized a research group of “Research on Support for Rheumatoid Arthritis Patients According to Life Stage” (Health, Labor and Welfare Science Research Grant) consisting of physicians, medical staffs (nurses, pharmacists, rehabilitation staffs) and representatives of patient groups, and collaborated to create “Guide for medical staff to support patients with rheumatoid arthritis according to their life stage”. In this lecture, I would like to think about support for RA patients according to their life stages, focusing on the introduction of the overall picture of the guide.

### S3-2

#### Patient support during the transition period

Masaaki Mori<sup>1</sup>, Takako Miyamae<sup>2</sup>, Toshihiro Matsui<sup>3</sup>

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Conflict of interest: None

Juvenile idiopathic arthritis (JIA) is defined as chronic arthritis of unknown cause that develops before the age of 16 and lasts for at least 6 weeks, and its type is classified into 7 types. The pathological type similar to rheumatoid arthritis (RA) corresponds to “articular type” JIA. As a first step towards engaging in patient support during the transition period, it is necessary to recognize that JIA and RA are not the same and there are several differences. The drugs approved by the JIA are fairly limited compared to RA, and methotrexate is the only approved standard treatment for conventional synthetic antirheumatic drugs. There are few drugs approved for biologics, and JAK inhibitors cannot be used in Japan yet. Uveitis is important as a complication of articulated JIA, and the prevalence of JIA-related uveitis in Japan is about 6%, and there is a high risk of girls

with oligoarthritis. For transitional patients to be followed up in the adult clinical department, it is necessary to encourage their independence, and for that purpose, a checklist for transitional patients according to age and a pediatric rheumatic disease transition support notebook “MIRAI TALK” are available. In addition, JIA is covered by medical expenses subsidies for pediatric chronic diseases and designated intractable diseases, and since the medical expenses subsidy system will be switched to transitional JIA patients at the age of 20, medical professionals will fully understand both systems. It is also important to help them prepare for higher education and work without stress to make them a member of society. In this lecture, referring to the “Transition Support Guide for Adult Clinicians”, we will outline the matters that should be shared among some medical stuffs based on the above-mentioned characteristics of the transition period, according to nine CQs.

### S3-3

#### Support during pregnancy and childcare

Sakiko Isojima

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Conflict of interest: None

The goal of rheumatoid arthritis treatment is to maintain remission and keep the patient's quality of life. For patients who wish to have a baby, it is important to provide support for pregnancy. In order for patients to have a better pregnancy and childbirth, it is important to preserve their fertility and maintain remission during pregnancy and postpartum by providing appropriate interventions in the following three stages: (1) preconception, (2) pregnancy, and (3) childcare. (1) preconception: It is important to share information about impact of disease activity and therapeutic drugs on pregnancy, and to maintain remission with available drugs during pregnancy. In addition, it is important to provide obstetric and gynecological information such as appropriate contraceptive methods and precautions to be taken during fertility treatment. Even for patients who do not wish to become pregnant immediately, it is important to preserve their fertility by providing information and sharing knowledge with a view to future pregnancy. (2) pregnancy: It is important to continue treatment with drugs that can be used during pregnancy to maintain remission, which will ultimately lead to a good pregnancy outcome. Information on support systems and consultation services available after childbirth should be provided during pregnancy to help reduce anxiety about childcare. (3) childcare: Arthritis is more likely to worsen after childbirth because of the burden on the joints due to childcare. It is important to devise a way of carrying the baby that minimizes the burden on the joints, a nursing position, and a bathing method. For patients who wish to breastfeed, it is important to maintain remission with medication that takes breastfeeding into consideration, and to prevent the progression of joint destruction during the childcare period. In addition, postpartum period is a time when mental changes are likely to occur, and the awareness and support of those around the patient are very important. Thus, in order to support RA patients during pregnancy and childcare, it is necessary to provide versatile support. In order to provide the best rheumatic care, the role of not only physicians but also healthcare professional is very important.

### S3-4

#### Multi-disciplinary approach for the total care of elderly RA patients

Motomu Hashimoto

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Conflict of interest: Yes

With the progress of RA treatment, rheumatologists can achieve the remission or low disease activity for elderly RA patients. However, we should pay more attention to preserve their ADL and QOL than to prevent the bone destruction. Multi-disciplinary approach is effective for achieving the total care of elderly RA patients. Needless to say, nurses are important for the early detection and prevention of serious infections or psychological distresses. Pharmacists should prevent polypharmacy and medication errors due to cognitive decline of the elderly. Physical therapists and dieticians will help prevent sarcopenia and retain the muscle

strength of the elderly. Social workers are helpful to prevent the social frail. In this seminar, the multidisciplinary approach for the total care of elderly RA patients will be discussed.

### S3-5

#### Support from nurses' perspective

Mie Fusama

School of Nursing, Takarazuka University

Conflict of interest: Yes

When providing patient support in rheumatoid arthritis (RA) treatment, it is necessary to consider patients' life stages. In addition, when providing support from nurses' perspective, it is important to first understand the needs of patients in the actual clinical setting and the support provided by nurses. According to the "Study on support for patients with RA depending on their life stage research" which was implemented on the nurses who are registered as scientific research of the Ministry of Health, Labor, and Welfare of Japan, the questions from patients to nurses and the actual support given by nurses were revealed. Nurses were often asked by patients about "RA in general", "drug actions / side effects", "self-injection", "medical expenses", and "daily life". Considering the life stage, many nurses answered that they had no experience in supporting patients with JIA whose symptoms have developed during childhood, but the higher percentage of nurses answered that important contents for support are "patients having knowledge about their own illness", "patients' family having knowledge about their children's illness" and "knowledge of side effects and complications". Most of the support provided to patients of childbearing age was "effects of drugs", "effects of pregnancy on RA", and "effects of RA on pregnancy". Nurses considered that it was necessary to pay attention to "infection risk", "steroid / methotrexate", "osteoporosis / compression fracture", etc. in support for elderly patients. Referring to these findings, I would like to focus on patient-centered support considering their life stage that should be provided from nurses' point of view including psychosocial aspects.

### S3-6

#### Support from a Pharmacist's Perspective

Miho Tsujimura<sup>1,2</sup>

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Conflict of interest: None

Team medicine is "the provision of medical care that appropriately responds to the situation of patients by having various medical staff with high expertise share objectives and information, share tasks, and cooperate with each other to help each other". However, in actual medical practice, there are times when people outside their own specialty are assigned to other professions. This is not an accurate team medicine. Although the specialist may know more about the situation, it is important for the team to understand the entire team and work together. My goal in team medicine is to support patients by utilizing the characteristic that "pharmacists are knowledgeable about medicines". In order to do so, it is necessary to understand not only medicine but also the entire rheumatology care and to cooperate with other staff. I believe that team medicine means that the patient becomes a member of the team, and all staff members complement each other to achieve the goal of treatment. In order to maintain physical functions, it is important to detect adverse events before they become serious. Treatment of RA involves suppressing abnormal immunity. Patients with RA are accustomed to feeling unwell and may not be aware of complications of infection. As a member of the team, it is necessary for patients themselves to observe their own bodies closely, to notice any changes in their physical condition, and to promptly convey this information to medical institutions. RA patients come from a wide range of age groups. Because of the long-term relationship with a single patient, support in a wide range of fields tailored to the patient's life stage is necessary. It is important to involve not only medical professionals and patients' families involved in RA, but also staff from various fields and the local community in team medicine. We would like to consider what we can do as pharmacists in this context.

### S3-7

#### Multidisciplinary support for rheumatoid arthritis patients at different life stages-Support from the standpoint of physical therapists-

Noriyshi Shimahara<sup>1</sup>, Shinji Sato<sup>1</sup>, Norikazu Hijikawa<sup>2</sup>, Megumi Nakamaura<sup>3</sup>, Ako Ohnishi<sup>4</sup>, Yuki Tanaka<sup>4</sup>, Ayuko Sogabe<sup>5</sup>, Naoya Sawada<sup>5</sup>, Yasuaki Okuda<sup>5</sup>, Makoto Onishi<sup>5</sup>, Shogo Toyama<sup>6</sup>, Toshihiro Matsui<sup>7</sup>, Ryuichi Saura<sup>8</sup>

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Conflict of interest: None

Advances in drug treatment for RA have made it possible for patients to lead daily lives similar to those of healthy people. Rheumatoid arthritis treatment guidelines 2020 also clearly state that rehabilitation treatment should be continued to maintain physical functions. The purpose of rehabilitation therapy for RA today is not only to maintain function and improve the ability to perform daily activities, but also to improve and maintain the quality of life (QOL) of patients by helping them to regain the kind of life they want. However, even if remission is not achieved, it is important to listen to and carefully respond to the wishes and desires of patients at each stage of life, from diagnosis to treatment, life (transition, employment, pregnancy, geriatrics), terminal stage, and end-of-life care. It is important to listen to the wishes and requests of patients at each stage of life, such as gestational age, terminal stage, and end-of-life care, and to respond to them carefully. In addition, it is necessary to understand and accompany the patient experience, to promote understanding of the disease, and to increase adherence. In order to achieve this, it is important to consider medical treatment as a part of the patient's life without separating it from social life, to gain the trust of patients and their families, and to provide multidisciplinary cooperation and support to facilitate treatment selection and decision-making. In order to gain the trust of patients and their families and to facilitate treatment selection and decision-making, multidisciplinary cooperation and support must be practiced. At our hospital, we are working on medical treatment with the goal of improving QOL and helping patients acquire their desired lifestyle and social activities according to their life stage. Specifically, we have a system in which we listen to the wishes and requests of patients regarding their lifestyle and social activities, consult and collaborate with multiple professions, and continue to provide treatment and support through outpatient and inpatient care. In this context, the presenter, as a physical therapist, is involved in providing highly individualized rehabilitation treatment for RA with a focus on "nurturing activities" support, and is working to improve adherence to this treatment. In this symposium, we will report on the social life support for each life stage that RA patients desire from the standpoint of a physical therapist.

### S3-8

#### Support from the perspective of an occupational therapist

Shinya Taguchi<sup>1</sup>, Hideshi Yamazaki<sup>2</sup>, Tetsuo Takanashi<sup>2</sup>, Toshihiro Matsui<sup>3</sup>, Ryuichi Saura<sup>4</sup>

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Conflict of interest: None

With the progress of therapeutic drugs, the purpose of rehabilitation therapy for rheumatoid arthritis (RA) has changed, from maintaining and improving functions under low disease activity or during the course of treatment toward remission, to supporting patients to participate in society and enjoy daily life as healthy people do. No matter how much progress is made in therapeutic drugs, in order for RA patients to lead a life similar to

that of healthy people, it is important to establish a system in which medical professionals provide continuous support according to the patient's life stage and patient journey. This issue is also discussed in this symposium as "multidisciplinary support for rheumatoid arthritis patients at different life stages". It is no exaggeration to say that rehabilitation medicine is an indispensable piece of this system. Although our hospital is not fully equipped to provide support for patients with WOCBA-RA during the transition from childhood to adulthood or after pregnancy and childbirth, we do provide comprehensive outpatient rehabilitation services to help patients continue to work, participate in society, and live independently, which are important themes in each life stage of adulthood, adulthood, and old age. We provide comprehensive support in a multidisciplinary manner. In addition, although long-term support is normally desirable, immediate support necessary at each life stage, such as higher education and relocation, is also provided. As an occupational therapist, I have supported many patients with RA using my foresight and specialized skills in hand rehabilitation, orthotic therapy, and lifestyle guidance (joint protection and self-help devices) in the hope that they will be able to lead pain-free lives with deformity-free hands and participate in society without anxiety. In supporting patients with RA at different stages of life, it is necessary not only to have long-term relationships with patients, but also to have the skills to respond immediately to requests for support. In order to prevent functional disabilities such as deformity and pain in RA patients, and to enable RA patients to live daily lives, participate in society, and study without anxiety, occupational therapists, especially those concerned with ADLs, should be involved in support from an early stage, whether in the short or long term. In this symposium, we will discuss the role of occupational therapists in a multidisciplinary manner.

## S4-1

### Epidemiology and treatment of osteoarthritis

Hunter J David

Kolling Institute, University of Sydney, Sydney, Australia

Conflict of interest: None

Osteoarthritis (OA) is a highly prevalent, disabling disease affecting more than 500 million people worldwide. This substantial prevalence is accompanied by tremendous individual and socioeconomic burden. For most of the millions of people affected by OA, its development can be linked to multiple risk factors. For knee osteoarthritis, which accounts for approximately 85% of the burden attributable to OA, the leading risk factors are eminently modifiable, namely obesity and joint injury. As there is currently no cure for OA, this is of paramount importance and we hope to see increasing public health interventions to stem disease onset. The initial assessment for OA should include a complete history and physical examination, including ascertaining the effect of OA on function, quality of life, occupation, mood, sleep, social interactions, ability to engage within the community and leisure activities. A number of recent studies have demonstrated that the majority of patients do not receive appropriate care and have further highlighted the areas where we are not serving our patients well by under-utilizing efficacious, evidence-based lifestyle and behavioural management, particularly exercise and weight loss. Active, non-pharmacologic interventions are the mainstay of OA management and should be tried first, followed by or in concert with medications to relieve pain when necessary. These core treatments (often referred to as non-pharmacologic/ conservative therapies) include education, weight management/ diet, promotion of physical activity, strengthening exercises and behaviour change support. Optimal uptake of recommendations and adherence to behaviour change modifications are key elements of OA treatment and can be enhanced by education, establishing treatment goals, and regular monitoring. Referral of patients with end-stage OA to a surgeon should be considered when all appropriate conservative options, delivered for a reasonable period, have failed.

## S4-2

### Mechanisms of synovial joint development, maintenance, and degeneration

Taku Saito

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Conflict of interest: Yes

Articular cartilage is formed in the synovial joint cavity during skeletal development. Previous studies indicate that articular and growth plate cartilage are derived from different cell sources and regulated by different signaling pathways. Articular cartilage is composed of the superficial zone and the deeper zone, which have different characteristics and roles against mechanical loading and contribute to the smooth movement of synovial joints. Degeneration of articular cartilage leads to osteoarthritis, the most prevalent joint disorder. I introduce molecular mechanisms underlying these biological and pathological events.

## S4-3

### Application of iPS cell-derived cartilage to regenerate articular cartilage damage

Noriyuki Tsumaki

Department of Biochemistry and Molecular Biology, Graduate School of Medicine, Osaka University

Conflict of interest: Yes

Cartilage consists of chondrocytes embedded in abundant extracellular matrix (ECM). Chondrocytes produce and maintain ECM, and ECM is necessary for the chondrocytes to sustain their chondrocytic property including the production of cartilage ECM. Articular cartilage, when damaged through trauma, has only limited capacity for repair, probably because the damage causes a loss of cartilage ECM, disrupting the chondrocytic environment. The continued use of joints with damaged cartilage and poor repair capacity gradually expands the damaged area on the joint surface, resulting in debilitating conditions such as osteoarthritis. Human induced pluripotent stem cells (hiPSCs) are reprogrammed somatic cells that have pluripotency and self-renew capabilities. We have developed a method by which human iPSCs (hiPSCs) are differentiated toward chondrocytes that produce ECM to prepare cartilage (hiPSC-derived cartilage). We are studying the use of hiPSC-derived cartilage as a curative material to be transplanted into the defect of articular cartilage. To reduce the cost of this regenerative medicine, allogeneic transplantation is preferable. hiPSC-derived cartilage shows low immunogenicity like native cartilage, because the cartilage is avascular and chondrocytes are segregated by the extracellular matrix. After performing pre-clinical tests by transplanting iPSC-derived cartilage into defects created in the articular cartilage of model animals, a clinical test is being implemented.

## S4-4

### Join pain in osteoarthritis

Xu Cao

Johns Hopkins University, Baltimore, USA

Conflict of interest: None

Joint pain is the defining symptom of osteoarthritis (OA) but its origin and mechanisms remain unclear. Here, we investigated an unprecedented role of osteoclast-initiated subchondral bone remodeling in sensory innervation for OA pain. We show that osteoclasts secrete netrin-1 to induce sensory nerve axonal growth in subchondral bone. Reduction of osteoclast formation by knockout of receptor activator of nuclear factor kappa-B ligand (*Rankl*) in osteocytes inhibited the growth of sensory nerves into subchondral bone, dorsal root ganglion neuron hyperexcitability, and behavioral measures of pain hypersensitivity in OA mice. Moreover, we demonstrated a possible role for netrin-1 secreted by osteoclasts during aberrant subchondral bone remodeling in inducing sensory innervation and OA pain through its receptor DCC (deleted in colorectal cancer). Importantly, knockout of *Netrin1* in TRAP-positive osteoclasts or knock-down of *Dcc* reduces OA pain behavior. In particular, inhibition of osteoclast activity by alendronate modifies aberrant subchondral bone remodeling and reduces innervation and pain behavior at the early stage of OA. In addition, osteoblast secreted prostaglandin E2 (PGE2) during aberrant subchondral bone remodeling induces pain and OA progression in mice. Specific deletion of the major PGE2 producing enzyme cyclooxygenase 2 (COX2) in osteoblasts or PGE2 receptor EP4 in peripheral nerve markedly ameliorates OA symptoms. Mechanistically, PGE2 sensitizes dorsal root ganglia (DRG) neurons by modifying the voltage-gated sodium channel Na V1.8,



evidenced by that genetically or pharmacologically inhibiting NaV1.8 in DRG neurons can substantially attenuate OA. These results indicate that netrin-1 derived from osteoclasts induce sensory innervation for OA pain. Moreover, drugs targeting aberrant subchondral bone remodeling could attenuates OA pain through rebalancing PGE2 production and Na V1.8 modification.

## S4-5

### Efficacy of anti-NGF antibody in osteoarthritis

Marc Hochberg

University of Maryland School of Medicine, Baltimore, USA

## S5-1

### SARS-CoV-2-associated vasculopathy and vasculitis - an enigmatic disease

Akihiro Ishizu<sup>1</sup>, Daigo Nakazawa<sup>2</sup>, Sakiko Masuda<sup>1</sup>, Yuka Nishibata<sup>1</sup>, Utano Tomaru<sup>3</sup>, Tamihiro Kawakami<sup>4</sup>

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Conflict of interest: None

[Objective] SARS-CoV-2 has caused the COVID-19 pandemic. Recent studies have revealed that thrombotic events contribute to its high mortality. In addition, accumulated case reports suggest the association of SARS-CoV-2 infection with vasculitis. This study aimed to demonstrate the expected mechanism of SARS-CoV-2-associated vasculopathy and to clarify the association between SARS-CoV-2 and vasculitis. [Methods] Literatures were reviewed to draw a schema that demonstrates the mechanism of SARS-CoV-2-associated vasculopathy. Gene expression profiles of peripheral blood neutrophils were compared between before and after cocultivation with SARS-CoV-2. Systematic review was performed to know the trends of SARS-CoV-2-associated vasculitis. Skin tissues biopsied from an IgA vasculitis (IgAV) patient with SARS-CoV-2 infection were subjected to histological examinations. [Results] SARS-CoV-2 can infect vascular endothelial cells via ACE2 as its receptor and injure the cells. Platelets and neutrophils activated by DAMPs released from the damaged cells aggregate on the endothelial surface and form NETs. Normal density granulocytes were led to NET formation by cocultivation with SARS-CoV-2 with a post-translational rather than transcriptional mechanism. When the pubmed engine was searched for the indexes of SARS-CoV-2 and vasculitis, 303 papers were hit in the Case Report category at November 26, 2021. They included 114 papers mentioned Kawasaki disease, 28 papers mentioned ANCA-associated vasculitis, and 16 papers mentioned IgAV. Severe leukocytoclastic vasculitis with NET deposition was observed in the skin of the patient with IgAV with SARS-CoV-2 infection. [Conclusion] SARS-CoV-2 induces NETs directly and indirectly, resulting in a formation of robust immunothrombi implicated in the mechanism of SARS-CoV-2-associated vasculopathy. Although it remains elusive whether SARS-CoV-2 can be an etiology of vasculitis, it may trigger the development of some kinds of vasculitis.

## S5-2

### Useful biomarkers in the management of vasculitides

Jun Ishizaki

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Conflict of interest: None

By using rituximab and the C5a receptor inhibitor avacopan for ANCA-associated vasculitis (AAV) and tocilizumab for Takayasu arteritis and giant cell arteritis, steroid-free treatment has become more realistic in the management of vasculitides. However, relapse remains common in AAV and large vessel vasculitis (LVV). Although traditional acute-phase indicators such as CRP and ESR are used in clinical practice as biomarkers of

disease activity and predictors of relapse, these biomarkers lack the sensitivity and specificity required for monitoring the disease activity of AAV and LVV. Moreover, in patients with LVV receiving tocilizumab, CRP levels decrease quickly and may not correctly reflect the disease activity. The usefulness of ANCA monitoring for patient management decisions in AAV is limited, and BVAS, a structured clinical assessment of AAV, does not include ANCA monitoring. True remission may not be achieved in many patients without clinical symptoms, and persistent vascular inflammation may increase the risk of subsequent relapse. Therefore, additional markers of disease activity are needed in addition to transition to therapeutic strategies using molecular targeted drugs to decrease relapse, decrease steroid-related adverse events and improve patient outcomes. We identified several promising biomarkers of disease activity and organ involvement in AAV using a targeted proteomics approach with serum samples obtained from a Japanese nationwide large cohort study. In a quantitative analysis of 135 biomarker candidates, tissue inhibitor of metalloproteinase-1 (TIMP-1) was the best performing marker of disease activity, able to distinguish highly or mildly active AAV from remission during remission-induction therapy. Serum TIMP-1 levels also proved useful as a predictor of relapse and sustained remission in maintenance therapy. In this symposium, we would like to discuss the limitations of existing activity markers and the possibilities of novel serum biomarkers in patients with AAV and LVV.

## S5-3

### Emerging molecular targeted therapy of microscopic polyangiitis and granulomatosis with polyangiitis - when, which and how to use?

Masayoshi Harigai

Division of Rheumatology, Department of Internal Medicine, Tokyo Women's Medical University School of Medicine

Conflict of interest: Yes

Recent progress in basic and translational researches of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has revealed that the orchestration of innate and adapted immunity contribute to the development of the disease. Treatments aiming at breaking a vicious cycle composed of complements, neutrophils, cytokines, and neutrophil extracellular traps are expected to bring about high proportions of achieving and maintaining remission with a low dose of glucocorticoids (GCs) or even without GCs. The first targeted therapy approved in Japan for microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) is rituximab (RTX). The landmark studies, RAVE and RITUXIVAS demonstrated non-inferior efficacy of RTX versus oral and intravenous cyclophosphamide (CY), respectively, with comparative safety in patients with newly diagnosed or relapsed MPA and GPA. LoVAS study addressed doses of concomitant GCs with RTX in patients with MPA and GPA. Reduced-dose prednisolone was non-inferior to high-dose prednisolone in the proportion of patients achieving remission at month 6. PEXIVAS study enrolling MPA and GPA with renal involvement or pulmonary hemorrhage also demonstrated non-inferiority of reduced-dose GCs in terms of death or end-stage kidney disease. Avacopan is the second targeted therapy approved for MPA and GPA in Japan. In ADVOCATE Phase III clinical trial, patients with active MPA or GPA received either 30 mg avacopan twice daily or prednisone on a tapering schedule in combination with rituximab or cyclophosphamide. The trial met its two primary endpoints: avacopan showed non-inferiority to prednisone for achieving remission at 26 weeks and superiority for maintaining remission at week 52. Application of the ample evidence to treatment strategy is a next challenge for physicians treating AAV.

## S5-4

### Optimizing treatment of large vessel vasculitides-the time is now

Takahiko Sugihara<sup>1</sup>, Hajime Yoshifuji<sup>2</sup>, Haruhito A Uchida<sup>3</sup>, Yoshikazu Nakaoka<sup>4</sup>

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Conflict of interest: Yes

Systemic inflammatory findings of Takayasu arteritis (TAK) and giant cell arteritis (GCA) respond well to treatment with glucocorticoids (GCs), but increasing cumulative doses of GCs are required to control frequent relapse, and progressive arterial stenosis or vasodilatation may still occur. To prevent the progression of vascular damage and reduce the cumulative dose of GCs, the importance of adjunct therapy is being increasingly recognized. The Japanese Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis (JPVAS) published a 2017 narrative guide on the management of TAK and GCA. The treatment strategy of GCA in Japan was almost similar to those of the 2018 update of the EULAR recommendations for the management of large vessel vasculitides (LVV). These recommended that tocilizumab should be used in selected patients who had relapses or high risk of GC-associated adverse events. In the ACR guideline, the members conditionally recommend the use of oral GCs with tocilizumab over oral GCs alone for patients with newly diagnosed GCA. For patients with TAK, it was recommended to add immunosuppressive drugs to GCs as initial treatment in ACR and EULAR. 2017 Japanese guide and EULAR recommendation share the same point about the use of tumor necrosis factor inhibitors and tocilizumab, but the position of ACR was quite different. However, most of all recommendations were based on very low evidence and expert opinions. We should clarify the treatment goals for TAK and GCA and establish a framework for an algorithm to achieve such treatment goals. In cooperation with the LVV members of the JPVAS, using the Delphi method, we surveyed and integrated expert opinions on remission criteria for TAK and GCA, treatment goals, and treatment algorithms for achieving those goals. The JPVAS study group is also conducting several cohort studies of GCA and TAK, and we will show the effectiveness and safety of the treatment in this symposium.

## S6-1

### Elucidation of novel mechanism of osteoclast differentiation in rheumatoid arthritis

Noriko Komatsu

Department of Immunology, Graduate School of Medicine and Faculty of Medicine the University of Tokyo

Conflict of interest: None

Rheumatoid arthritis (RA) is an autoimmune disease, characterized by inflammation and destruction of bone and cartilage in joints. In RA, there are three kinds of bone destruction: bone erosion, periarticular and systemic bone loss. RANKL is essential for osteoclast differentiation. The indispensable role of osteoclasts play was proven by basic studies as well as clinical application of anti-RANKL antibodies. Thus, it is important to clarify which type of cells produce RANKL and how RANKL expression is regulated. We found that RANKL on synovial fibroblasts are primary responsible for bone erosion in autoimmune arthritis using cell-type specific RANKL knock-out mice. We recently reported that bone marrow plasma cells promote osteoclastogenesis and periarticular bone loss. Integration of single cell RNA-sequencing with biological studies clarified heterogeneity of synovial fibroblasts as well as immune cells including T cells and macrophages in RA synovium. Synovial fibroblasts in arthritis are divided into inflammatory and tissue-destructive subsets, both of which interact with the immune system to exacerbate joint inflammation and bone erosion. IL-6 produced from inflammatory synovial fibroblasts convert Foxp3<sup>+</sup>T cells into Th17 cells (exFoxp3<sup>+</sup>Th17 cells), the most potent osteoclastogenic T cells, which in turn promote RANKL on tissue-destructive synovial fibroblasts. Recently, we identified that synovial fibroblast-specific enhancer region that critically contributes to bone erosion by regulating RANKL expression. We are now investigating the molecular mechanisms underlying the tissue-destructive fibroblast phenotypes. Here, I will provide an overview of advances in understanding of bone destruction in RA based on clarification of immune-fibroblast-bone triangle interplay.

## S6-2

### Resident synovial macrophages as gate-keepers of joint inflammation

Gerhard Krönke

University of Erlangen, Germany

Conflict of interest: Yes

Macrophages (MΦs) are considered to contribute to chronic inflammatory diseases such as rheumatoid arthritis (RA). However, both the exact origin and role of MΦs during inflammatory joint disease have remained unclear. Using scRNA sequencing and 3D imaging approaches we were recently able to address the heterogeneity of synovial macrophage subsets as well as their differential roles during onset and progression of RA.

## S6-3

### Identification of a novel arthritis-associated osteoclast precursor macrophage: its therapeutic potential

Masaru Ishii

Osaka University Graduate School of Medicine

Conflict of interest: Yes

Osteoclasts have a unique bone-destroying capacity, playing key roles in steady-state bone remodelling and arthritic bone erosion. Whether these two populations of osteoclasts in different tissue settings arise from the same precursor states of monocytoid cells is presently unknown. Here, we show that osteoclasts in pannus originate exclusively from circulating bone marrow-derived cells and not from locally resident macrophages. We identify CX<sub>3</sub>CR1<sup>hi</sup>Ly6C<sup>int</sup> macrophages (termed “arthritis-associated osteoclastogenic macrophages [AtoMs]”) as the osteoclast precursor (OP)-containing population in the inflamed synovium, comprising a subset distinct from conventional OPs in homeostatic bone remodeling. Tamoxifen-inducible FoxM1 deletion suppressed the capacity of AtoMs to differentiate into osteoclasts in vitro and in vivo. Furthermore, synovial samples from human rheumatoid arthritis (RA) patients contained CX<sub>3</sub>CR1<sup>+</sup>H-LA-DR<sup>hi</sup>CD11c<sup>+</sup>CD80<sup>+</sup>CD86<sup>+</sup> cells that corresponded to human AtoMs, and osteoclastogenesis was inhibited by the FoxM1 inhibitor, thiostrepton, constituting a potential target for RA treatment. In this presentation I will show the update of characterization, function and differentiation of AtoMs, specially focusing on their potential as a novel target for treating joint and bone erosions in arthritic diseases.

## S6-4

### Synovial tissue macrophages in joint homeostasis, Rheumatoid Arthritis, and disease remission

Mariola Kurowska-Stolarska

Research into Inflammatory Arthritis Centre Versus Arthritis (RACE), University of Glasgow, Glasgow, UK

Conflict of interest: None

Until recently, synovial tissue macrophages were mainly recognised as the main producers of pathogenic TNF. Advances in single-cell omics facilitated discovery of different synovial tissue macrophage populations providing an atlas of their discrete phenotypic clusters. This, together with interrogation of their functions *ex-vivo* and in experimental models, have re-defined human and mouse synovial tissue macrophage biology, opening new opportunities to better understand the pathology of the arthritic joint. These studies identified the synovial tissue macrophage clusters that form a protective lining barrier and actively participate in remission of Rheumatoid Arthritis (RA). In this presentation, we discuss how distinct functions of different macrophage clusters shape the synovial tissue environment in health, during inflammation and disease remission, and whether these recent findings can inform clinical outcomes and novel treatments for RA.

## S6-5

### Myeloid-derived suppressor cells (MDSC) in rheumatoid arthritis

Akio Morinobu

Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University

Conflict of interest: Yes

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population with immunosuppressive function derived from immature bone

marrow cells. Mouse MDSC is defined by a surface marker of CD11b<sup>+</sup> Gr-1<sup>+</sup>. It also has a marker of granulocytes, but differs from neutrophils in that it has an immunosuppressive function. Although it is well-studied that MDSC suppresses cancer immunity in cancer-bearing conditions, little is known about the role of MDSC in autoimmune diseases. MDSC is divided into two subpopulations, polymorphonuclear MDSC (PMN-MDSC) and monocytic-MDSC (M-MDSC), both of which negatively regulates inflammation by suppressing T cells and myeloid cells. We showed that PMN-MDSC was significantly increased in the spleen of SKG mice, and that adoptive transfer of MDSC reduced the severity of arthritis. In addition, MDSC and CD11b<sup>+</sup>Gr-1<sup>dim</sup>CD11c<sup>+</sup> cells were increased in the lungs of SKG mice, and the latter are regulatory dendritic cells with immunosuppressive ability differentiated from MDSC. It is thought that increasing MDSC number may lead to treatment, and we found that JAK inhibitors and metabolic inhibition increase MDSC. On the other hand, there are still unknowns about the function and differentiation of MDSC. It has been reported that in some model mice MDSC may exacerbate arthritis, and MDSC exerts different functions by differentiating into myeloid cells such as dendritic cells and osteoclasts. In addition, because the surface markers of MDSC differ in humans, the analysis of MDSC in human autoimmune diseases is not enough. In this talk, I will report on recent findings on MDSC.

## S7-1

### Interpreting immune disease GWAS signals with single cell transcriptomics from immune cells

Gosia Trynka

Wellcome Sanger Institute

Conflict of interest: None

Translating variants from genome-wide association studies (GWAS) to function can provide insights into disease biology and improve treatment options. We and others previously demonstrated that variants associated with immune diseases are enriched in enhancers and promoters whose activity is upregulated upon T cell activation. During activation, T cells undergo extensive gene expression changes. Understanding the regulation of this process could help explain how genetic variants influence the response to infections and immune diseases. We generated a single-cell expression quantitative trait loci (eQTL) map across a T cell activation time-course in 655,349 CD4<sup>+</sup> naive and memory T cells from 119 healthy individuals. We identified 6,407 eQTL genes, of which 2,265 (35%) were dynamically regulated during activation. We integrated eQTLs with GWAS associations for immune-mediated diseases and observed 127 colocalizations, with significant enrichment for dynamic eQTLs. Our results emphasize the importance of studying context-specific gene expression regulation and provide insights into the mechanisms underlying genetic susceptibility to immune-mediated diseases.

## S7-2

### Cross-tissue, single-cell stromal atlas identifies shared pathological fibroblast phenotypes in four chronic inflammatory diseases

Ilya Korsunsky<sup>1,2,3,4,5</sup>, Kevin Wei<sup>1</sup>, Mathilde Pohin<sup>6</sup>, Edy Kim<sup>7,8</sup>, Francesca Barone<sup>9</sup>, Fiona Powrie<sup>6</sup>, Christopher Buckley<sup>6,10</sup>, Michael Brenner<sup>1,7</sup>, Soumya Raychaudhuri<sup>1,2,3,4,5,11</sup>

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search, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK

Conflict of interest: Yes

Pro-inflammatory fibroblasts are critical to pathogenesis in rheumatoid arthritis, inflammatory bowel disease, interstitial lung disease, and Sjögren's syndrome, and represent a novel therapeutic target for chronic inflammatory disease. However, the heterogeneity of fibroblast phenotypes, exacerbated by the lack of a common cross-tissue taxonomy, has limited the understanding of which pathways are shared by multiple diseases. To investigate, we profiled patient-derived fibroblasts from inflamed and non-inflamed synovium, intestine, lung, and salivary glands with single-cell RNA-sequencing. We integrated all fibroblasts into a multi-tissue atlas to characterize shared and tissue-specific phenotypes. Two shared clusters, CXCL10<sup>+</sup>CCL19<sup>+</sup> immune-interacting and SPARC<sup>+</sup>COL3A1<sup>+</sup> vascular-interacting fibroblasts were expanded in all inflamed tissues and additionally mapped to dermal analogues in a public atopic dermatitis atlas. We further confirmed these human pro-inflammatory fibroblasts in animal models of lung, joint, and intestinal inflammation. This work represents the first multi-donor, cross-tissue, human, single-cell fibroblast atlas revealing shared pathogenic activation states across four chronic inflammatory diseases. The talk will focus on the computational challenges in analyzing complex, single-cell data of inflammatory diseases and present analytical tools and frameworks for addressing these challenges.

## S7-3

### Novel function of MHC molecules in the pathogenesis of autoimmune diseases

Hisashi Arase<sup>1,2</sup>

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Conflict of interest: Yes

The major histocompatibility complex (MHC) is a central molecule in the immune system. The MHC is also a highly polymorphic gene that is strongly involved in susceptibility to many autoimmune diseases. Therefore, the elucidation of the mechanism by which specific MHCs are involved in disease pathogenesis is important to our understanding of the pathogenesis of autoimmune diseases. Because the major function of MHC is the peptide presentation to T cells, abnormal T cell response has been considered to be the major cause of autoimmune diseases. On the other hand, the production of autoantibodies is observed in many autoimmune diseases, but the mechanism underlying their production remains unclear. We have shown that MHC class II molecules exhibit a chaperone-like function to transport misfolded proteins in the endoplasmic reticulum to the outside of cells. Furthermore, misfolded proteins transported to the cell surface have been shown to be the targets of various autoantibodies produced in autoimmune diseases. More importantly, the binding efficiency of autoantibodies against self-antigens bound to MHC class II molecules with specific alleles was significantly associated with the risk of autoimmune diseases associated with the respective MHC class II alleles. These findings suggest novel mechanisms underlying autoimmune diseases mediated by misfolded proteins complexes with MHC class II molecules.

## S7-4

### Genetics of rheumatoid-associated interstitial lung disease

Philippe Dieude<sup>1,2</sup>

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Conflict of interest: None

Despite its high prevalence and mortality, little is known about the pathogenesis of RA-associated interstitial lung disease (RA-ILD). For now, the complete genetic architecture of RA-ILD remains to be identified. Given phenotypic similarities between RA-ILD and idiopathic pulmonary fibrosis (IPF), it has been hypothesized that the two diseases may share additional risk factors including susceptibility genes. In a first genet-



ic case control-association study, through WES, coding mutations in genes linked to familial pulmonary fibrosis (FPF) were investigated. The burden test revealed an excess of *TERT*, *RTEL1*, *PARN* or *SFTPC* mutations for RA-ILD patients (OR=3.17 95%CI [1.53-6.12];  $p=9.45 \times 10^{-4}$ ) supporting the contribution of FPF-linked genes to RA-ILD susceptibility.<sup>1</sup> Following these findings, it has been hypothesized that the strongest risk factor for the development of IPF, the *MUC5B* rs35705950 variant, would also contribute to the risk of ILD in patients with RA. In a multiethnic genetic case-control association study, it has been demonstrated that the *MUC5B* rs35705950 variant was a risk factor for RA-ILD (OR=3.1 95%CI [1.8-5.4];  $p=7.4 \times 10^{-5}$ ) specifically associated with radiologic evidence of UIP HRCT pattern (OR=6.1 95%CI [2.9-13.1];  $P=2.5 \times 10^{-6}$ ).<sup>2</sup> Supplementary investigations suggested a contribution of both *TOLLIP* rs5743890 and *IVD* rs2034650 in RA-ILD susceptibility similarly to that reported in IPF.<sup>2</sup> These findings support the rationale for common pathogenic pathways opening new avenues for future intervention in RA-ILD, notably with drugs that proved active in IPF. Lastly, a recent GWAS performed in the Japanese population identified the *RP43-UMAD1* rs12702634 variant as a risk factor for RA-ILD (OR=2.04 95%CI [1.59-2.60];  $p=1.5 \times 10^{-8}$ ).<sup>3</sup> The exact role of *RP43-UMAD1* rs12702634 in RA-ILD susceptibility in non-Asian populations remains to be investigated. 1. Juge PA, et al. Eur Respir J 2017 2. Juge PA, et al. N Engl J Med 2018 3. Shirai Y, et al. Ann Rheum Dis 2020

## S7-5

### Microbiome analysis of autoimmune diseases

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Conflict of interest: Yes

Microbiome is the genetic material of all the microbes that live on and inside the human body and has biological interaction with host. Microbiome is now considered as “a new organ in our body”, and plays essential roles in a variety of human diseases including metabolic, psychiatric, and autoimmune diseases. Thus, how to interpret and integrate human meta-genome data is becoming an important clinical research topic. Previously, microbiome analysis was done by using 16S rRNA gene sequencing, which amplify 16S rRNA regions of bacteria. Recently, metagenomic shotgun sequencing, which massively sequences all genomes in microbiome, becomes available. We have developed an *in silico* pipeline handling metagenomic shotgun sequencing data to conduct case-control metagenome-wide association studies (MWAS). We conducted MWAS on a set of autoimmune diseases, and identified disease-specific features of the microbiome (e.g., increased genus *Prevotella* in rheumatoid arthritis [RA] and genus *Erysipelatoclostridium* in multiple sclerosis). We found several evidences of disease-specific host-pathogen interaction (e.g., dosage correlation of RA-associated genus *Prevotella* with *P. gingivalis*). Systemic lupus erythematosus (SLE) MWAS and integrative analysis with blood metabolites identified positive correlation between SLE-associated genus *Streptococcus* and blood acylcarnitine. Further, we developed a pipeline to conduct whole virome analysis, and found that crAss-like phages decreased in the gut microbiome of the RA and SLE patients. On the other hand, infectious targets of crAss-like phages and their relevance with disease status is still elusive. These results demonstrated substantial contribution of microbiome in the biology of autoimmune diseases. We would like to introduce our ongoing approaches to visualize, integrate, and interpret the human microbiome data.

## S8-1

### Systemic sclerosis: treat-to-target strategy and treatment evidence

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Conflict of interest: Yes

Systemic sclerosis (SSc) remains a refractory condition with poor functional and survival outcomes. This is attributable primarily to the extremely diverse clinical course and distribution of organ involvement. The pathogenesis of SSc includes microangiopathy and chronic inflammation,

leading to accumulation of extracellular matrix and resultant irreversible fibrosis resulting in distortion of the normal tissue architecture. This pathogenic process is analogous to that observed in rheumatoid arthritis, in which persistent synovitis leads to articular cartilage and bone destruction, resulting in functional impairment due to joint deformity. Therefore, successful experiences in developing treatment strategies in patients with rheumatoid arthritis can be applied also to SSc. These include early interventions, treat-to-target (T-2-T) strategy, and disease modification. For this purpose, it is necessary to construct the concept and definition of “disease activity”, “low disease activity”, and “clinical remission”. Factors that predict the progression of skin sclerosis and interstitial lung disease at an early stage need to be identified as “prognosis factors”. In terms of treatment, data from randomized controlled trials of potential “disease-modifying therapies” have been accumulated recently. In addition, early interventions have been shown to be more effective than delayed intervention. In this lecture, we introduce the global efforts for the upcoming T-2-T treatment strategy in SSc patients.

## S8-2

### The significance of the early diagnosis of systemic sclerosis in clinical practice

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Conflict of interest: Yes

Systemic sclerosis (SSc) is characterized by excessive fibrosis of the skin and various organs, microvascular injury, and autoimmunity. However, there has been no concept explaining these characteristics unitarily. From the point of view of wound healing, SSc is the disease captured at the phase of remodeling but is difficult to recognize at the inflammatory phase. Thus, there is no treatment available, which can achieve “reverse remodeling”. However, the recent development of treatment enables us to have a concept that we should treat the patients at a “very early” phase to avoid missing the timing of inflammation and stop or slow down the process of remodeling. Practically, this concept is clearly reflected in the “treatment goal of SSc-ILD” in the guideline for ILD associated with connective tissue diseases recently published. Thus, it is required for all physicians who treat patients with SSc to understand that patients should be diagnosed as early as possible for the improvement of their outcomes. Attempts for early diagnosis were already examined for years globally. Of the characteristics of SSc, vascular involvements such as the Raynaud phenomenon or abnormality of nail-fold capillaries can be detected at an earlier phase of the disease compared with other organ involvements. Also, anti-nuclear antibodies are detected in 95% of SSc patients and the detection of SSc-associated autoantibodies is also important for specificity. Although these findings have a weak association with the prospect for the future diagnosis of SSc when it is applied solely, those have a substantial association when they are combined. Based on these data, EUSTAR proposed that patients can be classified into “very early diagnosis of systemic sclerosis (VE-DOSS)” if they have Raynaud phenomenon, puffy fingers, and abnormal findings of nail-fold capillaries and/or SSc-associated autoantibodies. In this session, we will summarize the recent topics of this issue and discuss our perspectives.

## S8-3

### Update on the Diagnosis and Treatment of Immune-Mediated Necrotizing Myopathy

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Conflict of interest: None

Classification criteria for immune-mediated necrotizing myopathy (IMNM) by the ENMC international workshop are as follows: 1) All clinical criteria, such as symmetric predominantly proximal muscle weakness, with the exception of rash; 2) Elevated serum CK; 3) Other laboratory criteria (either electromyography, MRI, or myositis-specific antibodies); and 4) Muscle biopsy criteria include “g” and exclude all others [Neuromuscular Disorders. 2004;14:337]. The muscle biopsy criteria “g” are as follows: Many necrotic muscle fibers as the predominant abnormal histo-



logical feature: Inflammatory cells are sparse or only slight perivascular; Perimysial infiltrate is not evident; MAC deposition on small blood vessels or pipestem capillaries on EM may be seen, but tubuloreticular inclusions in endothelial cells are uncommon or not evident. However, there is no clear definition or quantitative cut-offs for the terms such as “many”, “sparse”, and “slight”. Nevertheless, IMNM can be differentiated from other forms of inflammatory myopathies (IIMs) only by a muscle biopsy. In addition, pathological features of necrotizing myopathy have also been reported in myopathy patients associated with anti-aminoacyl-tRNA synthetase antibodies, cancers, and lupus. Clinical outcome and response to treatment are also highly varied among patients with IMNM. Thus, clinical evidence supporting the validity for such biopsy-based classification is not sufficient. On the other hand, there is emerging evidence suggesting the link between clinical condition and antibodies against SRP and HMGC-R, representative antibodies in IMNM. Generally, muscle symptoms are more severe and more refractory in anti-SRP IIMs than in anti-HMGCR IIMs. Pathological significance of these antibodies has also been suggested [Ann Rheum Dis. 2019;78:131]. Thus, antibody-driven classification might be more straightforward than biopsy-based classification. Treatment strategies based on IIM subtypes including IMNM is not established.

## S8-4

### Anti-aminoacyl tRNA synthetase antibodies syndrome (AAS): Disease concept and recent advances in managing interstitial lung disease associated with AAS

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Conflict of interest: Yes

Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies characterized by several organ involvements such as muscle, skin, heart, and lung. Interstitial lung disease (ILD) has major pulmonary involvement and the prevalence of ILD is approximately 40%. ILD is a poor prognostic factor in PM/DM and the management of PM/DM-ILD is important. On the basis of clinical course, ILD is divided to 2 types: acute/subacute with rapidly progression over several weeks or months and chronic with slowly progression over years. Acute/ subacute ILD is associated with DM and clinical amyopathic DM and has poor prognosis compared with chronic ILD. It is reported that the relation between clinical manifestations and myositis-specific antibodies (MSA). MSA associated with ILD are anti-MDA5 and anti-ARS antibodies. Anti-ARS antibodies are detected in 20-30% of patients with PM/DM. Patients with anti-ARS antibodies present common clinical manifestations: myositis, arthritis, Raynaud's phenomenon, mechanic's hand, and ILD, and are known as anti-ARS syndrome (AAS). Eight types of anti-ARS antibodies are reported and anti-Jo-1 anti-bodies are most common. The commercially available assay for anti-ARS antibodies can detect 5 types: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, and anti-KS, but not other types. Chest HRCT shows nonspecific interstitial pneumonia pattern with organizing pneumonia (OP) or OP pattern with fibrosis. The findings are characterized by infiltrative shadows and gland glass opacities around the bronchial bundle with traction bronchiectasis. The clinical course of AAS-ILD is subacute or chronic. Patients with AAS-ILD are treated with the combination with high dose glucocorticoids and immunosuppressants. The initial treatment is usually good, but some patients may have recurrence of ILD during therapeutic course. The Japanese Respiratory Society and the Japan College of Rheumatology collaborated to publish the guide focusing ILD associated with connective tissue disease and proposed the therapeutic algorithm for PM/DM-ILD based on the evidence and expert consensus. This paper addresses the disease concept of AAS and reviews recent advance in managing AAS-ILD.

## S8-5

### Cancer screening in idiopathic inflammatory myopathies and treatment of cancer-associated myositis

Yukie Yamaguchi

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Conflict of interest: None

Among idiopathic inflammatory myopathies, the risk of malignancy is known to be increased, especially in dermatomyositis. Among them, elderly patients, positivity for anti-TIF1 $\gamma$  antibody, severe skin rash, and the presence of dysphagia significantly increase the risk of malignancy, and thus require a more detailed cancer screening. On the other hand, amyopathic dermatomyositis, the presence of interstitial lung disease, and positive cases of anti-Jo-1 antibody do not increase the cancer risk, thus the characteristics of clinical factors related to cancer-associated myositis (CAM) have recently been clarified. Since patients with CAM may be refractory to treatment, and administration of steroids and immunosuppressive agents may increase the risk of surgical complications and promote tumor progression, it is desirable to consider cancer screening according to the risk. On the other hand, although there are numerous reports on the organs of incident malignancies, they are not significantly associated with any particular type at this time. Therefore, there is no sufficient evidence or guidelines for cancer screening methods. In general, imaging tests such as CT, GF/CF are performed with reference to physical findings and blood tests, and breast, gynecological, and urological examinations are also important. In the case of CAM, both the malignancy and myositis need to be treated, and the content and timing of the treatment are often troubling in clinical practice. In general, when the myositis is not severe, treatment of the malignancy is given priority, but in cases of dysphagia, treatment of myositis should be given priority, otherwise the risk of aspiration pneumonia increases. Once the malignancy is under control, the myositis is often well controlled, thus appropriate treatment for both should be considered in each case. In this lecture, we would like to discuss the clinical factors related to CAM, methods of screening for malignancy, and actual treatments.

## S8-6

### Update of treatment strategy and prognostic factors in patients with anti-MDA5 autoantibodies positive dermatomyositis and rapidly progressive interstitial lung disease

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Conflict of interest: Yes

Idiopathic inflammatory myopathies (IIMs) are a disease group characterized by proximal muscle weakness and myalgia due to muscle inflammation. Dermatomyositis (DM), one of IIMs, manifests muscle inflammation as well as typical cutaneous lesion such as Gottron's sign or papules or Heliotrope rash. However, it has been well known that some patients only show typical skin manifestations without (amyopathic DM: ADM) or mild muscle inflammation (hypomyopathic DM: HDM) with no obvious muscle symptoms and these patients are defined as clinically ADM (CADM) because they have no muscle weakness or myalgia clinically. DM often occurred with other manifestations, polyarthritis, interstitial lung disease (ILD), myocardial involvement and malignancy during their clinical course. Among these involvements, rapidly progressive ILD (RP-ILD) complicated with DM is the most important risk factor because of its treatment resistant and poor outcome. Therefore, prompt correct diagnosis and subsequent appropriate treatment of this condition are crucial. Since the discover of anti-MDA5 antibodies, elucidations of prognostic factors in patients with DM and RP-ILD has been reported and these results are useful in clinical practice. As for the progress of treatment, the effectiveness of intensive treatment with high-dose corticosteroid and multiple immunosuppressives has been described. As additional effective therapies, mycophenolate mofetil, Janus Kinase (JAK) inhibitor, Rituximab, intravenous immunoglobulin therapy and blood purification therapy have also been reported. In this symposium, latest findings of prognostic factors and treatment strategies in patients with DM and RP-ILD are reviewed.

## S9-1

### Actual status of support for transition to adulthood in pediatric rheumatic disease treatment facilities and future issues

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Conflict of interest: None

In the case of rheumatic diseases, there are many cases in which patients with childhood onset are followed in adult departments even after they reach adulthood, so it is important to provide support for transition to adulthood based on the aspect of supporting independence and medical continuity. There are also cases in which people are confused by the difference in the medical environment, self-discontinue their hospital visits due to inadequate communication with medical professionals, and are unable to receive appropriate medical care. In order to ensure a seamless transition from childhood to adulthood, it is necessary to provide support for the transition during childhood care, and to ensure that medical information is appropriately transferred and that there is sufficient communication between patients and medical personnel when they receive adult care. As a result of a questionnaire survey of facilities that treat pediatric rheumatic diseases, 52% of the facilities responded that activities to support the transition to adulthood were being conducted. In addition, 65.8% of the facilities did not have a support organization for transition to adulthood at this time. On the other hand, about 30% of the facilities experienced cases where patients returned to their own facility after being referred to adult medicine. The reason for this was often the lack of familiarity with the adult medical department. Only 42% of the respondents use the booklet provided by the Society, which contains medical information for patients to carry. As for the problems related to the support for transition to adulthood, many of the freely stated opinions indicated the perception that there is a lack of mutual understanding between patients and medical professionals and between medical professionals. Human resources and time constraints related to support for transition to adulthood, as well as the development of additional reimbursement for such support, were also considered as future issues.

## S9-2

### Transition medical services of juvenile idiopathic arthritis by Japanese orthopedic surgeon

Atsushi Kaneko

Department of Orthopaedic Surgery and Rheumatism, Nagoya Medical Center

Conflict of interest: None

In “adult transitional treatment” for articular juvenile idiopathic arthritis (JIA), there are many cases where continuous treatment is necessary even after adulthood depending on the disease type, and it is important to continue seamless medical care from childhood to adult medical care. Due to changes in the environment, such as the transition of pediatric to adult medical care that has been hospitalized for many years and life events such as going on to higher education and finding employment, it is possible that transitional medical care may not go smoothly. In addition, depending on the region, the Department of Rheumatology cannot be selected as an adult medical department, and requests for transitional care may come to orthopedics. Furthermore, in joint type of JIA patients where the disease period, growth period, and puberty overlap, there may be effects on mental and physical maturity, and there are cases where a decrease in independence and sociality is observed, and consideration may be required for response. In addition, consideration is also required for the different drug and medical expenses subsidy system of the insurance adaptation from RA. First of all, DMARD therapy for the control of disease activity is appropriately performed, and when limb joint symptoms and dysfunction remain, physical function evaluation, especially image evaluation by simple X-ray image is performed, the contents are explained to the patient side in time, and non-pharmacotherapy and surgical treatment are tried.

## S9-3

### Problems and solutions for autoinflammatory diseases from the perspective of transitional medicine and transitional support

Hiroaki Ida

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Conflict of interest: Yes

Autoinflammatory disease is a disease that causes repeated systemic inflammation, often with fever and inflammation of local parts such as joints, skin, intestines, eyes, and bones. Although it was thought to be a

foreign disease, the number of patients was unexpectedly large from case reports and epidemiological surveys in Japan, and it has recently been well recognized by clinicians including rheumatologist. Familial Mediterranean fever (FMF) is the most common autoinflammatory disease for which the disease gene is known, and is important as a differential diagnosis for fever of unknown origin in Japan. There are many adult onsets, but pediatric onsets are often severe and complete type of FMF with variants in *MEFV* exon 10. In FMF of childhood onset, the number of cases of shifting to internal medicine/adult medicine after the age of 16 is increasing. One of the problems with FMF is the difficulty of diagnosis. There is national confusion as to how to diagnose FMF in patients with fever of unknown origin and periodic fever, which have many gene polymorphisms in Japan. In 2021, the FMF diagnostic flow chart was revised to emphasize clinical symptoms rather than gene variants. It was also emphasized that a solid differential diagnosis should be made instead of easily diagnosing FMF. In transitional medicine for autoinflammatory diseases, working groups have been formed and are being carried out by the Japan Pediatric Society, the Pediatric Rheumatology Association of Japan, the Japan College of Rheumatology, and the Japanese Society for Immunodeficiency and Autoinflammatory Diseases. A questionnaire survey of the Japan College of Rheumatology councilor revealed that the physician was more resistant to medical treatment for autoinflammatory diseases than other rheumatic diseases (Miyamae T, et al. Modern Rheumatol. 2017; 27: 1047-50). For FMF and cryopyrin-associated periodic syndrome (CAPS), which often occur in childhood, due to inadequate acceptance of internal medicine and adult doctors, the creation of a transitional guide for each disease that summarizes the points of medical care for each disease is in progress. In addition, reliable diagnosis of FMF and acquisition of knowledge of diseases are very important issues in advancing transitional medical care in the future. In this talk, I would like to describe the current problems and solutions in transitional medicine for autoinflammatory diseases.

## S9-4

### Establishment of a transitional medical care support system for pediatric patients with chronic diseases in Nagano Prefecture: Nagano System, past & future

Kiyohiro Takigiku

Transitional Medical Care Center, Nagano Children's Hospital

Conflict of interest: None

We describe the past efforts and future goals of the transition medical support in Nagano Prefecture. In 2011, Nagano Children's Hospital started to provide transitional medical support mainly in the outpatient clinic, and in two years, 1175 patients with congenital heart disease and 118 patients with pediatric cancer were supported. In order to further expand the program to pediatric chronic diseases across the entire hospital, we made the nursing support team and outpatient clinic by professional nurses in 2015. In 2018, the team was scaled up to the Transitional Medical Support Committee. We have constructed our own system to support the independence of patients and their families to raise their awareness by using original tools such as transition support guide for medical staff, patient summaries for each age group, questionnaires and checklists for each age group, and transition medical pamphlets. In 2020, the prefectural government will open a medical transition support center at Shinshu University. We have strengthened cooperation with Shinshu University and the prefectural welfare department. In addition, as a new project, fertility preservation care for pediatric cancer patients was started in 2019 in cooperation with obstetricians in the prefecture. And as for employment issues, cooperation with Hello Work became possible in our hospital. In 2021, we opened our own transitional care support center in our hospital, set up an outpatient center so that doctors can coordinate full-scale transitional medical care, and took steps to strengthen cooperation with medical institutions in the prefecture. The “Nagano System” is now being developed as a model case of an independent children's hospital.

## S9-5

### Establishment of Health Care System for Patients with Adult Congenital Heart Disease in Collaboration with Children's Hospital -Nagano Model

Hirohiko Motoki

Conflict of interest: None

**Background:** Despite the best efforts, healthcare for adult patients with congenital heart disease (ACHD) has proved challenging owing to the increased load on pediatricians. This presentation aimed to discuss the process of establishment of the ACHD care system as a collaborative effort between Shinshu University Hospital and Nagano Children's Hospital. **Methods and Results:** (1) Establishing an outpatient clinic for transition, (2) cooperation agreement for inpatient care between 2 hospitals, and (3) quality management of diagnostic imaging and educational meeting for adult cardiologists were the 3 major challenges in our model. Among 99 patients who visited the transition clinic in the children's hospital between May 2014 and December 2016, 3 returned to the pediatrician's clinic. Between June 2013 and December 2017, 273 patients visited the ACHD center in Shinshu University Hospital. Until December 2017, mortality and fatal arrhythmia was noted in 3 and 2 cases, respectively. Catheter ablations for arrhythmia were performed in 12 cases. Four cases of pregnancy with moderate/severe ACHD or estimated as high risk were managed with healthy livebirths. Surgical interventions for moderate/severe ACHD were performed in collaboration with children's hospital or Sakakibara Heart Institute. **Conclusions:** Patients were successfully transferred to adult cardiology departments. Surgical and nonsurgical interventions were provided for ACHD. Collaborations between adults and pediatric cardiologists would be helpful to establish healthcare systems for ACHD.

## S9-6

### Medical Condition and Issues of Adult Patients with Childhood-Onset Systemic Lupus Erythematosus

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Conflict of interest: None

Data on medical condition of adult patients with childhood-onset systemic lupus erythematosus (SLE) are limited. In the Childhood-Onset SLE in The Netherlands study, 111 childhood-onset SLE patients were included, and the median disease duration was 20 years [Arthritis Rheumatol. 2019;71:290]. Damage such as myocardial infarctions began occurring after 5 years. Most patients (62%) experienced damage, predominantly in the musculoskeletal, neuropsychiatric, and renal systems. Multivariate logistic regression analysis showed that damage accrual was associated with disease duration (odds ratio [OR] 1.15,  $p < 0.001$ ), antiphospholipid antibody positivity (OR 3.56,  $p = 0.03$ ), and hypertension (OR 3.21,  $p = 0.04$ ). In the University of California San Francisco Lupus Outcomes Study, average disease duration for the childhood-onset SLE and adult-onset SLE subgroups ( $n = 90$  and  $795$ , respectively) was 16.5 and 13.4 years, respectively [Arthritis Rheum. 2009;61:13]. Childhood-onset SLE subjects had a higher frequency of SLE-related renal disease than adult-onset SLE subjects (56% vs. 37%;  $p < 0.001$ ). In the following study using the same longitudinal cohort, childhood-onset SLE subjects ( $n = 113$ ) were more likely to report steroid-related damage (OR 1.7, 95% CI 1.1-2.8) in the adjusted analysis as compared to those with adult-onset SLE ( $n = 922$ ) [Semin Arthritis Rheum. 2019;49:267]. The transition from pediatric to adult rheumatology care represents a particularly vulnerable time for patients with childhood-onset SLE [ACR Open Rheumatol. 2021;3:260]. In a cross-sectional study, patients 14 to 20 years of age with juvenile idiopathic arthritis or childhood-onset SLE ( $n = 61$  and  $9$ , respectively) were recruited from pediatric transition and young adult clinics at McMaster University in Canada. The most commonly reported challenges were seeing the physician alone (without parents), making one's own appointments, picking up prescriptions, and independent transportation for appointments.

## S10-1

### Role of the Nerve Growth Factor in Pain During Knee Osteoarthritis and Its Treatment Potential

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sity

Conflict of interest: Yes

The chief complaint in patients with knee osteoarthritis (OA) is joint pain; however, refractory pain occurs that cannot be suppressed by existing treatment methods. Therefore, there is an urgent requirement for the development of a new treatment. The nerve growth factor (NGF) is involved in the development of inflammatory and neuropathic pain, and the clinical trials conducted on knee OA have reported that anti-NGF antibodies have a high analgesic effect. The synovium and subchondral bone are important pain sources in knee OA. We found that patients with symptomatic knee OA had significantly higher expression of NGF in synovium and subchondral compared with asymptomatic knee OA, suggesting that the expression of NGF itself is involved in pain aggravation, regardless of the degree of cartilage degeneration during progression of OA. According to the results of our basic research using OA model, the expression of NGF increases early in the synovium and decreases in the advanced stage and its expression remains high in the cartilage from early to advanced stage, whereas it gradually increases in the subchondral bone. Density of CGRP-immunoreactive sensory nerves was increased following the increase in the expression of NGF, and when the activity of NGF receptors was blocked, the painful behavior caused by OA and its nerve growth was suppressed. NGF is closely related to knee pain and local nerve growth, and clinical trials are currently evaluating the efficacy of anti-NGF antibodies and NGF receptor antagonists. Unfortunately, despite its confirmed analgesic effect, tanezumab, which is one of anti-NGF antibodies, has been found to be associated with rapidly progressive knee OA; therefore, it has not been approved by the European Medicines Agency and U.S. Food and Drug Administration. In this symposium, I would like to introduce our research results and recent findings and describe the role of NGF in knee OA pain as well as its therapeutic potential.

## S10-2

### Current status and future prospects of NSAIDs (including topical NSAIDs) in conservative treatment for osteoarthritis

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Conflict of interest: None

Osteoarthritis (OA) is a disease that begins with degeneration of articular cartilage and causes pain and joint deformity. Basic studies have identified proteinases involved in cartilage degeneration (ADAMTSs-4, -5 and MMPs-1, -3, -13, etc.) and molecules relate to pain (PGE<sub>2</sub>, nerve growth factor: NGF, etc.) and the molecular mechanism of pathogenesis of OA has become clearer. In the guideline for non-surgical management of knee OA by OARSI, topical non-steroidal anti-inflammatory drugs (NSAIDs) were strongly recommended as level 1A, followed by oral selective COX-2 inhibitors or NSAIDs as level 1B. On the other hand, OA disease modification therapy (disease/structure modification) that protects or repairs articular cartilage is on demand. Although there are some reports that selective COX-2 inhibitors or NSAIDs may have cartilage protection or repair effects, recent clinical study manifested that loss of joint space was increased in patients who have taken NSAIDs. We have investigated the effects of selective COX-2 inhibitor on the expression of factors involved in OA pathology using human synovial cells and found that MMPs and NGF induction was rather promoted by selective COX-2 inhibitor, which was suppressed by exogenous addition of PGE<sub>2</sub>. Further investigation revealed that PGE<sub>2</sub> induces DUSP (dual-specificity phosphatase)-1, which is a dephosphorylating enzyme of MAP (mitogen-activated protein) kinase that transmits inflammatory stimulation. PGE<sub>2</sub> was found to have novel bioactivity to suppress OA pathology by suppressing the expression of MMPs and NGF through up-regulation of DUSP-1 in a negative feedback manner. In this presentation, the current status of NSAIDs in OA conservative treatment will be shared and the future prospects that have emerged from our finding of potential disease modifying property of DUSP-1 will be discussed.



## S10-3

### Efficacy of Duloxetine and Opioids for Osteoarthritis Pain

Yuya Kawai<sup>1</sup>, Junichi Nakamura<sup>1</sup>, Shigeo Hagiwara<sup>1</sup>, Keijiro Kanno<sup>1</sup>, Sei Yano<sup>1</sup>, Junpei Shoda<sup>1</sup>, Yousuke Tsurumi<sup>1</sup>, Masahiko Suzuki<sup>2</sup>, Seiji Ohtori<sup>1</sup>

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Conflict of interest: None

Pharmacologic treatment is one of the fundamental treatments for osteoarthritis as well as an education program and exercise therapy. In the past, most of the analgesics prescribed for osteoarthritis were non-steroidal anti-inflammatory drugs (NSAIDs), but since 2010, drugs with various analgesic mechanisms have been available. While many analgesics are now available, it is not easy to decide which drug to prescribe to which patient. Duloxetine is a serotonin-noradrenaline reuptake inhibitor (SNRI), and its analgesic effect is due to the activation of the descending pain inhibitory system. Tramadol has been prescribed the most among opioids for the treatment of osteoarthritis, and it is a drug with dual activity: it is an opioid agonist on mu ( $\mu$ ) receptors and a monoamine reuptake blocker with consequent potentiation of serotonergic and adrenergic pathways. The 2019 American College of Rheumatology (ACR) guidelines conditionally recommend the use of both duloxetine and tramadol for osteoarthritis, while the International Osteoarthritis Research Society (OARSI) guidelines make only duloxetine conditionally recommended for use in knee osteoarthritis. In the latest version of the Clinical Practice Guidelines for the Management of Chronic Pain, the use of duloxetine is strongly recommended, and tramadol is weakly recommended in patients with chronic musculoskeletal pain that lasts more than three months. Both guidelines do not recommend the long-term use of strong opioids due to problems of addiction and abuse. In addition, the possibility of progression of osteoarthritic changes after opioid administration has recently been reported. Therefore, clinicians need to provide appropriate pharmacotherapy. In this session, the efficacy of duloxetine and opioids for the treatment of knee osteoarthritis and hip osteoarthritis will be reviewed with up-to-date evidence.

## S10-4

### Effectiveness of hyaluronic acid injection for osteoarthritis of the hip

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Conflict of interest: None

**Background** Knee osteoarthritis (KOA) and hip osteoarthritis (HOA), which are weight-bearing joints of the lower extremities, are major causes of functional disability and chronic pain in the elderly. In the 2019 OARSI guidelines, for KOA, there are many reports on the efficacy of pharmacotherapy, including hyaluronic acid arthroplasty (IAHA), while there is no effective conservative treatment for HOA except for oral NSAIDs and patient education. The purpose of this study is to assess the effectiveness of IAHA for patients with HOA. **Subjects and Methods** Six patients (Male/Female: 1/5, mean 58.5 years (54–61 years)) diagnosed as HOA. The affected side was unilateral in 4 cases and bilateral in 2 cases. All patients were Grade 2 in the Kellgren-Lawrence (KL) classification. We used ultrasound guidance with convection probe. We injected one of diclofenac-bound hyaluronic acid to under the capsule the femoral head-neck junction. We stopped the injection when the patient complained pain. We found the expansion of the joint capsule was considered to be accurate administration. The mean follow-up period was 10 weeks (8 to 14 weeks). The NRS (Number rating scale) was used to evaluate pain, with 0 being no pain at all and 10 being the most severe pain imaginable. Results We were able to confirm the expansion of the joint capsule in all cases. The mean NRS before injection was 5.1 points (range: 4–8 points), and the mean NRS after injection was 3.2 points (range: 2–6 points). 3 out of 6 patients complained of severe pain at the time of injection. It disappeared spontaneously in all patients. 2 out of 6 patients requested total hip arthroplasty after injection. Discussion IAHA was effective in reducing pain in patients with early to advanced stage hip arthropathy of grade 2 on the KL classification. Ultrasound guidance was useful for accurate injection into the hip joint. Patients complained of pain at the time of administration, requiring

prior explanation and follow-up observation after injection.

## S10-5

### Platelet-rich Plasma (PRP)

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Conflict of interest: Yes

The molecular pathogenesis of osteoarthritis (OA) is complex, and the mechanism of pain development is still unclear. One of the non-surgical therapies for OA is platelet-rich plasma (PRP) therapy, but PRP has a variety of ways in preparation, and the proportion of blood cell types in PRP varies depending on how it is prepared, so bioactive substances (BS) in PRP varies greatly as well. We started PRP therapy for athletes in 2011 and experienced many athletes improving their symptoms for post-traumatic arthritis. Then, the use of the therapy was expanded to apply it to middle-aged and elderly patients with OA and arthritis as well. It is currently used in patients with rheumatic arthritis whose disease control is good. Previous studies using molecular and cellular biological methods have shown that the mechanism of action of PRP therapy on OA is the “tissue repair effect” of growth factors and the “anti-inflammatory effect” of BS such as IL-1 and TNF- $\alpha$  signal inhibitors. However, there is still little clinical evidence for PRP therapy in patients with OA. The response rate of PRP therapy for knee OA treated at our hospital was approximately 60% when the patients who met the OMERACT-OARSI criteria were calculated based on the Patient-Reported Outcome Measures (PROMs). We considered it necessary to investigate the therapeutic effect with objective measures other than PROMs, and examined the changes in biomarkers by collecting joint fluid and urine before and after PRP therapy. And, we found that TNF- $\alpha$  and MMP-3 in the joint fluid significantly decreased. In addition, urinary CTX-II, a marker of cartilage destruction, significantly decreased as well. These results suggest that PRP may have anti-inflammatory and cartilage protective effects on knee OA. Analysis of BS in PRP has revealed big differences among individual BS, suggesting that this may contribute to individual differences in PRP response rates. In this symposium, we would like to provide information by adding a literature review to the results of our basic and clinical studies.

## S11-1

### Changes in the treatment of rheumatoid arthritis and future challenges

Kunihiro Yamaoka

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Conflict of interest: Yes

The treatment of rheumatoid arthritis has proven to be extremely effective with molecular targeted therapies that specifically inhibit specific molecules since the approval of the first biologics in Japan in 2003. There has been a significant improvement in the control of joint destruction and improvement of activities of daily living with the improvement of remission and low disease activity rate, the decrease in the amount and rate of concomitant steroid use, and the spread of prophylactic drug administration. However, we are still far from precision medicine, which involves adjusting medications after remission induction and administering the right drug to the right patient. Five JAK inhibitors have recently been approved in Japan as new anti-rheumatic drugs, and their efficacy is not in doubt. New molecular targeted therapies are also being developed, but their therapeutic efficacy remains difficult to surpass existing treatments. The aspect of adverse events associated with immunosuppression as a characteristic of rheumatoid arthritis treatment remains the same for all drugs, but the debate on safety, especially for JAK inhibitors compared to biologics, has recently attracted attention. In addition to thromboembolism and malignancy, the increase in herpes zoster is a serious and solvable problem in Japan. In this symposium, we will introduce the antirheumatic drugs developed so far and discuss the challenges JAK inhibitors face.



## S11-2

### New molecular-targeted therapies for large-vessel vasculitis

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Conflict of interest: None

Takayasu arteritis (TAK) and giant cell arteritis (GCA) cause inflammatory damage on important blood vessels such as the aorta, other large arteries, and cervicocerebral small/medium-sized arteries. Relapses are often seen in the clinical course of TAK and GCA. Advances by current researches will lead to the use of molecular-targeted drugs for the two refractory diseases as customized treatments according to the patients' pathophysiology in the near future. However, currently, although insurance application to tocilizumab (TCZ) was approved for TAK and GCA, clinicians may consider that TCZ still has challenges due to the experience of relapsed cases under the use of TCZ and the difficulty of disease activity estimation by the masking effects of TCZ on CRP. Recently, there have been increasing reports of cases treated by molecular-targeted drugs other than TCZ, but their effectiveness has not been established. This lecture will discuss how to select these molecular-targeted drugs in the near future. The most important thing is to clarify the pathological mechanism of TAK and GCA. However, it is still under research at present. This lecture will give a simple explanation using cartoons on (1) pathological characteristics of TAK and GCA, (2) analysis of peripheral blood lymphocytes, (3) autoantibody researches, and (4) genetic analysis. Although TAK and GCA are rare diseases, many randomized controlled trials (RCTs) are currently conducted. Similarly to the history of the drug development for rheumatoid arthritis, these RCTs can be understood as practical experimental approaches prior to the elucidation of the pathophysiology. This lecture will evaluate the approaches to five main molecules, namely IL-6, TNF- $\alpha$ , IL-12/23, Janus kinases, and CTLA-4.

## S11-3

### ANCA associated vasculitis

Tomonori Ishii

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Conflict of interest: Yes

The basis for the treatment of ANCA-related vasculitis is induction therapy and maintenance therapy. Many clinical studies have been conducted using these treatments, which are summarized in the clinical practice guidelines of each country. Induction therapy is mainly combined with intravenous cyclophosphamide or rituximab therapy, in addition to the administration of glucocorticoids. Maintenance therapy primarily involves the use of azathioprine and rituximab, whereas combination therapy with mycophenolate mofetil and methotrexate has also been proposed. However, in some cases, it is difficult to induce remission even with such treatments. In addition, even if remission occurs, it is difficult to maintain remission and the disease can recur. Furthermore, in cases where it is difficult to reduce the dosage of glucocorticoids, the quality of life cannot be maintained because of the side effects of steroids. Therefore, a new approach for the development of therapeutic agents is required. Molecular targeted drugs are focused and less likely to cause widespread side effects. Among them, if there is a drug that can aid in reducing the dose of glucocorticoids, then the clinical merit is substantial. Rituximab is one of the targeted therapies directed towards B cells. Similar to AAV clinical trials targeting T cells, there is a clinical trial using abatacept. However, this study is a single-arm open-label study, and clinical trials with a high level of evidence by randomized control trials are expected in the future. A drug that has been used as a molecular-targeted therapy for cytokines is mepolizumab, an anti-interleukin 5 antibody, and has been approved as a therapeutic drug for eosinophilic granulomatosis with polyangiitis, a disease in which the pathological condition due to the allergic mechanism plays an important role in vasculitis. Avacopan, a complement C5a receptor inhibitor, which suppresses the complement pathway, was approved in Japan in 2021 as a therapeutic agent for AAV. A pivotal study that led to the approval is called the ADVOCATE study. In this study, treatment was based on the administration of rituximab or cyclophosphamide, along with a usual group using steroids and a group using avacopan, and the therapeutic benefits in each

group were compared. The results of this double-blind comparative study show that the avacopan group (steroids were used in low doses) is non-inferior to the steroid-treated group.

## S11-4

### Novel targeted therapies for systemic lupus erythematosus - One drug does not fit all

Shinsuke Yasuda

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Conflict of interest: Yes

Systemic lupus erythematosus (SLE) is a prototype of systemic autoimmune disease affecting multiple organs at diverse severity. Despite advancement in our knowledge on genetics and epigenetics, immunopathology and cellular based gene expression, patients with SLE have not appreciated enough benefit in terms of their disease control, organ damages, quality of life as well as prognosis. Although many targeted therapies have been developed for SLE in clinical trials, most of such attempt did not reach their primary endpoints partly because of the trial design, background treatment, evaluation of the efficacy and heterogeneity of the disease itself. Recently, standardized evaluation tool for clinical trials, such as SRI or BICLA, have been introduced. These clinical endpoints are still harsh comparing to ACR20 generally used in rheumatoid arthritis. Still, two monoclonal antibodies have been approved for the treatment for lupus patients for moderate disease activity. One is belimumab, anti-BlyS monoclonal antibody (mAb) approved in 2011 by FDA and in 2017 in Japan, the other is anifrolumab, anti-IFNAR mAb approved in 2021 in Japan. Besides these two, several mAbs are on trial for SLE or lupus nephritis, including anti-IL-17 secukinumab, anti-BDCA2 BIIB059, and anti-CD20 obinutuzumab. Besides mAbs, low-dose IL-2 administration is on trial. Inhibitors for signaling molecules are also good therapeutic target for lupus. For example, JAK family members, Btk, mTOR and calcineurin. A novel calcineurin inhibitor voclosporin is on clinical trial in patients with lupus nephritis. Because of the heterogeneity in SLE, one drug does not fit all. We would like to discuss how we should take advantage of novel targeted therapies for lupus.

## S11-5

### Molecular targeted therapy in Behcet's disease

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Conflict of interest: Yes

Behçet's disease (BD) is a chronic multi-systemic inflammatory disorder that involves mucocutaneous tissues, eyes, joints, gastrointestinal tract, vascular and central nervous systems. The goal of treatment is to suppress acute inflammatory exacerbations and recurrences to prevent irreversible organ damage. Here, I first summarize therapeutic approaches for individual lesions according to the Japan guidelines and EULAR recommendations, and then discuss molecular targeted therapy including TNF inhibitors and a phosphodiesterase (PDE) 4 inhibitor in BD. Anti-TNF- $\alpha$  monoclonal antibodies are options for serious manifestations in the eyes, gastrointestinal tracts, vascular, and central nervous systems. The agents are indicated for refractory lesions to conventional therapies including corticosteroids and immunosuppressants in general, but the early introduction is encouraged in patients having unfavorable prognostic factors. For example, the agents are recommended for intestinal lesions with inadequate response to 5-ASA or more than moderate severity even when corticosteroids have not been used. Apremilast, a PDE 4 inhibitor, is used for refractory oral ulcers after successful a global RCT. Accumulated experiences using apremilast in the real world have suggested beneficial effects on non-oral manifestations. Recent immunogenetic studies have suggested novel therapeutic targets such as IL-1, IL-6, the IL-IL-23-IL-17 axis, and the JAK-STAT pathway in BD. Clinical studies using inhibitors for these molecules have shown some benefits, but the evidence levels are too low to be recommended. It is hard to recruit sufficient numbers of patients in prospective studies because of the rarity of the disease. In addition, the lack of standard criteria of therapeutic efficacy or disease activity makes hard to conduct a meta-analysis. The issues should be overcome in

near future.

## S12-1

### Long-term Treatment Strategy in Elderly Rheumatoid Arthritis Patients. -In the Light of TBCR data-

Nobunori Takahashi

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Conflict of interest: Yes

Methotrexate (MTX) is the first-line treatment for rheumatoid arthritis (RA), and the current standard of care is to initiate treatment with a sufficient dose of MTX as soon as the diagnosis of RA is made, and to use molecular-targeted drugs if the response is inadequate. Since MTX is a renally excreted drug, patients with age-related renal dysfunction are at higher risk of hepatic injury and myelosuppression due to increased blood levels. Currently, there are four classes of molecular target drugs available in Japan (anti-TNF inhibitors, anti-IL-6R inhibitors, Abatacept, and JAK inhibitors), and anti-TNF inhibitors. In particular, anti-TNF inhibitors require a sufficient amount of MTX to maximize their efficacy. Therefore, it is often necessary to choose from among anti-IL-6R inhibitors, Abatacept, and JAK inhibitors. In long-term RA treatment, the long-term retention rate is an important indicator in evaluating the value of a drug because it depends on the balance between efficacy and safety. Especially in the elderly, it is important to select drugs that take into account not only efficacy but also long-term safety. There are many data on the use of anti-IL-6R inhibitors and Abatacept without MTX, but the discontinuation rate due to adverse events is higher than that with MTX. JAK inhibitors are also used frequently in the elderly because there are drugs such as peficitinib that show blood levels independent of renal function, and many drugs have low-dose options. Even in apparently healthy elderly patients, there is a concern about potential or future deterioration of visceral function. When choosing between biologics (protein-based drugs) and JAK inhibitors (low-molecular-weight compounds) in terms of long-term safety, biologics are considered to be more advantageous because they are less dependent on visceral function in drug metabolism. We will discuss safe and effective treatment strategies for elderly patients with RA in light of the TBCR data.

## S12-2

### Current status and issues of RA treatment read from NinJa data

Toshihiro Matsui

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Conflict of interest: Yes

NinJa (National Database of Rheumatic Diseases in Japan) is a nationwide RA database that was started in 2002 mainly by the hospitals of the National Hospital Organization (NHO). In 2020, 49 facilities from 27 prefectures nationwide participated in NinJa, which include not only NHO facilities (19), but university hospitals (12), private hospitals (8), public hospitals (6), and clinics (4). The number of registered patients has been more than 15,000 since 2014, covering 2-3% of RA patients in Japan. The current status and issues of RA treatment read from NinJa data are as follows. # The average age of registered patients increased from 61.2 (NinJa2002) to 66.9 years (NinJa2019), and the average age of onset increased from 46.6 to 52.7 years year by year. The number of patients aged 75 and over increased from 10.4 to 31.0%. # DAS28-ESR remission rate increased from 10.9 to 46.0%, but recently slowed down. The progress of joint destruction has not been improved in the early stage of disease. The average age at death is 70.6 → 77.7 years, showing a further improvement. The rate of artificial joint replacement decreased from 4.8 to 1.2%, but the ratio of small joint surgery increased. # MTX usage rate has been declining in recent years (59.9%). Biologics usage has been flat for several years (27.3%), JAK inhibitors has been increasing up to 4.0% recently, steroids (63.0 → 31.6%), and NSAID usage (72.5 → 27.2%) have been on the decline. About 20% of people in remission also use steroids. #With aging, the usage rate of MTX and biologics decreased, csDMARDs and steroid usage increased, and the remission rate decreased. # The hospitalization rates for infections, malignancies, and osteoporosis are increasing. The

prevalence of tuberculosis has improved to the same level as the general population, and that of herpes zoster among JAK inhibitor users is on the decline. The SIR of all malignant tumors remained at about 1, and that of malignant lymphoma continued to change at 3-4.

## S12-3

### Present Japanese medical care trend of rheumatoid arthritis -data from ANSWER (Kansai Consortium for well-being of rheumatic disease patients) Cohort-

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Conflict of interest: Yes

The importance of observational studies including patients who are not suitable for randomized control study (such as aged or with complications) is well recognized. We established the Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort, including eight institutes (Kyoto University, Osaka University, Osaka Medical College, Kansai Medical University, Kobe University, Nara Medical University, Osaka City University, and Osaka Red Cross Hospital) in 2016. It is a multicenter registry of rheumatic disease patients in the Kansai district of Japan, including both rheumatologist and orthopaedics. Recently, we established general incorporated association called ANSWER Cohort Consortium in 2019, to further promote our clinical studies. We would like to show our present activities, future plan, and present medical care trend of RA in this symposium.

## S12-4

### IORRA Cohort

Eiichi Tanaka

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Conflict of interest: Yes

Although the results from randomized controlled trials (RCT) are considered to have a higher evidence level, it is hard to evaluate long-term outcomes in patients with rheumatoid arthritis (RA) using RCT since RA is a chronic disease. There was no prospective observational cohort study in Japan until the establishment of the IORRA (Institute of Rheumatology Rheumatoid Arthritis) study in 2000. Data from approximately 3-5,000 RA patients is collected biannually from all RA patients in our institute and 21 years longitudinal data (110,000 patients-years) has been accumulated. A database consists of 3 domains, mainly self-reported patient's assessment, physician's assessment and laboratory data. In the IORRA, the proportion of the patients who achieved DAS28 remission increased from 8.4% in 2000 to 60.8% in 2020, and most recently approximately 80% of the RA patients are well-controlled. IORRA has clarified a lot of evidences in Japanese RA patients such as advances in RA treatment, usefulness of tight control, life prognosis, usefulness of methotrexate (MTX), various comorbidities and risk factors in RA patients, economic studies, joint surgery, and genomic research in RA, and many scientific papers have been published. The concept of IORRA is transplanted into all post-marketing surveillance (PMS studies) of biological DMARDs (bDMARDs), and the IORRA stimulated the establishment of other registry studies of RA in Japan, indicating that importance of cohort study in rheumatology has become greater and greater. In this session, I will introduce some representative evidences through the IORRA cohort and future issues such as treatment for difficult-to-treat (D2T) RA and elderly RA patients.

## S12-5

### Current status and challenges of the treatment for elderly-onset RA in CRANE cohort

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icine, St. Marianna University School of Medicine, <sup>2</sup>Department of Medicine and Rheumatology, Tokyo Metropolitan Geriatric Hospital, <sup>3</sup>Department of Lifetime Clinical Immunology, Tokyo Medical and Dental University

Conflict of interest: Yes

The CRANE cohort is a prospective monocentric cohort of 197 MTX-naïve elderly-onset patients with moderate to high disease activity, enrolled in 2008-2015. Treatments targeting low disease activity (LDA) were implemented based on shared decisions of the patient and the attending rheumatologist. Treatment with MTX was initiated in patients with poor prognostic factors, and MTX was increased to the maximum tolerable dose. The subsequent line of treatment was a TNF inhibitor with or without MTX as the first biological DMARD, followed by different TNF inhibitors, with or without MTX, or tocilizumab, or abatacept. Treatment could not be intensified due to comorbidities or the patient's own decision in 69 (35.0%) of the 197 patients. The remaining 128 patients adhered to the treat-to-target (T2T) strategy throughout the three years. At week 156, simplified disease activity index (SDAI)-LDA, SDAI-remission, sustained SDAI remission, and HAQ disability index  $\leq 0.5$  was achieved in 84.4%, 57.8%, 42.2%, and 70.3% of the 128 patients adhering to T2T, and in 58.0%, 34.8%, 14.5%, and 43.5% of the 69 patients who did not adhere. In addition to higher disease activity at baseline, ACPA positive, bony erosion at baseline, initial treatment responses at week 12, cumulative disease activity during the initial 12 weeks, and non-achievement of LDA at week 24 were good predictors of clinically-relevant radiological progression at week 52. MTX-associated AEs were observed in 101 (60.5%) of the 167 patients receiving MTX, at a mean (S.D.) dose of MTX of 9.9 (2.8) mg/week. Serious adverse events of any type were reported in 61 patients, and chronic lung disease at baseline, past history of malignancy, and higher disease activity during the three years were identified as risk factors for SAEs. We will show the effectiveness and safety of T2T for very old onset RA, and associated factors with physical function in the present symposium.

## S12-6

### Nagasaki University RA Cohort Study: Focus on Kyushu Multicenter Rheumatoid Arthritis Ultrasound Prospective Observational Cohort Study (KUDOS)

Shin-ya Kawashiri<sup>1,2</sup>, Tohru Michitsuji<sup>2</sup>, Yushiro Endo<sup>2</sup>, Chieko Kawahara<sup>2</sup>, Atsushi Kawakami<sup>2</sup>

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Conflict of interest: None

We have been promoting research using the community-dwelling adults' cohort, the Nagasaki early arthritis cohort, and the RA treatment cohort. In this symposium, we will mainly introduce the Kyushu area multicenter prospective RA ultrasound cohort study (KUDOS) focusing on treatment evaluation by joint ultrasound. We have been promoting the cohort study for RA patients introduced molecular targeted therapeutic drugs (biologic DMARDs or JAK inhibitors) in collaboration with multi-center in Kyushu region from 2013 [Kyushu Multicenter Rheumatoid Arthritis Ultrasound Prospective Cohort in Japan: UMIN 000012524]. In this study, we have evaluated disease activity every 3 months by musculoskeletal ultrasound (MSUS), and have analyzed associations between MSUS score, clinical disease activity, radiographic change, and serum biomarkers. The strength of this study is that a highly objective outcome can be obtained due to the MSUS assessment. As of August 2021, 426 patients have been enrolled. Although multi-center clinical study using MSUS assessment is rare in the world, the standardization of MSUS evaluation is indispensable. We will introduce the standardization of MSUS evaluation in this study. Regarding serum biomarker analysis, comprehensive analysis of cytokines and chemokines using a multi-suspension array and autoantibody isotype analysis in collaboration with Leiden University have been performed. Factors associated with the therapeutic response of synovitis detected by MSUS and the differences between the drugs have become clear so far. In addition, we report the results of analysis using KUDOS data on the recent topics "Difficult-to-Treat RA" and "Elderly RA".

## S13-1

### The pathogenesis of Behçet's syndrome; Inflammation caused by mitochondria DNA-rich exosome

Hyota Takamatsu

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Conflict of interest: None

Behçet's disease (BD) is an autoinflammatory disease with periodic and recurrent symptoms, including oral ulcer, genital ulcer, uveitis, and skin lesion. Vasculitis due to the over-activation of neutrophils has been suggested as a pathological feature. However, it remains unclear how the characteristic symptoms of BD occur. Here, we show that monocytes secrete mitochondrial DNA (mtDNA) from cells via exosomes when pyroptotic cell death occurs. In this process, activation of Caspase-1 induces mtDNA leakage from mitochondria to the cytoplasm via Gasdermin-D. Caspase-1 also promotes the generation of intraluminal membrane vesicles that take up the leaked mtDNA and are secreted as exosomes. The secreted mtDNA-rich exosomes promote leukocyte mobilization and cytokine production via NLRP3 and TLR9. We also found that high levels of serum mtDNA-containing exosomes due to hyper-responsive to the inflammasome-activating stimuli cause the pathological manifestations of BD. Collectively, the over-secretion of mtDNA-rich exosomes due to over-activation of Caspase-1 and followed inflammation caused by mtDNA-rich exosomes may be the pathogenesis of BD.

## S13-2

### Trans-ancestry genome-wide association study identifies novel genetic mechanisms in rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic inflammatory disease with joint destruction, and its cure has not been achieved yet. The establishment of new therapies and the identification of predictive markers are essential steps to improve the clinical practice of RA. Since many genetic risk factors of RA have not been detected, it is expected that advances in genetic research will identify new drug targets and improve the prediction of the disease state. Here, we collected genotype data from 276,020 individuals, including five ancestries of Europeans, East Asians, South Asians, Africans, and Arabs, and performed a large-scale genome-wide association study (GWAS) of RA. A trans-ancestry meta-analysis identified 124 risk loci, among them 34 were novel, which provided novel insight into RA etiology. Candidate genes at the novel loci include i) *TNIP1* and *TNIP2*, inhibitors of NF- $\kappa$ B, ii) *TNFRSF11A* (RANK), a key molecule in osteoclast differentiation, and iii) *WISP1*, a gene highly expressed in sublining fibroblasts of the synovial tissues. These results reconfirmed that the TNF pathway and joint tissues are involved in the genetic risk of RA. In addition, the fine-mapping analysis identified many risk alleles with high posterior probability. Furthermore, this study established a model for calculating a polygenic risk score (PRS) with high predictive accuracy (PRS is a score based on individual genotype, and research for other diseases suggested that PRS is useful for precision medicine). This large-scale genetic study involving multiple ancestries surpassed that of single-ancestry studies in the variant discovery power, fine-mapping accuracy, and PRS prediction performance. This presentation will discuss the new findings obtained in this research and the challenges of future RA genetic research.

## S13-3

### Alveolar infiltrating T cell analysis in rheumatic lung disease

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Conflict of interest: None

Interstitial lung disease in rheumatoid arthritis and collagen disease is



an important condition that determines the life prognosis. Triggered by various factors such as genetic / environmental factors, autoimmunity, and aging, chronic inflammatory conditions are caused by alveolar epithelial disorders, microvascular endothelial disorders, and lymphocyte activation, etc. Later, it develops into fibroblast aggregation, extracellular matrix production from myofibroblasts, and subpleural honeycombing, leading to respiratory failure. Immunosuppressive therapies, including glucocorticoids and biopharmacy, or fibrosis-suppressing agents, and adjuvant therapies are used, but are often advanced, and effective suppression methods have not been sufficiently established. From reports on T cell aggregation and the subpopulation bias in the lung, the presence of self-reactive T cells, and the association of specific HLA and T cell-related genes with SNPs, the association of T cells with pathological conditions is assumed. In addition, there are reports of pathological improvement by suppressing T cell activation and immune-related adverse events by immune checkpoint inhibitors in animal models and case accumulation studies. However, there are still many unclear points about the characteristics of alveolar infiltrating T cells and their role in pathogenesis. Analysis in an animal model combining collagen-induced arthritis and airway inflammation revealed the characteristics of pulmonary infiltrating effector T cells. In our laboratory, we have clarified the characteristics of T cells in bronchoalveolar lavage fluid in rheumatic diseases together with a joint research facility, and recently reported on them. In this symposium, we will review the current status of alveolar infiltration T cell analysis, including self-examination cases, and describe issues and prospects.

### S13-4

#### Tissue-resident memory T cells and autoimmune diseases including systemic lupus erythematosus

Manabu Fujimoto

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Conflict of interest: Yes

Internal and external factors are complicatedly involved in the development of autoimmune diseases, in which T cells play a crucial role. In vivo, memory T cells include central memory T cells and effector memory T cells, as well as tissue-resident memory T cells. Resident memory T cells do not return to circulation and remain in the tissue after migrating to the tissue. Not only its existence has been established, but it has been shown that it occupies a large fraction among memory T cells. Tissue-resident T cells work at the front line of biological defense against invasion of microorganisms in barrier tissues that are in contact with the outside world, such as skin, gastrointestinal tract, respiratory system, and reproductive tract. Its presence has also been clarified in non-barrier tissues such as tissues, joints, liver and pancreas, and its involvement in pathological conditions of inflammatory diseases, allergic diseases and autoimmune diseases and its role in tumor immunity have been reported. In this talk, I will introduce recent findings of tissue-resident T cells and their roles in skin autoimmune diseases and systemic autoimmune diseases such as SLE.

### S13-5

#### Checkpoints for B cell differentiation in SLE

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Conflict of interest: Yes

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease characterized with the emergence of various autoantibodies and deposit of immune complex. Such clinical characteristics indicates the disease relevance of B cells. Indeed, genome-wide association studies and functional genomics studies highlighted B cells as pathogenic cell types in SLE. B cell receptors (BCR) undergo V (D) J recombination and junctional insertion/deletion at the bone marrow and somatic hypermutation at germinal center. This process produces vast variety of BCR repertoire which promptly react to foreign pathogens. On the other hand, B cells which react to autoantigens are eliminated through central/peripheral

checkpoints. In SLE, the mechanism how auto-reactive B cells are expanded in the patients was elusive for a long time. Recently, maturation of antibody-secreting cells through extra-follicular pathways and their auto-reactivity was reported in SLE, although further investigation with large-scale cohort was warranted. Here, we utilized ImmuneNexUT cohort, which consist of RNA-seq data of peripheral immune cells from >590 cases including >130 SLE patients for BCR repertoire analysis. CDR3 length is one of the classical indices of repertoire skewness. Here we observed that CDR3 length in naïve B cells was extremely shortened among autoimmune disease patients. Further, integrative analysis with transcriptome data indicated the association of interferon activity with this shortness. Thus, abnormality in central checkpoints under the influence of interferon was suggested in autoimmune diseases. Further, VDJ gene usage was skewed among plasmablasts and unswitched-memory B cells in SLE. This skewness was associated with extra-follicular maturation pathway and peripheral helper T cell signature in transcriptome. Thus, abnormality in peripheral checkpoints was also suggested in SLE. In this session, we will discuss the B cell abnormality in SLE from the perspective of multi-omics analysis.

### S14-1

#### Confronting the Novel Coronavirus Infections: Focusing on New Therapies and Vaccines

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Conflict of interest: None

In Japan, the first case was reported on January 16, and in early February, a case of mass infection aboard the Diamond Princess was confirmed, drawing worldwide attention to the situation. Since then, the global spread of the disease has been well documented, with more than 200 million people infected and more than 5 million deaths reported so far. Due to the fact that it is a new type of pathogen, we were forced to deal with the situation in a hand-to-mouth manner regarding the characteristics of infectious diseases, diagnosis, treatment, and infection control. During this period, it has become clear through the efforts of the Cluster Response Team and others that the so-called three densities, i.e., crowded, sealed, and close together, are important risk factors. This infection is basically spread by droplet and contact, but the importance of infection by saliva dispersal through conversation and vocalization has been clarified. The virus infects not only the pharynx and nasal cavity but also the salivary glands, and high concentrations of the virus are shed in saliva. In addition, it has been shown that the virus infects the salivary glands using ACE-2 as a receptor, and the characteristics of this disease, which infects systemic organs via vascular endothelial cells, have been clarified. It is also important to consider the mechanism of coagulation abnormalities and thrombus formation that are often experienced in severe cases. In addition to rapid genetic testing, antigen/antibody testing is now available for the diagnosis of this disease. Vaccination is progressing at a rapid pace, and the number of infections, severe cases, and deaths among the elderly is steadily decreasing. On the other hand, an increasing number of severe cases among people in their 40s and 50s, who have not yet been vaccinated, has become a new problem. As for therapeutic agents, in addition to remdesivir and dexamethasone, the JAK inhibitor baricitinib and antibody cocktail therapy have been approved. After 18 months of dealing with this disease, it is safe to say that the level of diagnosis, treatment, and prevention has definitely improved. I would like to share recent information on the direction of development of new therapeutic agents and the current status and effectiveness of vaccination, with a focus on the treatment and prevention of new coronavirus infections, to see what new findings have emerged at the time of this presentation.

### S14-2

#### Humoral immune response and therapeutic antibody development against SARS-CoV-2

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Conflict of interest: None

COVID-19 has not yet been controlled, even though vaccines are gradually becoming available. In addition to the spread of the infection, various mutant strains have been found worldwide, and increased infectivity and immune evasion have become new concerns. In April 2020, when the number of patients infected with COVID-19 increased rapidly in Japan, Keio University started “Keio Donner Project” to overcome COVID-19 by integrating the technologies and experiences of both clinicians at the university hospital and basic researchers at the medical school. Our department focuses on the detailed analysis of patient samples, and has performed studies to produce autoantibodies from antibody-producing cells in diseased tissues of patients with autoimmune diseases and to analyze their reactivity in detail. Now, we apply this research on COVID-19 and perform two practical studies. The first is the SARS-CoV-2 neutralizing antibody detection system, which is a modified method of testing antibody autoreactivity. In collaboration with MBL, we have developed a commercially available neutralizing antibody assay kit, which also enables multi-samples automated assay. We have also developed a neutralization assay for the variant strains, and are examining the time course of neutralizing titer against each strain in patient sera. The second is the development of therapeutic neutralizing antibodies derived from peripheral blood of convalescent patients with COVID-19, which is a modification of autoimmune disease tissue-derived autoantibody production. From the large number of produced antibodies, we have selected the superior antibodies through various screenings and performance evaluations such as authentic virus neutralization assays, mutation resistance evaluation, structural studies, and animal experiments. While there are numerous competitors and many issues other than the research content, we are trying to develop a COVID-19 specific therapeutic originating from Japan.

### S14-3

#### Treatment of COVID-19 (antiviral and anti-inflammatory drugs)

Atsushi Ogata

Osaka Habikino Medical Center

Conflict of interest: None

COVID-19 is a severe viral infection caused by the SARS-CoV-2 virus that causes severe pneumonia, often followed by critical condition by excessive inflammation. The disease progresses from mild stage (before pneumonia), then the virus multiplies and leads to moderate stage (pneumonia). After virus has expanded, immune reaction causes inflammation in lung (pneumonia) and excessive systemic inflammation in some. At November 2021, one antiviral drugs (lemdesivir) and two anti-SARS-CoV-2 antibody (casirivimab/imdevimab and sotrobimab) and two anti-inflammatory drugs (dexamethasone and baricitinib) had been approved for COVID-19 in Japan. Antiviral drugs are less effective once the virus has multiplied, so it is important to use them during mild or asymptomatic periods (before the virus has multiplied). In contrast, anti-inflammatory drugs are ineffective in mild disease without severe inflammation but rather it may be adverse because of their immunosuppressive effects in mild disease. In moderate to severe patients who need oxygen, anti-inflammatory drugs should be started. However, anti-inflammatory drugs are inadequate to suppress in established cytokine storm. Therefore, it should be used just before established cytokine storm to avoid the entering vicious circle of cytokine activation. After severe disease, anti-viral therapy and antibody therapy are not important because of inadequate response. Other candidates include the oral antiviral drugs molnupiravir and favipiravir, and the anti-inflammatory drugs tocilizumab and Sarilumab. Even with more treatment options, the basic therapeutic strategy is the same. When the virus amount is low and the disease is mild, antiviral drugs should be used to suppress viral replication as much as possible, and antibody therapy should be used to eliminate uncontrolled produced viruses. Even if pneumonia is not avoided, anti-inflammatory therapy should be used to prevent it become critical.

### S14-4

#### SARS-CoV-2 vaccination in patients with rheumatic diseases

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Conflict of interest: None

The risk of developing COVID-19 in patients with rheumatic diseases is reported to be 1.5 times higher than that in healthy individuals. Although various SARS-CoV-2 vaccines have been developed, two mRNA vaccines have been mainly introduced in Japan, and more than 70% of the Japanese population has already been vaccinated with two doses. Although there have been a few reports of exacerbation of rheumatic diseases and new cases of rheumatic diseases after vaccination, in the majority of patients, there is no significant impact on disease activity. Therefore, active vaccination is strongly recommended, especially in patients with stable rheumatic diseases. It has been reported that patients with rheumatic diseases who complete the vaccination have a better prognosis for COVID-19. In addition to concerns about adverse reactions due to the novel mechanism of the vaccine, the degree of efficacy of the vaccine in patients with immunosuppressed rheumatic diseases has been a focus of attention. The induction of antibodies to spike proteins has been widely studied as a means of assessing vaccine efficacy. It is also known that cellular immunity also acts as an effect of vaccines. The titer of anti-spike protein antibodies induced by vaccines has been reported to vary with the rheumatic disease agents used. Patients receiving bDMARDs have relatively favorable immunogenicity. On the other hand, rituximab and mycophenolate mofetil are known to reduce the efficacy of the vaccine. Temporary suspension of immunosuppressive therapy before and after vaccination should be considered upon a careful assessment of each case. In patients using rituximab, antibody production is known to be suppressed for long periods of 6 months or more after administration. Because the titer is known to decrease over time, the third vaccination is also recommended for patients with rheumatic diseases, especially those who are considered to have a poor response to the vaccine than healthy individuals.

### S14-5

#### Autoimmune rheumatic disease (AIRD) patients and infectious diseases: Lessons from the pandemic of COVID-19

Kenji Oku

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Conflict of interest: None

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has led to a renewed awareness of infection control in patients with autoimmune rheumatic diseases (AIRD) and the treatment of AIRD under infectious epidemics. The results of a registry study of AIRD with Coronavirus disease 2019 (COVID-19) conducted by the Japan College of Rheumatology showed that high-dose glucocorticoid was a poor prognostic factor, but DMARDs and molecular targeted therapies were not. On the other hand, inadequate suppression of activity in AIRD has been reported to lead to increased susceptibility to infection, which was also suggested in COVID-19. Abnormalities in immune system such as defect type I interferon secretion or cytokine storm were found to be associated with the development and aggravation of COVID-19. The pathological knowledges and therapeutic agents in AIRD contributed to the treatment of COVID-19. On the other hand, the first mRNA vaccination was generally safe and remained effective in patients with AIRD.

### S15-1

#### Health economics assessment in rheumatoid arthritis treatment - Based on the 2020 Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis

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Conflict of interest: Yes

The introduction of biological DMARDs (bDMARDs) has resulted in significant advances in treatment strategies for rheumatoid arthritis (RA). On the other hand, rising RA care costs have caused concern, placing a heavy burden on society as well as RA patients. In the 2020 updated of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis, “Health economics assessment in rheumatoid arthritis treatment” was incorporated as a separate chapter. Among them, “Category of medical expenses”, “Current status of RA medical costs in Japan”, “Importance of the pharmacoeconomic assessment (cost-effectiveness) of expensive medications in RA treatment”, “Evidence on the cost-effectiveness studies in RA treatment”, “Evidence on the indirect costs (work disability) in RA treatment”, and “Biosimilars in RA” were explained respectively. The IORRA study has shown that RA patients’ financial burden is increasing and that direct and indirect costs associated with progression of functional impairment or decline in quality of life (QOL). In addition, pharmacoeconomics is the scientific discipline that evaluates both the clinical benefits and economic efficiency of a drug to determine whether it is worth the cost. The IORRA study has also shown that the cost-effectiveness of bDMARDs in the treatment of RA and found that the use of bDMARDs in Japanese RA patients is justified in the long term from an economic perspective. Furthermore, the development and widespread use of biosimilars may have a positive impact on RA medical costs. At this symposium, I would like to explain the health economics assessment in rheumatoid arthritis treatment using various evidences including the IORRA data from the standpoint of being involved in the preparation of the 2020 updated of the Japan College of Rheumatology clinical practice guidelines for the management of RA.

## S15-2

### Management of rheumatoid arthritis patients from a cost-effectiveness perspective

Isao Matsushita

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Conflict of interest: Yes

It has been reported that the higher the disease activity and the greater the functional disability induced the higher the direct medical costs. Since early initiation of treatment for RA has been shown to reduce disease activity, earlier diagnosis and therapeutic intervention are necessary for cost-effectiveness. In addition, management of patients with RA using a composite measure that includes joint findings in daily practice will enable lower control of disease activity and thus increase cost-effectiveness. QALYs (quality-adjusted life years) and ICERs (incremental cost-effectiveness ratio) are used to discuss cost-effectiveness. 1 QALY is one year spent in perfect health, and the ICER is the cost required to obtain 1 QALY. In Japan, it is reported that an ICER of 5.4 million yen or less is acceptable. It was reported that the ICER of using bDMARDs compared with MTX is less than 5 million, so I believe that bDMARDs should be included as a treatment option without hesitation when csDMARDs treatment is ineffective. In order to further improve the cost-effectiveness of bDMARDs, the use of biosimilars is important. Several studies comparing original TNF inhibitors with biosimilars have shown comparable efficacy, and the Rheumatoid Arthritis Clinical Practice Guidelines 2020 also recommends the use of biosimilars as well as original biologics. On the other hand, reducing the dose and extending the duration of bDMARDs while maintaining good control of disease activity can also be cost-effective. Some evidence suggests that low disease activity can be maintained even with a reduction in the dose of bDMARDs. If therapeutic goals are achieved and maintained, it may be possible to consider reducing the dose or extending the duration of bDMARDs under careful management. In this symposium, we would like to discuss RA treatment from the aspect of cost-effectiveness with some evidence.

## S15-3

### Cost-effectiveness of bDMARDs and tsDMARDs in terms of efficacy for rheumatoid arthritis: A randomized controlled trial

Hiroaki Matsuno

Matsuno Clinic for Rheumatic Diseases

Conflict of interest: None

Both biological originator disease-modifying antirheumatic drugs (boDMARDs) and targeted synthetic DMARDs (tsDMARDs) have shown excellent efficacy against rheumatoid arthritis (RA), enabling complete remission of RA, a disease previously considered difficult to treat. However, both drugs are priced high. For boDMARDs and tsDMARDs other than interleukin-6 (IL-6) inhibitors, patients with standard body weight and on standard dosage must make monthly co-payments of 30,000 yen or more if they are supposed to cover 30% of their medical bills. Studies on quality-adjusted life years and incremental cost-effectiveness ratio, which examined these drugs from a medical economics standpoint, drew positive conclusions on their cost-effectiveness because both drugs showed excellent efficacy. The premium for usefulness is also considered in determining drug prices in Japan. Accordingly, among articles reporting previous randomized controlled trials, those describing Disease Activity Score-28 for RA with C-reactive protein (DAS28-CRP) in the efficacy assessment were extracted, and the cost of each drug necessary to reduce DAS28-CRP by 1 point was calculated from the drug price. Articles with many patients having similar demographic characteristics were selected for drug comparison, but it was not possible to match all articles regarding the time to response evaluation, presence/absence of concomitant drugs, and patient medical history. While the result interpretation is limited and restrictive, biological similar DMARDs (bsDMARDs) and IL-6 inhibitors were found beneficial when drug prices were considered, although tsDMARDs were more effective for reducing DAS28-CRP. Moreover, all three bsDMARDs (infliximab, etanercept, and adalimumab) were superior to boDMARDs in cost-effectiveness to reduce DAS28-CRP by 1 point. When treating RA with high-priced DMARDs, it is necessary to select drugs based on the patients’ condition and economic status.

## S15-4

### Usefulness and problems of biosimilar treatment for rheumatoid arthritis

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Conflict of interest: None

The average income of Japanese earners decreased from 4,550,000 yen in 1992 to 4,360,000 yen in 2019. Aging rates and increased health-care costs make it difficult for Japan to support these financial demands, and the costs need to be reduced. Biologics or JAKi are effective, but expensive treatments for rheumatoid arthritis (RA). Biosimilar (BS) treatment is a promising option to reduce the costs of RA treatment. Infliximab-BS, etanercept (ETN)-BS, and adalimumab-BS are approved for RA in Japan. The retention rate of the ETN-originator is good due to low immunogenicity and the risk of mycobacterium infection for ETN is low compared with antibody agents. Evidence to support the use of ETN for the treatment of reproductive-age women is abundant. Thus, we frequently use ETN-BS at our institute. The SDAI was statistically worse for ETN-OR at initiation (22.3), compared with ETN-BS at initiation (4.3) and at 6 months (5.3) in a retrospective study of 42 RA patients who switched from ETN-OR to ETN-BS. Particularly, the tender joint counts and global assessment were worse. A nocebo effect is suspected. Thus, rheumatologists should take the nocebo effect into consideration when switching from OR to BS. ETN-OR 50 mg/w was the most effective treatment in the Japanese phase III JERA study. However, ETN-OR 20 mg/w was also more effective than MTX. A half dose of ETN-BS is a promising option for RA patients who are narrow-fisted; a post-hoc analysis of the JERA trial showed no statistical differences in the effectiveness between 50 and 20 mg/w. In 6/8 RA patients who were treated with half a dose of ETN-BS (50 mg/2w), the half dose was effective when treatment was continued. ETN-BS was increased from 50 mg/2w to 50 mg/w in 2 cases. The patient-paid cost of the ETN-BS half dose is about 10,000 yen /month per patient, which can be paid by more patients in clinical practice. Thus, the development of new treatment strategies should consider the financial burden for RA patients.

## S15-5

### Optimized Treatment of Rheumatoid Arthritis on the Basis of Public Medical Insurance

Saburo Matsubara

Center for Arthritis and Clinical Rheumatology Matsubara Clinic Kumamoto Japan

Conflict of interest: None

As for the treatment of the rheumatoid arthritis (RA) in Japan, most of the patients are treated in the usage of the public medical insurance. The limitation of the treatment sometimes occurs in the treatment of RA especially in the intractable cases. Since artificial intelligence is introduced into insurance assessment for the medical treatment from September 2021 by the financial stringency of our country, we have encountered the increment of the return of insurance receipt in the current situation. It is necessary for rheumatologists to perform good treatment of RA, having known the enough knowledge of the insurance rules as well as that of the treatment of RA. Under this situation, the point of the recommended treatment for RA was listed below. 1) Appropriate evaluation of the arthritis by the careful inspection and palpation 2) Adequate usage of *composite measures* of disease activity in RA. 3) Early induction of the remission by the proper use of the rheumatoid arthritis treatment algorithm 4) Early detection of the synovitis flare by the ultrasonogram 5) Minimization of arthritis flare up by the adequate operation of T2T As for the therapeutic drugs, it is rare that the usage of them was denied by the public medical insurance except in the case of contraindications. However, the blood test for diagnoses or follow-up are apt to deny as the tendency medical treatment by the public medical insurance. Furthermore, permissible frequency of the image inspection is not clear. In this presentation, I will explain them in detail about the measures for these insurance problems.

## S16-1

### The birth story of PLEASURE-J

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Conflict of interest: Yes

Although pregnancies complicated by rheumatic diseases are risky for both mother and child and require careful handling, there are very few epidemiological studies that can serve as a reference. The main reason for this is that the number of cases handled by a single institution is small. There is a need to create evidence unique to Japan. It was also my pledge to work for this purpose when I was elected as a member of the board of directors in 2015. The Subcommittee on this issue was established, and we started preparations for this study (PLEASURE-J). I received the encouraging support of the President and other members of the Board of Directors. Initially, the protocol was to be developed to study pregnancy outcomes in pregnancies complicated by SLE, but it developed into a large-scale disease registry for men and women in a wide age range from 6 to 40 years old. In the poster room at the 2019 Annual Meeting, there was a corner that could have been mistaken for a pharmaceutical company's exhibit, but it was the demonstration of the REDCap system being used for registration by the working group members. As you can see, PLEASURE-J was born and has grown so far thanks to the efforts of not only the committee members, but also the younger members of the working group and the strong support of the society office. However, above all, the registry is only possible because of the doctors who have registered cases and the patients who have cooperated with the questionnaire. We have a responsibility to make the most of such valuable data. We have introduced a system of public solicitation of research questions to create an environment in which any attending physician who has registered a case can utilize the data and conduct original clinical research. For this reason, I would like to share the secret story of the birth of PLEASURE-J with some boasting and complaining.

## S16-2

### The potential for evidence-making using the JCR supported registry of young patients in the early stage of systemic lupus erythematosus

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Conflict of interest: Yes

The PLEASURE-J study is a multicenter prospective registration study initiated as a project of the Collagen Pregnancy Registry Subcommittee, to clarify the prognosis and the impact of medical care on patients' quality of life of young patients with systemic lupus erythematosus (SLE) in Japan. The enrollment began in April 2019 at 31 sites nationwide for young patients with early-stage diagnosed SLE within 1 year of diagnosis and younger than 40 years of age at diagnosis, and 197 cases from 57 sites are currently enrolled. The study is characterized by the following four points. Firstly, the study is a unique early diagnosis disease registry for young people, with a wide age range from childhood to adulthood. In addition, we try to continue to track cases annually for at least 10 years. This will not only allow us to examine the differences in clinical presentation between children and adults but may also reveal how treatment in childhood and adolescence affects patients' subsequent growth, disease activity, physical dysfunction, and reproductive health. Secondly, it collects patient-reported outcomes, including information on health and disease-related quality of life, stress, sleep, and exercise, as well as disease activity, treatment, and accumulated organ damage. These data are expected to provide new insights into the psychological problems of SLE patients. In addition, the study will collect information on the pregnancy outcomes of a sub-cohort of patients and the development of their children. We hope to provide some encouragement to women with SLE who are struggling to take care of their children. Finally, we have introduced an open call system for research questions, creating an environment in which any attending physician who has registered a case can use the data to conduct their own clinical research. In this lecture, we will review the history of the PLEASURE-J study and discuss ways in which the study can be further developed.

## S16-3

### Characteristics of Childhood-Onset Systemic Lupus Erythematosus and Prospects for Consistent Cohort Studies in Children and Adults

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Conflict of interest: Yes

SLE is also a common autoimmune disease in children. The pathogenesis of SLE is the same in all age groups, but the prognosis is worse in childhood-onset SLE (cSLE) than in adult-onset SLE due to a more rapid clinical course and more severe disease. The average age of onset of cSLE is 12 years. The incidence of lupus nephritis in cSLE is recognized to be high, with more than 70% of cases showing Class II or higher renal pathology (silent lupus nephritis), even with normal urine findings. On the other hand, organ involvement of the nervous, cardiovascular and respiratory systems is rare in childhood and appears more than ten years later. Recent advances in therapy and the development of treatment guidelines have



greatly improved the prognosis of cSLE. However, cSLE remains one of the most common pediatric rheumatic diseases with a meager treatment-free remission rate. Its long-term prognosis and quality of life in transition and adulthood are influenced by the disease itself and the accumulation of organ damage caused by glucocorticoids and other therapeutic agents. As a high proportion of children with cSLE continue to require medical care after transfer to an adult department, there is a need to clarify the differences in the pathogenesis of cSLE and the problems associated with the transition to adult care, and to establish guidelines for the treatment of cSLE in adulthood. Pleasure-J is the first large-scale registry of cSLE in Japan with comprehensive coverage of both pediatric and adult cSLE. The potential benefits of this registry for the medical care of cSLE include: 1. a joint registry with adult cases, allowing for comparisons and clarification of the characteristics of cSLE; 2. long-term follow-up of more than ten years, providing high-quality clinical data on long-term outcomes, including pregnancy into adulthood; and 3. the study is planned to be conducted under the All Japan system in combination with clinical samples.

## S16-4

### Functional genomics for understanding the sex difference in autoimmune diseases

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Conflict of interest: Yes

Most of the autoimmune diseases show strong sex bias and predominated by female patients. This is the distinctive feature of autoimmune diseases. On the contrary, the risk of severe COVID-19 infection is higher among males. These examples indicate the sex difference in immune system. To understand the reason of sex difference might lead to understanding the pathogenesis of these disorders. Systemic lupus erythematosus (SLE) predominantly affects women of childbearing age and frequently flares during pregnancy. This clinical observation supports the relevance of sex hormone in its pathogenesis, although the causal relationship is still unclear. Among females, one allele of X chromosome is inactivated (XCI). Despite, some genes are known to escape this inactivation, which result in higher expression of those genes among females than males. Such XCI escape genes include TLR7 and TASL, which have known pathogenic roles in SLE. Thus, XCI machinery may be involved in SLE pathogenesis. The effect of sex-hormone and the extent of XCI is different according to cell types. To understand the relevance of these machineries to autoimmune diseases, investigating them among immune cells may be important. We have investigated the sex difference among autoimmune diseases with ImmuNexUT database, which is a functional genomics database of immune cells from immune-mediated patients. So far, we identified female-specific gene regulatory machinery and its association with the regulation of immune-associated genes. Also, cell type specificity of XCI escape genes was identified. In the near future, another layer of information such as single-cell RNA-seq data might contribute to the elucidation of sex bias-associated cell types and female-specific gene regulatory machinery at one cell resolution. In this session, we want to review the reports about the sex difference in autoimmune diseases and discuss about the utility of functional genomics approach with disease cohort for this area.

## S17-1

### Advanced understanding of the pathophysiology of Spondyloarthritis

Georg Schett

FAU Erlangen Nürnberg, Germany

Conflict of interest: None

Spondyloarthritis (SpA) is part of a group of tightly related clinical phenotypes that is defined by shared molecular pathogenesis resulting in excess prolonged inflammation in the various tissues affected. SpA comprises a set of specific drivers that drive an aberrant immune response and consequent development of chronic disease that necessitates therapeutic

intervention. These drivers comprise genetic, biomechanical, metabolic and microbial factors that facilitate a robust and continuous mobilization, trafficking and homing of immune cells into the target tissues, such as the skin, the entheses or the joints. The role of genetic variants involved in the immune response, the contribution of mechanical factors triggering an exaggerated inflammatory response (mechanoinflammation), the impact of adipose tissue and altered lipid metabolism and finally the influence of intestinal dysbiosis in the disease process are discussed. Furthermore, the function of the key orchestrating cytokines in SpA is reviewed with a focus in describing their respective place in the disease process. Finally, the nature and the mechanisms of inflammatory tissue responses, immanent to SpA are summarized in this lecture.

## S17-2

### What should we aim for in treatment of SLE?

Eric Morand

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Conflict of interest: None

Systemic lupus erythematosus (SLE, lupus) remains a condition of high unmet need. Patients with SLE face an uncertain long term future, with low quality of life, high morbidity, and high mortality that has remained unchanged this millennium. It is now clear that both uncontrolled disease activity, and treatment burden especially in relation to glucocorticoid dose, both contribute to the risk of poor lupus outcomes - and therefore we need to find ways to achieve the combination of low disease activity and low glucocorticoid exposure if we are to meaningfully improve patient outcomes. In recent years separate consensus methodologies have resulted in definitions of low disease activity and remission for lupus. The Lupus Low Disease Activity State (LLDAS) has now been prospectively validated to be protective against damage accrual, flare, low quality of life, and mortality; LLDAS allows minimal clinical or serological active disease and up to 7.5 mg/day of prednisone. In parallel, a remission definition produced by the DORIS group incorporates the complete absence of clinical disease activity measured by SLEDAI, but allows serological activity and treatment including up to 5 mg/day prednisone; DORIS remission is less well validated than LLDAS and may be no more protective. Large cohort studies indicate that many patients do not achieve these states in a sustained way with standard therapy - therefore, we need to do better. Regardless of measurement nuances, both LLDAS and remission now allow treat-to-target concepts to be applied in lupus, both in everyday practice and in research studies. LLDAS has been successfully deployed as a secondary outcome measure in clinical trials, meaning that the targeted therapies now available can be used to achieve LLDAS. However, the field awaits formal treat-to-target intervention studies wherein patients not at target received protocol-based treatment escalations until target is achieved.

## S17-3

### Managing Rheumatoid Arthritis: Now and the Future

Jon T Giles

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Conflict of interest: Yes

In only a few decades, the outlook for a person newly diagnosed with rheumatoid arthritis has changed from near-certain unrelenting discomfort and progressive debility to a manageable condition in which all activities and life expectations can be reliably maintained for most patients. Patients with delayed diagnosis and treatment and those resistant or refractory to therapies are still encountered, but with less frequency. Underlying this shift is the availability of a wide variety of highly effective therapies and the general acceptance of treat-to-target strategies aiming for low disease activity or remission. However, even within this framework, we still lack the ability to identify the ideal treatment strategy for a given patient without trial and error. Moreover, RA- and non-RA-associated comorbidities may exclude some therapies that may have been effective. Most of all, there are no evidence based ways to prevent RA in the pre-RA phase or strategies to ensure treatment-free remission. Efforts happening today focused on personalized treatment choices, effective management of comorbidities, and maintenance of remission will likely translate to even bright-



er outcomes for the RA patient of the future. Perhaps even more exciting are efforts to understand the pre-clinical phase of RA with a goal of disease prevention or amelioration. These current efforts to change the treatment paradigm of RA for the future will be highlighted in the presentation.

## **S17-4**

### **COVID-19 in autoimmune inflammatory rheumatic diseases**

Jeffrey A Sparks

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Conflict of interest: None

This invited lecture will detail progress of COVID-19 in systemic autoimmune inflammatory rheumatic diseases. First, we will discuss COVID-19 susceptibility and outcomes related to the general population. We will also detail the rheumatic-specific factors such as immunosuppressive medications, disease activity, and severity that affect COVID-19 outcomes. We will discuss the role of re-purposing of rheumatic medications to treat COVID-19. We will discuss long-term outcomes of COVID-19 that include disease activity, systemic inflammation, autoimmunity, and symptoms. Finally, we will discuss management of rheumatic patients in the COVID-19 era, related to telehealth, vaccines, variants, and early outpatient treatment.

## **S17-5**

### **Treatment of interstitial lung disease in autoimmune diseases**

Masataka Kuwana

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Conflict of interest: Yes

Interstitial lung diseases (ILDs) are among the most serious complications associated with connective tissue diseases (CTDs), and lead to significant morbidity and mortality. ILD can be present in most types of CTDs, including rheumatoid arthritis, systemic sclerosis, polymyositis or dermatomyositis, Sjögren's syndrome, and mixed connective tissue disease. The management of CTD-ILD is challenging due to extreme diversity of clinical course, treatment response, and outcomes, and the lack of robust clinical trial data. Currently, decision of treatment indication is made by expertise of physicians, based on clinical course, underlying CTDs, biomarkers such as autoantibodies, histopathological findings and high-resolution CT patterns, because of lack of evidence-based prognostic prediction algorithm. In chronic ILD, it is important to detect and treat progressive fibrosing ILD (PF-ILD), which leads to restrictive ventilatory impairment and resultant respiratory insufficiency due to progression of fibrosis in the lung parenchyma, early in the course of the disease. Finally, immunosuppressive regimens with corticosteroids and/or immunosuppressants have been a mainstay of the treatment of CTD-ILD, but in recent years, there have been accumulating data showing potential efficacy of molecular-targeted drugs targeting cytokines such as IL-6, T cells and B cells. On the other hand, the effect of antifibrotic agents such as nintedanib on preventing lung function decline is shown in patients with PF-ILD. However, there are still many issues to be solved, such as in what cases, at what timing, when to use them properly or in combination, and long-term efficacy and safety profiles. This lecture features updated information of predictors for progression and poor outcomes, and clinical trial/registry data in patients with CTD-ILD.

## **S18-1**

### **Genomics-driven approaches for personalized medicine**

Yukinori Okada<sup>1,2</sup>

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Conflict of interest: Yes

Recent development of genome sequencing technology changed the bottleneck of genomic studies from construction of large-scale genome sequence data into interpretation of the sequenced genomes. While the large-scale human genome studies have successfully identified thousands

of genetic variants associated with human complex traits, the methodologies towards clinical and social implementation of personalized medicine is still elusive. Genomics analysis, highlighted as trans-layer omics analysis integrating omics data based on human genetics, is considered as a promising approach. Polygenic risk score (PRS), estimation of individual's disease risk based on large-scale genome-wide GWAS summary statistics, shows higher prediction accuracy than previous methods. While subtle population structure among and within ancestries can induce bias in baseline estimation of PRS, individuals with high PRS values could be candidates for primary care before disease onset, including rheumatoid arthritis). PRS also can be interpreted as instrumental variables distributed among the population. By utilizing clinical biomarker PRS on health outcome, we identified causal risk of obesity, high blood pressure, and low C-reactive protein levels on lifespan. As for autoimmune diseases, human leukocyte antigen (HLA) alleles have prominent effects on both disease onset and subtype classification. HLA imputation analysis has identified risk HLA variants on numerous autoimmune diseases. Accurate estimation of individual's HLA alleles is essential in personalized medicine. We recently developed convolutional deep learning-based HLA imputation software of DEEP\*HLA, which enabled more accurate estimation of rare HLA alleles than previous methods. Integration of PRS, HLA, and other human trans-omics resources should contribute to personalized medicine of autoimmune diseases. We would like to introduce recent researches on genomics-driven personalized medicine.

## **S18-2**

### **Pathobiological Approaches to Precision Medicine**

John D Isaacs

Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

Conflict of interest: None

As rheumatologists we now have a broad selection of therapies for our patients, particularly biologic drugs. However, many of these drugs have been developed agnostic to the fundamental pathobiology of rheumatic diseases and, to an extent, have been retrofitted when trials demonstrated efficacy. For example, TNF inhibitors and rituximab were developed for distinct indications and only subsequently found to benefit certain rheumatic diseases. Furthermore, some of our small molecule drugs have ill-defined mechanisms of action but are highly effective in poorly demarcated patient subsets. In the twenty years since the first biologic therapies were approved for the treatment of rheumatic diseases our understanding of disease pathobiology has increased substantially, not least due to technologies such as single cell sequencing. We now have a wealth of data that not only implicates new therapeutic targets but which should also help us to target existing therapies more effectively. Much of this new information has been derived from studies of the target tissue, which is completely appropriate. A future challenge, however, will be to identify a means to identify targetable pathobiological subtypes without the requirement for invasive investigation. In my presentation I will provide an update of rheumatic disease pathobiology and how this is catalysing precision medicine approaches.

## **S18-3**

### **Precision medicine using immunophenotypic analysis**

Shingo Nakayama, Yoshiya Tanaka

First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Conflict of interest: None

In rheumatic diseases, advances in biological molecular-targeted therapies have led to remarkable progress in the treatment. Although systemic lupus erythematosus (SLE) and psoriatic arthritis (PsA) are representative rheumatic diseases characterized by multiple organ manifestations, their clinical, molecular, and genetic heterogeneity makes it difficult to manage all cases based on a single kinetic molecular theory. This molecular and clinical heterogeneity of the diseases often poses a therapeutic challenge and it is difficult to improve all of these various symptoms simultaneously with the use of limited drugs. Therefore, precision medicine is an urgent concern that is required to overcome this issue. We attempted to take a

broader view of the molecular heterogeneity of SLE and PsA using immunophenotyping. In SLE, we found that patients with active SLE could be divided into three subgroups based on T-cell heterogeneity. Patients with similar clinical manifestations had different immunophenotypic features, but those who were resistant to treatment were most often found in the T follicular helper cell-dominant group. Furthermore, the study in patients with PsA showed that selecting specific biologics such as TNF, IL-12/23 or IL-17 inhibitors according to the four different immunophenotypes of peripheral blood lymphocytes was shown to produce high therapeutic responses. Thus, subgrouping of heterogeneous diseases could be the basis for precision medicine, which would boost therapeutic strategies for clinically and molecularly heterogeneous diseases such as SLE and PsA. In the near future, it is expected that multi-omics analysis such as genomics, transcriptomics, proteomics, and metabolomics will be integrated with immunophenotyping to realize personalized medicine with higher accuracy.

## S18-4

### Precision medicine by multiomics analysis

Katsuya Suzuki, Masaru Takeshita, Kotaro Matsumoto, Jun Inamo, Maho Nakazawa, Yasushi Kondo, Keiko Yoshimoto, Tsutomu Takeuchi  
Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University

Conflict of interest: Yes

Precision medicine, which provides optimal treatment for each patient's characteristics, has long been considered a dream of the future. The multi-omics approach has been applied to understand pathophysiology and to discover biomarkers and drug targets for immune mediated rheumatic diseases. To enable precision medicine, molecular profiling, especially comprehensive molecular analysis called "omics" performed using individual biological samples, is a powerful, state of art scientific approach. Applying this approach, we first attempted to understand molecular state in patients with primary Sjogren's syndrome and found the significant association of molecular signatures with disease state. (Ann Rheum Dis. 2017) We then discovered the molecular effects of disease-modifying antirheumatic drugs (DMARDs), including biological DMARDs, that target specific signaling pathways in patients with rheumatoid arthritis (RA) (Nat Commun. 2018). Before our study, collecting such a comprehensive multiomic data has considered to be very costly and uncertain for the contribution to precision medicine. Fortunately, a series of our multiomic analysis opened new avenues. We also deepened this approach by focusing on T cells from RA patients and found interesting and important clues for precision medicine. (Ann Rheum Dis. 2020, Arthritis Rheum 2021, Sci Rep. 2021) Recently, we expanded to molecular profiling for patients with large vessel vasculitis (LVV) and showed new possibility in this area. (Arthritis Res Ther. 2019, Clin Trans Immunology. 2021) In this seminar, I particularly focus on precision medicine by multiomics analysis and discuss current status and future perspective.

## S18-5

### Future perspectives on precision medicine in rheumatic diseases

Daniel Aletaha  
Division of Rheumatology, Medical University Vienna, Austria

## S19-1

### Surgical intervention for the finger and wrist joints

Hajime Ishikawa, Asami Abe, Hiroshi Otani, Kei Funamura, Satoshi Ito, Masanori Sudo, Sayuri Takamura, Kiyoshi Nakazono, Akira Murasawa  
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Conflict of interest: None

In the era of biologics and JAK inhibitors, patients with low disease activity require aesthetic reconstruction of the finger and wrist joints, as well as pain relief and functional recovery. In recent years, balance restoration using a soft tissue structure without bone preparation has been recommended. However, 1) local tissue is fragile after smoldering inflammation of RA; 2) muscle atrophy and myostatic contracture occurs with the

gradual progression of deformity over a long period of time; and 3) joint contracture appears with arthrosis. Therefore, joint-preserving surgery is limited for joints with mild deterioration. Joint-preserving surgery includes the modified Thompson-Littler method for the swan-neck deformity, the Ohshio method for the boutonniere deformity, centralization of the extensor tendons, intrinsic release, and crossed intrinsic transfer for ulnar drift of the fingers. Arthroplasty or fusion is indicated for the severely deformed hand with contracture and/or considerable joint deterioration. When inserting a silicone implant (Swanson) to the MP joint, appropriate tension is determined by making a gap of approximately 12 mm between the two bones. Bending  $\geq 60^\circ$  is a risk factor for implant fracture. Implant arthroplasty of the PIP joint is not recommended for joints with lateral instability of  $>30^\circ$  or hyper-extension/flexion deformity. Radiocarpal arthrodesis provides painless stability, however, in some cases, ankylosis occurs. To prevent this loss of mobility, combination of the midcarpal arthroplasty or expansion of the surgical indications for TWA should be considered. In cases with an unstable ulnar stump, stabilization using the FCU or ECU tendon is required to prevent extensor tendon rupture and impingement of the radius. Unless RA is completely cured by pharmacotherapy, surgical intervention for the hand is needed as a complementary treatment, as patients have unmet needs.

## S19-2

### Functional recovery with total elbow arthroplasty in patients with rheumatoid arthritis

Keiichiro Nishida<sup>1</sup>, Yoshiyuki Matsuyama<sup>2</sup>, Ryoza Harada<sup>3</sup>, Yoshihisa Nasu<sup>4</sup>, Ryuichi Nakahara<sup>4</sup>, Toshifumi Ozaki<sup>1</sup>

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Conflict of interest: None

The elbow joint plays a crucial role in the reaching motion of the hand to a desired position in space, and a range of motion (ROM) of 30-130 degrees is considered sufficient for almost all activities of daily living. The elbow joint is not weight-bearing, but it is a load-bearing joint, taking about one-half of the body weight in activities such as standing on the hand, lifting objects, and using a cane. The frequency of elbow involvement in rheumatoid arthritis (RA) is estimated to be 20-65%. Total elbow arthroplasty (TEA) is a well-established surgical technique for the treatment of end-stage elbow destruction in patients with RA, which provides excellent pain relief and improves ROM. In Japan, the Japan Orthopaedic Association - Japan Elbow Society (JOA-JES) score has been used to assess elbow function before and after TEA, while the Mayo Elbow Performance Scale (MEPS) has been used worldwide. In recent years, in addition to objective evaluation by physicians, Patient Reported Outcome (PRO), a direct evaluation of the effectiveness of treatment by patients, has become increasingly important. The Japanese version of the Patient Related Elbow Evaluation (PREE-J) is a reliable and reproducible PRO for elbow disorders in the Japanese population. In our previous study, the PREE-J correlated significantly with MEPS DASH and Hand20 before TEA and with DASH and Hand20 after surgery. The effect size was significantly higher than that of DASH and Hand20. In this study, we examined 82 elbows of 72 patients with RA (mean age 63.5 years, mean duration 22.9 years) who underwent TEA between January 2012 and December 2019 and clinical data were evaluated preoperatively and at 1 year postoperatively. Preoperative/postoperative elbow ROM and grip strength were significantly improved, and PREE-J, MEPS, DASH and Hand20 were significantly improved postoperatively. Grip strength was correlated with all elbow PROs in PREE-J, DASH and Hand20, and significantly correlated with duration of disease and total Larsen score of 15 joints of hand. The PREE-J was significantly correlated with the total Larsen score, suggesting that the PREE-J reflects not only elbow function but also overall upper limb and hand function. Thus hand deformity and joint destruction affect grip strength, making grip weakness a barrier to patient-reported recovery of elbow function after TEA.

### S19-3

#### **QOL recovery by shoulder surgery in patient with rheumatoid arthritis**

Katsuaki Kanbe

Nippori Orthopaedics and Rheumatic Clinic

Conflict of interest: Yes

Development of joint destruction was predicted in era of COVID-19 for RA patients with treatment of immunosuppression drug as high dose of MTX. As for shoulder joint, the severe joint destruction should be needed to decide TSA ever before. However, RSA enable to shoulder desfunction such as cuff tear with ADL difficulty over 65 years recently. We reported ARASHI score was valuable for measure large joint destruction then shoulder improvemet was reported by biologic DMARD (Kanbe K, et al. *Mod Rheumatol*. 27(6):938-945, 2017.). The radio graphic progression of shoulder joint was 14.6% at 52 weeks, on the other hand improvement was 36.6%. Therefore tight medical treatment is important before surgery. In these days we performed arthroscopic rotator cuff repair in RA patients. Disease duration is key point to select shoulder arthroscopic surgery or RSA. Under 10 years of D.D. should be undertook arthroscopic synovectomy. Over 10 years we selected RSA in shoulder. QOL was investigated by HAQ-DI 9 years after shoulder surgery. We foud low HAQ-DI significantly in the group with rehabilitation after sugery. Therefore shoulder surgery should be needed with multidisciplinary therapy in RA patients.

### S19-4

#### **Best timing for lower limb joint surgery in patients with rheumatoid arthritis -for recovery from frailty -**

Toshihisa Kojima, Nobunori Takahashi, Shuji Asai, Kenya Terabe, Mochihito Suzuki, Yoshifumi Ohashi, Kenji Kishimoto, Kyosuke Hattori, Shiro Imagama

Department of Orthopedic Surgery, Nagoya University Hospital

Conflict of interest: None

Drug treatment for rheumatoid arthritis has made great progress. On the other hand, it is often difficult to completely control all arthritis. Residual arthritis causes joint destruction and physical dysfunction. The revised RA clinical Guidelines 2020 proposed a non-drug therapy algorithm. If arthritis remains, it is recommended to appropriately evaluate physical function and to consider surgical therapy together with rehabilitation treatment. Not only the patient's subjective evaluation but also the objective value (physical function measurement value) is important to determine appropriate timing for joint surgery. We have shown that timed up and go test (TUG) is useful for assessing the effectiveness of surgery. 9.0 seconds is a cut-off value corresponding to HAQ remission, and it was also shown that achieving this value by surgery further improves the QOL (EQ-5D). In order to achieve 9.0 seconds after surgery, it is necessary to have 12 seconds before surgery, which is considered as an index of the timing of lower limb surgery. Recently, Japan is a super-aging society, and it is thought that we should aim to extend healthy life expectancy as much as possible in RA treatment. When considering extending healthy life expectancy, evaluations such as frailty and sarcopenia are also important. The walking speed according to the criteria for frail and sarcopenia is 1.0 m/s. We are conducting a prospective cohort study (Fairy study) on flail of RA patients at Nagoya University. The TUG corresponding to a walking speed of 1.0 m/s was estimated to be 11.4 seconds. If joint surgery is performed at this timing, the patient could have good TUG9.0 seconds or less. Joint surgery in RA treatment can be a useful tool for recovery from frailtyand extending healthy life expectancy.

### S19-5

#### **Hip surgery and functional recovery in the patients with rheumatoid arthritis**

Yuya Takakubo<sup>1,2</sup>, Michiaki Takagi<sup>2</sup>

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Conflict of interest: None

The hip joint, along with the knee joint, is considered essential for upright bipedal walking in humans. The hip joint is a ball joint consisting of a bony, mortar-shaped acetabulum and a spherical femoral head, surrounded by strong ligaments. The drug treatment of rheumatoid arthritis (RA) has progressed rapidly since around 2000, and a paradigm shift has also occurred in surgical treatment. In particular, it has been reported that the number of surgeries for RA patients has decreased worldwide, especially for joint arthroplasty. However, even with the current progress in drug therapy, it is difficult to control the progression of joint destruction in large joints, especially in hips with Larsen 2 or greater changes, even with the administration of biologics. Total hip arthroplasty (THA) is the mainstay of surgery for RA-related hip disorders. THA is an arthroplasty that is expected to have the most stable results. Artificial joints are indicated for patients with moderate or more degree of joint destruction because they can be expected to provide reliable pain relief, improved range of motion, and joint stability after surgery. Since the progression of joint destruction significantly affects daily activities even at a young age, some cases are performed regardless of age. Although osteotomy and hip arthroscopy are not commonly used for RA-related hip disorders, their indications may be expanded in the future if changes of the hip joint are similar to those of osteoarthritis due to advances in drug therapy. As the number of elderly RA patients and patients with RA increases and the duration of the disease prolongs, the number of hip disorders accompanied by rheumatic changes with the progression of osteoarthritis is expected to increase.

### S19-6

#### **Foot and ankle surgery for patients with rheumatoid arthritis aiming functional recoveries**

Koichiro Yano

Orthopedic Surgery, Tokyo Women's Medical University

Conflict of interest: None

Foot and ankle surgery for patients with rheumatoid arthritis (RA) has progressed drastically in the recent years. Although deformity corrections in rheumatoid foot and ankle surgeries are widely available, functional recoveries after surgeries are insufficient. The purpose of this presentation was to introduce surgeries for rheumatoid foot and ankle deformities that target functional recoveries. Joint-preserving surgery is a preferred surgery for rheumatoid forefoot deformity over joint-sacrificing surgery. Previous studies have shown that plantar pressure after the surgery becomes similar to that of the normal foot and an improvement in the range of motion (ROM) is achieved by starting ROM exercises of the toes in the early postoperative phase. However, we often find many patients suffering from "stiff-toe", despite performing early ROM exercises. Hence, through our study, we have tried to recover the function of the feet by balancing the extensor and flexor tendons and controlling the amount of bone shortening. Total ankle arthroplasty (TAA), or arthrodesis, is performed for the disorders of the tibiotalar joint in patients with RA. Arthrodesis ensures sufficient pain relief and deformity correction. Since techniques of arthroscopic surgery have progressed recently, minimum invasive arthrodesis is also performed. However, disadvantages of arthrodesis include a loss of ROM and nonunion and disorder of the adjacent joint. Since RA is an inflammatory disease with multiple joint disorders, the risk of its occurrence in adjacent joints is high after arthrodesis. Therefore, TAA should be preferred over arthrodesis for the disorders of the tibiotalar joint in patients with RA. Since RA foot and ankle disorders result in various deformities, severe joint destructions, and skin weakness, it is a difficult pathological condition to ensure functional recovery. Therefore, more studies aiming functional recoveries should be conducted in the future.

### S20-1

#### **The role of the Rare Disease Data Registry of Japan "RADDAR-J" to elucidate the pathology of rare disorders**

Fumihiko Matsuda

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Conflict of interest: Yes

There are more than 10,000 rare diseases globally. The total number of patients with rare disorders is considered 6-8% of the population, although



the number of patients with each disorder is small. In Japan, approximately 300 research groups are responsible for epidemiological studies, establishing diagnostic criteria and guidelines, research on the pathogenesis, and clinical trials of rare diseases. For cross-sectional research on rare diseases aiming to develop new treatments and new drugs, it is essential to consolidate and analyze a variety of high-quality information in an integrated manner. However, each group manages the data separately, and sharing and utilization of accumulated data have been insufficient. To address this critical issue, we set out to establish an integrative rare disease analysis platform, “RADDAR-J”, since FY2016 to accumulate and integrate various information collected by rare disease research groups in a unified manner. We have established collaboration with 58 rare disease research groups to date. Forty of the 58 groups are currently constructing registries using the standard data management system of RADDAR-J, and 27 of these groups have started registering patient information. From FY2021, we have started designing a system that enables long-term stable and autonomous operation. In addition to further increasing the number of collaborating groups to improve the comprehensiveness of information, we promote the following projects to make maximum use of accumulated knowledge in the established integrated analysis infrastructure. 1. Designing a system to provide the data to intractable disease research groups and companies to promote secondary use of the data. 2. Implementation of corporate matching with regulatory compliance, efficiency, and needs assessment to stimulate the development of therapies and drug discovery through secondary use of data 3) Analysis of information on patients with intractable diseases accumulated in the registry and support for the generation of evidence that will contribute to creating and revising treatment guidelines. We expect such research and development will accelerate the study of rare diseases, the development of new treatments and drug discovery, and the realization of high-quality medical care.

## S20-2

### Registry study for IgG4-related disease

Hajime Yoshifuji<sup>1</sup>, Hideki Ishikawa<sup>2</sup>, Seiji Nakamura<sup>3</sup>

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Conflict of interest: None

The Japan Agency for Medical Research and Development (AMED) envisioned an intractable disease platform, which can manage clinical information and samples of patients with intractable diseases, participated by the research group for IgG4-related disease (IgG4-RD). However, some clinicians who specialize in intractable diseases may be worried that “although a new system was invented, it may not be a realistic system, or it may increase the burden on the physicians”. This lecture will explain the features of the platform for IgG4-RD, discussing on both the advantageous and challenging points. The disadvantages of the conventional clinical individual questionnaire were the lack of data on patients with mild disease who were not covered by medical expenses subsidies, and the lack of death information because it only targeted live patients. The platform for IgG4-RD covered definite, probable, and possible patients of IgG4-RD, and enabled the utilization of personal information (e.g. name and address) and the annual follow-up surveillances. Furthermore, we established a linked system connected to the pre-existing omics/genetic researches. Before the intractable disease platforms were started, we conducted a hand-made epidemiological surveillance for IgG4-RD, supported by AMED. It was possible to use case report form with the minimal necessary items, to input data by the experts of IgG4-RD, and to add items as a feedback after the discussion on the interim results. In fact, an important result was obtained by the added items. The challenging points of the platform for IgG4-RD were a burden of data input, a variation of case collection rates between the facilities, and the fact that the interpretation of the input items varied depending on the inputters. As countermeasures to these challenging points, we defined mandatory entry items, sent frequent newsletters, and created an entry guidance brochure.

## S20-3

### Registry research of the research group on autoimmune diseases

Masaaki Mori<sup>1,2</sup>, Takahiko Sugihara<sup>2</sup>

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Conflict of interest: Yes

The research group on autoimmune diseases of the Ministry of Health, Labor and Welfare is currently working on systemic lupus erythematosus, primary antiphospholipid antibody syndrome, dermatomyositis/polymyositis, mixed connective tissue disease, Sjögren's syndrome, adult still disease, and juvenile idiopathic arthritis are treated as target diseases. 7 diseases are treated as target diseases and are in charge of 5 subcommittees. All of them are rare diseases, but due to the difference in frequency and the diversity peculiar to the disease, it has not been possible to construct a disease registry mainly by the research group. However, due to the recent trend that the intractable disease platform system has become common for all other intractable diseases, the research group has become more motivated to build a disease registry with an eye on the future. Preparations will begin in the second half of 2019, and a draft of the EDC will be prepared from April 2020. As a common purpose for each disease, the goal is long-term observation for 10 years or more, focusing on long-term prognosis. In addition, an intractable disease platform group has been organized within the research secretariat, and two or more members have been selected from each subcommittee to study the content of basic and clinical research along with the derivation method, centered on collaboration with AMED research. In addition, an intractable disease platform group has been organized within the research secretariat, and two or more members have been selected from each subcommittee to study the content of basic and clinical research along with the derivation method, centered on collaboration with AMED research. Registration has actually started in February of this year, and as of December 6, 2021, 69 has been registered. So, we are looking for smooth promotion by taking sufficient measures from now on.

## S20-4

### Registry study of autoinflammatory syndromes in Japan

Ryuta Nishikomori

Department of Pediatrics and Child Health, Kurume University School of Medicine

Conflict of interest: Yes

Autoinflammatory syndromes are hereditary diseases in which inflammation is the main pathology. Among hereditary autoinflammatory syndromes, familial Mediterranean fever, which is the most frequent in Japan, has a prevalence of 1 in 100,000, and other autoinflammatory syndromes are extremely rare, with a prevalence of approximately 0.01 ~ 0.1 in 100,000. In some autoinflammatory syndromes, identification of the causative genes, their elucidation of the pathogenesis, and drug discovery based on the pathogenesis have been achieved, and early diagnosis can prevent complications of organ damage and improve patient QOLs. Since the clinical findings are similar to those of rheumatic diseases, rheumatic disease specialists are positioned at the front line in the treatment of these diseases. Since it is a rare and intractable disease, it is difficult for a clinician to experience all the diseases. Therefore, it is important to accumulate the autoinflammatory syndrome cases nationwide in Japan to investigate their actual clinical features. Because it is also a hereditary disease, it requires lifelong administration of therapeutic drugs unless curative treatments such as hematopoietic cell transplantation have been developed. In addition, due to the unique nature of the therapeutic agents and the fact that they have not been developed for a long time, long-term prospective follow-up is essential to collect the reports of the side effects and the secondary failure. In order to improve the clinical practice and the QOLs of patients with autoinflammatory syndromes, the autoinflammatory syndrome guideline group funded by the Ministry of Health, Labor and Welfare (MHLW) has been working on a patient registry and is currently constructing a common registry system for primary immunodeficiency diseases and early-onset inflammatory bowel diseases in the Rare Disease Data Registry of Japan. In this symposium, I will talk regarding the con-



struction of a medical system for autoinflammatory syndromes and a nationwide survey of their patients, as well as the issues and problems in the ongoing registry study of the Rare Disease Data Registry of Japan. I hope that this talk will lead to the promotion of intractable disease registry research in Japan, and to the improvement of patient care and patient QOLs.

## S20-5

### Registry study of Castleman's disease and TAFRO syndrome in Japan

Atsushi Kawakami<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Remi Sumiyoshi<sup>1</sup>, Toshimasa Shimizu<sup>1</sup>, Naoki Hosogaya<sup>1</sup>, Shinpei Morimoto<sup>1</sup>, Yasufumi Masaki<sup>2</sup>, Shingo Yano<sup>3</sup>, Takayuki Shimizu<sup>4</sup>, Kazuyuki Yoshizaki<sup>5</sup>, Masao Mizuki<sup>6</sup>, Naoya Nakamura<sup>7</sup>, Yasuhiro Sato<sup>8</sup>, Hiroaki Niino<sup>9</sup>

<sup>1</sup>Nagasaki University, <sup>2</sup>Kanazawa Medical University, <sup>3</sup>The Jikei University School of Medicine, <sup>4</sup>Keio University, <sup>5</sup>Osaka University, <sup>6</sup>Osaka University Hospital, <sup>7</sup>Tokai University, <sup>8</sup>Okayama University, <sup>9</sup>Kyusyu University

Conflict of interest: None

Castleman disease (CD) is classified into a unicentric CD (UCD) in which lymph node lesions are localized and a multicentric CD (MCD) in which the lymph node lesions are multicentric. The disease type that requires immunoregulatory therapy is MCD. Most of MCD patients in Japan are negative with herpesvirus type 8 (HHV-8) infection and considered as the idiopathic MCD (idiopathic MCD: iMCD). Number of iMCD patients across Japan is reported about 1,500. In case of iMCD, a rare intractable inflammatory disease characterized by the presence of multiple lymph node swelling with an elevation of inflammatory response, the diagnosis is made by combining clinical findings and lymph node pathology, however, clinical findings of iMCD are further classified into 2 types as either the presence of TAFRO signs (Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis or Renal dysfunction, Organomegaly; defined as iMCD-TAFRO) or absence of TAFRO signs (defined as iMCD-NOS, not otherwise specified). In addition, lymph node pathology of iMCD are classified into 4 types. These observations strongly suggest the heterogeneity of iMCD to a large extent. Additionally, TAFRO syndrome, a number of the patients across Japan is reported about 400, is another newly identified rare inflammatory disorder of unknown etiology characterized by TAFRO signs resembling with iMCD, however, lymphadenopathy of TAFRO syndrome is usually mild and not diagnosed as iMCD by the current diagnostic criteria, the difference of TAFRO syndrome from iMCD being debating. Due to the necessity for immunoregulatory therapy, analysis for iMCD and TAFRO syndrome is often the main focus among CD, but, since iMCD-NOS, iMCD-TAFRO and TAFRO syndrome are rare and intractable inflammatory diseases containing the heterogeneity, it is crucial to build an integrated registry and repository system across Japan which able to accumulate a large number of certified cases for the evaluation as well as formulation of diagnostic criteria and severity classification index. These activities must be essential for the development of international consensus. In this symposium, we are going to introduce the current knowledge of iMCD and TAFRO syndrome obtained from the present registry as well as the ongoing registry research and future plans and prospects.

## S20-6

### Progress of the nationwide registry study of Behcet's disease

Yohei Kirino

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Conflict of interest: Yes

Behcet's disease is a heterogeneous disease that causes inflammation in various organs such as eyes, skin, joints, nerves, and intestinal tract. In rheumatoid arthritis, treat-to-target (T2T) has significantly improved joint prognosis. On the other hand, T2T has not yet been developed for Behcet's disease, and the development of disease activity measures and treatment targets is urgently needed. To solve these problems, the Behcet's disease registry led by Yokohama City University was started in 2018, and about 300 patients have been registered and followed up so far. In this database, patients' disease activity indices (e.g., BDCAF), medication status, genomic data, cytokines, and prognosis are tracked in detail on a yearly basis. In 2020, the National Behcet's Disease Registry Study was accepted as

an AMED project, and an electronic questionnaire based on RADDAR-J was developed. We have developed an electronic questionnaire that complies with RADDAR-J. Case registration has already started, and if detailed nationwide patient information is collected and followed, it is expected that (1) subtype analysis, (2) poor prognostic factors, (3) disease activity index, (4) pathogenesis, etc. will be clarified, and (5) treatment targets can be set. In addition, it will be possible to develop activity indices for each organ, such as special disease types and eye lesions. In this presentation, I would like to discuss the advantages and challenges of registry studies through the preliminary data of the registry studies that we are currently conducting.

## S20-7

### Towards the establishment of integrated registries in connective tissue disease-associated interstitial lung disease

Takahisa Gono<sup>1,2</sup>, Masataka Kuwana<sup>1,2</sup>

<sup>1</sup>Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, <sup>2</sup>Scleroderma/Myositis Center of Excellence, Nippon Medical School Hospital

Conflict of interest: Yes

Interstitial lung disease (ILD) is one of the leading causes of mortality in patients with connective tissue disease (CTD). Thus, appropriate management of ILD is required to improve prognosis in patients with CTD. However, there are various management issues regarding CTD-associated ILD (CTD-ILD). For instance, clinical course, treatment response and prognosis are highly variable among patients with CTD-ILD. In addition, it remains unknown how to predict prognosis more accurately and how to assess the status of ILD more appropriately to improve, prevent or slow the deterioration of ILD. On the other hand, the approach to patients with CTD-ILD is different between rheumatologists and respirologists: procedures and timing of evaluating the status of ILD, and treatment regimen on the management of patients with CTD-ILD. To solve those issues, "2020 guide for the diagnosis and treatment of interstitial lung disease associated with connective tissue disease" has been published by the joint committee of Japanese Respiratory Society and Japan College of Rheumatology in April 2020. This guideline provides each perspective from rheumatologists and respirologists on the procedure of the management of CTD-ILD patients and suggests comprehensive treatment targets according to the disease behaviors in CTD-ILD. However, we have realized several problems to be solved in this field: accumulating evidence on treatment, establishment of CTD-ILD assessment tools including patient-reported outcomes, and development of artificial intelligence system for predicting progression of ILD as well as prognosis. Nowadays, multi-disciplinary discussion (MDD) comprised of respirologists, radiologists and pathologists has been introduced in the diagnosis of ILD. There have been a few ILD registries involved in MDD across Japan. In this symposium, we will introduce our CTD-ILD registry and future perspectives to achieve seamless care with close cooperation between rheumatologists and respirologists.

## S21-1

### Epidemiological study designs and statistical analysis for pharmacoepidemiology

Hisashi Noma

The Institute of Statistical Mathematics

Conflict of interest: None

Pharmacoepidemiology is defined as "the study of the utilization and effects of drugs in large numbers of people". Also, pharmacoepidemiology can be considered as the application of epidemiological methods to pharmacological issues, particularly for safety issues. Some examples of pharmacoepidemiological studies involve descriptive studies for investigating usages of drugs, comparative studies to assess safety issues of drugs, and analytical studies to evaluate the effects of political actions by pharmaceutical administrations. One of the distinguishing characteristics for pharmacoepidemiology is that the main purpose is assessments of "safety" of drugs and the incidence rates of many target events are rare (e.g., less than 0.1%). In addition, these studies involve various patients with broad backgrounds compared with pre-marketing clinical trials. Thus, these studies

require large populations to conduct statistical evaluations with sufficient precisions, and database studies using secondary data have been conventionally adopted. In addition, due to the advances of information technology, real world data studies have also been adopted in recent studies, and the resultant evidence is considered to be used for pharmaceutical regulations. In this talk, I will provide gentle introductions for the methods of pharmacoepidemiology through concrete examples. Especially, I will review the epidemiologic study designs and statistical methods for these studies.

## S21-2

### Pharmacoepidemiology studies using databases

Kiyoshi Kubota

NPO Drug Safety Research Unit Japan, Tokyo, Japan

Conflict of interest: None

I. Usefulness of database studies Database studies can provide the information which the society needs in a timely fashion with a sufficient accuracy. I will introduce several database studies on the effectiveness and safety of Covid-19 vaccination published in 2021 from Western countries. Then, I introduce several database studies so far conducted in Japan. [1] Epidemiology diseases: Database studies of psoriasis and rheumatoid arthritis using national database (NDB) in Japan will be mentioned. [2] Drug utilization studies: Annual trend of uses of oral anticoagulant in patients with atrial fibrillation, and annual trend of uses of new antidiabetics and drugs for attention-deficit hyperactivity disorder will be mentioned. [3] Signal detection on the safety of drugs: Database studies to alert possible association between proton pump inhibitors and clostridium difficile infection will be mentioned. [4] Studies of the association of a drug and outcomes: A database study conducted in Japan on the association between drugs for dyslipidemia and diabetes onset, and a database study on the association between non-steroidal anti-inflammatory drugs and gastro-intestinal events will be mentioned. [5] Studies on the risk minimization strategies: Database studies to examine the risk minimization strategies to reduce cardiac regurgitation caused by anti-Parkinsonian drugs (ergot derivatives) will be mentioned. II. Improvement of reliability of database studies and related problems. Validation studies on claims-based definitions of “death”, acute myocardial infarction, and rheumatoid arthritis conducted in Japan will be mentioned. I will also mention the difficulty of record-linkage at the individual level between different data sources in Japan and relevant problems. Lastly, I will mention the need of exchange of the knowledge on handling of large data in database studies and fostering professional programmers in the future Japan.

## S21-3

### For obtaining research funding = From the perspective of research review

Takeo Asano

Department of Planning and Development, Japan Agency for Medical Research and Development

Conflict of interest: Yes

On April 1, 2020, AMED's Second Medium- to Long-Term Plan was launched. During the second plan period, we will further advance and consolidate the results we achieved during the five years of the first plan, as we seek to forge a smoother path toward a strong structure and operations. Under the Second Medium- to Long-Term Plan we will be deploying new medical technologies and techniques effectively across the full range of diseases, organizing our programs into integrated projects that are not limited to certain disease areas, but are instead focused on six modalities: drugs; medical devices and healthcare; regenerative, cellular, and gene therapies; genome data infrastructure; basic disease research; and seeds development and research infrastructure. These six integrated projects will provide the framework for promoting R&D relating to fields of disease that constitute social issues for Japan now or in the future (including cancer, lifestyle diseases, psychiatric and neurological disorders, diseases of old age and dementia, rare/intractable diseases, child development disorders, and infectious diseases). The review process for research support will proceed as follows. Grant applications will be evaluated in the following steps For each application submitted, an international panel of reviewers

will peer-review the grant application documents. At this stage, we expect a wide range of perspectives from the reviewers, which cannot be obtained only from Japanese reviewers. Then, at the final evaluation stage, an evaluation committee of AMED experts will review the documents and determine the provisional awardees. The evaluation committee will then interview the applicants directly to better understand their ideas and plans and decide whether to accept their proposals. In the lecture, we will also introduce the points to be considered when the proposal is reviewed.

## S21-4

### Investigator initiated trial

Yuko Kaneko

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: Yes

Clinical trials are an experimental clinical research on human participants, which are designed to evaluate the efficacy and safety of biomedical or interventions including new treatments for the approval by the authority. In Japan, after the 2003 amendment to the Japanese Pharmaceutical Affairs Law, pharmaceutical and medical device manufacturers could provide investigational products to clinician investigators to conduct a clinical trial under a Clinical Trial Notification, which is called investigator-initiated clinical trials sponsored and conducted by independent investigators. In these investigator-initiated clinical trials, the sponsor-investigator is responsible for designing the study and preparing the protocol as well as submitting the notification to the Pharmaceutical and Medical Devices Agency, the Japanese authority. While investigators face lots of hardships in conducting clinical trials as there are many unfamiliar tasks and regulations, investigator-initiated clinical trials are worthwhile and fulfilling as the aim of trials is to get the approval for drugs which we physicians are always eager to use in clinical practice. In this speech, I will talk about investigator-initiated clinical trials based on the experience of the trial of tocilizumab for adult-onset Still's disease which have been approved in Japan.

## Special Symposium

### SS1-1

#### Enhancing the career support system and the future

Sumiko Nagoshi

Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

Conflict of interest: None

According to the survey conducted by the Japanese Medical Science Federation in 2018, 63% of the 48 medical societies have committees to promote gender equality. There were also activities such as organizing symposia and leadership training workshops at the annual meeting, setting up a consultation desk and booths, holding science cafes for junior and senior high school students, and an award system for female researchers. There were also some attempts to increase the number of female board members, but it was reported that when they tried to nominate women as councilors or chairpersons, they were often turned down for reasons such as not being able to afford to take time off from hospital work to attend conferences and meetings due to the shortage of doctors in the workplace. The percentage of women among the 106 medical societies was 23%, compared to 10% for councilor delegates, 8% for directors, 13% for general abstract chairpersons and 8% for symposium chairpersons. There are still few women in leadership positions and decision-making positions. In recent years, support for childcare, shorter working hours, and a team doctor system have been developed for female doctors to continue their work, but there are still cases where they cannot get out of the “mommy track” and start their careers. If there is a supervisor who thinks, “I don’t want to encourage you to present at conferences because you seem to be having a hard time with childcare”, this is an “unconscious bias”. It is important for managers and supervisors to proactively provide opportunities for career development while confirming the intentions of the individual, and to fairly evaluate the results, which will help maintain the motivation of female doctors. Female doctors themselves need to free themselves from unconventional ways of thinking, and develop their careers and contribute to medicine and healthcare.

### SS2-1

#### When normal isn’t normal: understanding the skin in systemic lupus

J. Michelle Kahlenberg

Department of Internal Medicine, Rheumatology, University of Michigan, Ann Arbor, Michigan, USA

Conflict of interest: Yes

Systemic Lupus Erythematosus (SLE) is a heterogeneous disease affecting different organs in different patients. However, up to 93% of patients have some manifestation involving the skin, including rashes and sensitivity to ultraviolet (UV) light. Intriguingly, investigations of non-lesional skin of SLE patients have identified a propensity for skewed type I IFN production by keratinocytes which contributes to inflammatory responses as well as photosensitivity. In addition, methylation differences in SLE vs. healthy control keratinocytes point to a role for Hippo pathway activation in SLE keratinocytes that also contributes to a propensity for cell death. Additional investigation of non-lesional and lesional SLE skin through single-cell RNA-sequencing has identified that lesional and non-lesional SLE skin exhibits dramatic shifts in cell-cell crosstalk; CD16+ DCs were highly enriched in non-lesional skin and in cutaneous lupus lesions relative to control and were among the most active communicators as expressors of both ligands and receptors. Spatial transcriptomics demonstrated CD16+ DCs localizing most prominently in the superficial interfollicular dermis, enabling interaction with KCs and fibroblasts. Pseudotime analysis of paired circulating and skin myeloid cells revealed CD16+ DCs may arise from non-classical monocytes, with discrete shifts in myeloid cell transcriptional states, including a robust IFN education in the skin, detectable across this transition. Thus, non-lesional skin of patients with SLE exists in a type I IFN-rich, “prelesional” state. This affects gene transcription in all major skin cell types and dramatically alters cell-cell communication. Non-classical monocytes may infiltrate this environment to become CD16+ DCs that engage in crosstalk with diverse cell types as one of the earliest steps in the evolution of skin lesions.

### SS2-2

#### Somatic Mutations in Rheumatologic Diseases: VEXAS Syndrome and Beyond

Peter Grayson

National Institutes of Health, USA

Conflict of interest: None

The recent discovery of the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome proves that somatic mutations can cause monogenic inflammatory syndromes exclusively restricted to adulthood. In contrast to germline mutations, alterations in DNA that occur after the first zygotic division are referred to as somatic mutations. Somatic mutations occur throughout the lifespan, from early embryogenesis through adulthood. While somatic mutations have a well-established causal role in cancer, the role of somatic mutations in rheumatologic disease is less clear. To date, most genetic studies in rheumatologic diseases have focused upon the effect of germline variants or common disease risk-conferring single nucleotide polymorphisms. Understanding the relationships between cell-specific acquired mutations and inflammation is likely to yield key insights into causal factors that underlie many rheumatologic diseases. The objective of this talk is to detail how somatic mutations are likely to be relevant in many different rheumatologic diseases, with particular focus on the VEXAS syndrome. Identification of somatic mutations and monitoring clonal burden over time has potential to define new disease syndromes and novel biomarkers of disease activity, inform understanding of pathophysiology and disease prognosis, and unlock novel therapeutic approaches.

### SS3-1

#### Innovative Imaging in RA

Annamaria Iagnocco

Università degli Studi di Torino, Turin, Italy

Conflict of interest: None

During the lecture “Innovative Imaging in RA” the potential of advanced imaging for the objective assessment of the inflammatory process leading to structural lesions in rheumatoid arthritis (RA) will be discussed. The potential of imaging in advancing the field will be emphasized and new areas of research in the development in RA will be explored. Future treatments for RA may benefit from the application of enhanced imaging techniques which may also facilitate enhanced stratification and phenotyping of patients enrolled in new research studies. Early diagnosis and efficient assessment of the response to T2T treatment is critical for timely therapeutic intervention in RA. However, they lack effective diagnostic methods capable of detecting disease progression in its early stage and evaluating treatment efficacy in clinics. New imaging techniques that can detect in the early stage of disease and continuously monitor its progression will be presented and discussed.

### SS3-2

#### Innovative Imaging in PsA

Xenofon Baraliakos

Rheumazentrum Ruhrgebiet Herne / Ruhr-University Bochum, Germany

Conflict of interest: Yes

Modern imaging is important for the diagnosis, prognosis but also monitoring of psoriatic arthritis (PsA). Beyond peripheral imaging, detection of pathologies such as osteitis in the axial skeleton but also other technical advances like the understanding of the value of whole body magnetic resonance imaging (MRI) show the value of these developments. In addition to MRI, ultrasound is still one of the gold standards in imaging of patients with PsA and provides a clinic-based tool for evaluating both joint pathologies and extra-articular structures (especially enthesitis) including skin and nail disease. Recent studies have demonstrated subclinical disease in psoriasis without arthritis, as well as in PsA, with implications for diagnosis and treatment classification. Modern imaging can also facilitate decisions on tapering of expensive biologics, though real-world clinical studies are still lacking. The increase in novel PsA therapies should increase the utilization of modern imaging, providing both increased valida-

tion of imaging biomarkers as well as responsive outcome measures.

### **SS3-3**

#### **Precision medicine in RA**

Daniel Aletaha

Division of Rheumatology, Medical University Vienna, Austria

### **SS3-4**

#### **Precision Medicine in Psoriatic Arthritis**

Iain B McInnes

University of Glasgow, Glasgow, UK

Conflict of interest: None

Psoriatic arthritis is clinically heterogeneous both in terms of tissues involved ranging from synovium, entheses skin to include occasionally eye and gastrointestinal involvement. Moreover the long term prognosis is variable and as yet we are poorly able to predict this critical element of natural history. In the last decade a range of new therapeutics across varied modes of action have become available to us in the PsA field which has brought great benefits in terms of outcomes, but now raises the pivotal question namely - which is the appropriate MOA for a given patient at a particular time point in their disease? I shall summarise the key existing data and the potential technical possibilities looking to the future that will enable the precision medicine field to impact on PsA management.

## **Educational Lecture**

### **EL1**

#### **Patient-reported outcome in rheumatic diseases**

Yuko Kaneko

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: Yes

Patient-reported outcomes are symptom assessment which patients observe and provide with the patient's perspective on their well-being. Disease activity and health status of patients have been evaluated mainly with findings of blood tests, imaging, and physician assessment as they were considered objective and reliable. However, in recent years, there has been increasing emphasis to integrate outcomes that reflect symptoms and life impact of diseases of most relevance to patients as endpoints in clinical trials and as part of standard clinical assessments in practice. Patient-reported outcomes are outcomes assessed directly from the patient without interpretation from the physician, which are frequently discrepant from physicians' assessment. In the management of rheumatic diseases, understanding and making the best use of patient-reported outcomes are essential because main symptoms of rheumatic diseases such as pain and fatigue cannot be assessed with objective methods. In this session, I am going to talk about the importance and optimal use of patient-reported outcomes in rheumatic diseases.

### **EL2**

#### **Recent perspectives on mixed connective tissue disease (MCTD)**

Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan

Conflict of interest: Yes

In 1972, Sharp et al. proposed mixed connective tissue disease (MCTD) as a disease entity characterized by overlapping clinical features of systemic lupus erythematosus (SLE), systemic sclerosis, and polymyositis, as well as high titers of serum anti-U1-RNP antibody. In 2017, the MCTD Subcommittee of the Japan Research Committee of the MHLW for systemic autoimmune diseases, established the 2019 diagnostic criteria for MCTD. The criteria were assessed in an independent validation cohort and tested against preexisting criteria. The revised criteria facilitate an understanding of the overall picture of this disease by describing the concept of MCTD, common manifestations, immunological manifestation and characteristic organ involvement. Conditions with characteristic organ involvement include pulmonary arterial hypertension, aseptic meningitis and trigeminal neuropathy. Even if the overlapping manifestations are absent, MCTD can be diagnosed based on the presence of the characteristic organ involvement. Based on the criteria, the MCTD subcommittee also published the guideline for clinical management of MCTD, 2020, will aid the physician in easy and adequate decision-making for initiation of intervention to prevent organ damages.

### **EL3**

#### **What rheumatologists need to know about neurological examinations and neurological complications**

Takayoshi Shimohata

Department of Neurology, Gifu University Graduate School of Medicine

Conflict of interest: None

In the first half of the lecture, I would like to present a neurological examination that rheumatologists should know about syndromes caused by rheumatoid arthritis (RA) and neurological syndromes that are easily mistaken for RA. The first symptom that can easily be mistaken for RA is hand and foot deformities associated with parkinsonism (so-called striatal hand and foot). These deformities are caused by dystonia of extremities. These deformities are seen in the advanced stages of Parkinson's disease, as well as multiple system atrophy and corticobasal syndrome. I have experienced several patients in which these patients were misdiagnosed as having seronegative RA and treated with anti-rheumatic drugs. The rheu-



matologist should also be aware of neurological symptoms other than limb deformities, such as rigidity, involuntary movements, and characteristic gait disturbances. In addition, these parkinsonian patients may present with camptocormia, drop head syndrome, and Pisa syndrome as truncal dystonia. It is important not to misdiagnose this truncal dystonia as a spinal disease. The thalamic hand, which appears after a stroke in the thalamus, may also need to be differentiated from RA. In the second half of the lecture, I would like to present neurological complications of RA, such as cerebrospinal fluid leak syndrome and cervicogenic headache associated with atlantoaxial subluxation. Cervicogenic headache is a disease that presents with characteristic headaches, but it may be overlooked. In addition, I would like to show rheumatoid meningitis, peripheral neuropathy such as mononeuritis multiplex, and entrapment neuropathy, and methotrexate-associated lymphoproliferative disease.

## EL4

### Statistical Data Analysis for Observational Study

Ayumi Shintani

Osaka Metropolitan University, Graduate School of Medicine, Faculty of Medicine, Department of Medical Statistics

Conflict of interest: Yes

In clinical research using real-world data, due to lack of randomization, patients with treatment is tended to select according to their clinical backgrounds. As a result, the characteristics of patients in the treatment and control groups differ, making direct comparison of outcomes difficult. If this difference is ignored in the analysis, it often leads to unexpected results such as no effect of the drug or as if it is harmful, since treated patients often has a worse disease state than those without the treatment. A bias caused by this background difference between the comparison groups is called “confounding” and is a problem in the analysis of many real-world data. In order to prevent confounding, it is necessary to adjust for background discrepancies in multivariate analysis or to extract cohorts with similar backgrounds in advance using propensity scores. In cohort studies to determine whether or not a particular drug reduces the risk of death, there is a problem of “immortal time bias”, in which the treatment effect is erroneously added to the drug group when the analysis is grouped according to whether or not a particular drug was used at least once during the follow-up period when the outcome is observed. To prevent immortal time bias, the start time of treatment initiated during the follow-up period must be collected as data and considered in the analysis. It is important to correctly adjust for immortality bias using the propensity score point-wise matching method, time-dependent Cox proportional regression model, and other methods. In this presentation, I will explain the biases that are likely to occur in observational studies and the analysis methods that should be used in an easy-to-understand manner without using mathematical formulas.

## EL5

### Basic knowledge of rheumatoid foot

Tetsuro Yasui

Orthopaedic Surgery, Teikyo University Mizonokuchi Hospital

Conflict of interest: Yes

With the progress of drug treatment for rheumatoid arthritis, total number of orthopaedic surgeries for rheumatoid arthritis is on the decline, but the number of surgeries in foot and ankle region has not decreased. This does not mean that the drug does not work on the foot and ankle, but reflects the growing need for treatment of the foot and ankle and advances in surgical treatment. It can be said that a rheumatologist needs to have a basic background in foot and ankle disorders of rheumatoid arthritis. Clinical practice begins with assessing joint swelling and deformity. Deformation causes painful callus and skin ulcers. There are various types of deformations, but there are some typical deformation patterns such as the triangular foot. As a treatment, typical conservative treatments include insoles and orthopaedic shoes. Various methods have been proposed for surgery, but the common concept of surgery is achievement of deformity correction. By correcting the deformity by surgery, the patients can enjoy reduced pain, improved gait, and freedom of choosing shoes. The other option of surgery is total joint replacement of the ankle.

## EL6

### Conflict between Medical Ethics and the Law ~ A Case Study of a Transplantation Outside Japan through a Non-Profit Organization~

Giichiro Oiso

Hamamatsu University School of Medicine

Conflict of interest: None

This presentation will examine the relationship between medical ethics and the law using a case of transplantation outside Japan that the speaker experienced. X (male) was an outpatient at Hospital A for renal insufficiency. His doctor told him “the number of donor kidneys in our country is very small, and the possibility of transplantation is low even if he registers at a kidney bank”. After much deliberation, X heard about NPO B, which coordinates transplant operations in China, and decided to travel to China for the transplant. On the 39th day after the visit to the local hospital C, a 33-year-old female donor was found, and the transplant operation was performed on the same day, and the patient returned Japan. He visited the Y Hospital outpatient clinic for regular follow-up after the transplant. However, because the referral form X brought with him contained only five lines of bullet points on the clinical progress and no description of the surgery, Y Hospital judged that the medical treatment was suspected of unethical and refused to continue the treatment. X filed a claim for damages against Y Hospital for a breach of Article 19, Paragraph 1 of the Medical Practitioners Act (physician’s duty to provide medical treatment). Article 19, paragraph 1 of the Medical Practitioners Act states that “A physician engaged in medical treatment shall not refuse a request for medical examination or treatment without a justifiable reason”. If there is a “justifiable reason”, the doctor may refuse to treat the patient. In light of the current international situation growing problems of organ sales, transplant tourism in the context of the global shortage of organs, The Transplantation Society states “Organ trafficking and transplant tourism violate the principles of equity, justice and respect for human dignity and should be prohibited. Because transplant commercialism targets impoverished and otherwise vulnerable donors, it leads inexorably to inequity and injustice and should be prohibited” in The Declaration of Istanbul on Organ Trafficking and Transplant Tourism. In this lawsuit, the hospital argued that refusing to provide medical treatment in a breach of the Istanbul Declaration constituted “justifiable cause”, while the plaintiff argued that the Istanbul Declaration was not legally binding and that it was illegal because it was a breach of the duty to provide medical treatment. This case was headed for the Supreme Court, but the hospital won the case completely. Through this case, I will explain the relationship between medical ethics and law.

## EL7

### Transforming clinical trials in rheumatology: towards patient-centric precision medicine

Costantino Pitzalis

Queen Mary University of London, UK

Conflict of interest: Yes

Despite the enormous success of targeted therapies in the treatment of rheumatoid arthritis (RA), the lack of predictive biomarkers maintains current practice of ‘trial and error’ treatment allocation leading to variable and/or inadequate responses. In-depth characterization of the synovial tissue, easily obtainable through a safe, rapid and well tolerated ultrasound-guided biopsy technique, is bringing new insights into the diverse cellular and molecular features of this disease and their potential links with different clinical and treatment-response phenotypes. Such progress raises the tantalising prospect of improving response rates by matching the use of specific agents to the cognate target pathways that might drive particular disease subtypes in specific patient groups. For example, we recently demonstrated (Lancet 2021) that in patients with low/absent B-cell lineage expression signature (the target for rituximab) tocilizumab was superior to rituximab in the number of patients reaching low disease activity, major treatment response CDAI-MTR with only 12% reaching CDAI-MTR in the rituximab group vs four times as many 50% in the tocilizumab group. Thus, innovative patient-centric approaches are needed such as umbrella, basket and adaptive design to include molecular pathology in the clinical trials and transform the current unsustainable conventional developmental and regulatory approval pipeline. Such innovative approaches would, for example, enable testing the efficacy of an investigational new drug (IND)

in multiple disease indications in a single trial. This would require the recruitment of less patients and save costs (ethically and financially beneficial) and, most importantly, enriching for likelihood of patients response. Whilst the first step are being taken in this direction, it could not be emphasised more that this field is still in its infancy and there are a number of potential barriers to realising the premise of patient-centric precision trials.

## EL8

### Practical treatment strategy of interstitial lung disease associated with connective tissue disease

Masataka Kuwana

Department of Allergy and Rheumatology, Nippon Medical School

Conflict of interest: Yes

The prognosis of patients with connective tissue disease (CTD) has much improved nowadays, but interstitial lung disease (ILD) still remains as an intractable condition. In fact, ILD is the leading cause of mortality in idiopathic inflammatory myopathies and systemic sclerosis. The extreme diversity of clinical course, treatment response, and outcomes makes the management of CTD-ILD difficult. Some cases do not experience progression of ILD for a long time even without treatment, while others develop respiratory insufficiency within a few weeks. Currently, treatment decision is often made by expertise of physicians, based on clinical course, underlying CTDs, biomarkers such as autoantibodies, histopathological findings and high-resolution CT patterns. A series of disease behaviors of CTD-ILD have been proposed in a recently published guidelines, but proposal of a prognostic prediction algorithm is a future task. In chronic ILD, it is important to detect and treat progressive fibrosing ILD (PF-ILD), which leads to restrictive ventilatory impairment and resultant respiratory insufficiency due to progression of fibrosis in the lung parenchyma, early in the course of the disease. Finally, immunosuppressive regimens with corticosteroids and/or immunosuppressants have been a mainstay of the treatment of CTD-ILD, but in recent years, efficacy of molecular-targeted drugs targeting cytokines such as IL-6, T cells and B cells has been reported. On the other hand, the effect of antifibrotic agents such as nintedanib on PF-ILD is shown in patients with CTD-ILD. However, there are still many issues to be solved, such as in what cases, at what timing, when to use them properly or in combination, and long-term efficacy and safety profiles. This lecture features practical treatment strategy of CTD-ILD based on actual case series.

## EL9

### Infection control and prevention - What we learned from COVID-19

Naoki Hasegawa

Department of Infectious Diseases, Keio University School of Medicine

Conflict of interest: Yes

The emerging respiratory infectious disease, COVID-19 due to SARS-CoV-2 overwhelmed the world and became to pandemic instantly. COVID-19 intensively triggered attention from every aspect to control the disease expansion and an opportunity to discuss. It reminds us of the true meaning of standard precaution again, the most fundamental measure and concept in infection control. It is not after when pathogen is detected that the measure is taken, but anytime whenever you are involved in medical service. And the donning and doffing appropriate personal protective equipment in a proper manner is stressed. The correct understanding the relation between the infection rate, the incubation period, the infectibility and prevention in combination with the development of new diagnostic strategies. And it also should be noted that application of new diagnostic device must be based on prevalence of the disease determining pre-test probability, in addition to sensitivity and specificity. Positive predictive values and negative predictive values are important parameters to be considered. There have been many topics on infection control, such as airborne infection and aerosol mediated infection, eye guard, surgical smoke, physical distancing, three Cs, universal masking, reuse of a mask, thick contact and existence of virus in saliva, how to catch infectibility and its duration, the basic reproduction index, no touch disinfection (hydrogen peroxide fumigation and ultraviolet rays), three Cs, ventilation, CO<sub>2</sub> indicator, vaccine development, mRNA vaccine, herd immunity and variant virus. We learned various useful things through each topic to promote and

improve infection control and prevention. As basic strategy for infection control measure is an interruption in route of infection. It's indispensable to provide any medical practice to acquire an appropriate infection control measure, particularly hand hygiene in the correct manner at any moment as required.

## EL10

### Rheumatoid arthritis (RA) and Lymphoproliferative disorders (LPD)

Yasuo Suzuki

Division of Rheumatology, Tokai University School of Medicine

Conflict of interest: Yes

It has been known that RA patients have an increased risk of developing lymphoma since the 1980's. The link to immunosuppressive drugs raises concern for the development of lymphoma since the cases of reversible lymphoma by withdrawal of MTX were reported. A category of other iatrogenic immunodeficiency-associated LPD (OIIA-LPD) was described in the 4th edition of the WHO classification. Because the reports of OIIA in RA tend to increase in Japan, a clinical guide for the diagnosis and management of RA-related LPD by the joint working group composed of the member of JCR, Japanese Society of Hematology and the Japanese Society of Pathology is going to be published in 2022. The standardized incidence ratio of lymphoma varies from 3.43 to 8.21 in the Japanese RA registries and the standardized incidence rate is reported similar to the reports from oversea. Although the precise mechanisms of LPDs in RA are still unclear, aging or immunosenescence, chronic inflammation and immunodysfunction due to RA, iatrogenic immunodeficiency, and reactivation of EB virus have been cited as possible risk factors. OIIA occurs frequently in elderly RA patients with long-term MTX therapy and clinical features include frequent extra-nodular involvement such as lung, oropharyngeal mucosa, skin, and 40 to 70% of patients showed complete or partial regression after MTX withdrawal. Pathologically, OIIA includes reactive lesions and polymorphic LPDs as well as monomorphic lymphoma. Diffuse large B-cell lymphoma (DLBCL) is most frequent histological type, occupied about 40-50%. EBV-positivity was reported ranging from 45 to 55%. A recent multicenter study showed that relapse after spontaneous regression was not frequent except Hodgkin-type LPD and 5-year overall survival rate was about 80%. In this lecture, I discuss epidemiology, underlying mechanisms, clinicopathological features, clinical course and drug therapy for RA after LPDs along the clinical guide edited by the joint working group.

## EL11

### A variety of pulmonary diseases and complications in rheumatoid arthritis

Satoru Ito, Takuma Katano

Respiratory Medicine and Allergology, Aichi Medical University, Nagakute, Japan

Conflict of interest: Yes

Pulmonary diseases and complications are recognized as important extra-articular manifestations because they are responsible for a significant portion of pulmonary dysfunction, impaired health-related quality of life, and the mortality in patients with rheumatoid arthritis (RA). It is also known that chronic inflammation in the respiratory system causes citrullination of lung tissue peptides, which may result in generation of the anti-citrullinated peptide antibody. RA-related pulmonary diseases, including interstitial pneumonia (IP), airway abnormalities, and co-existence of both IP and airway diseases, are highly diverse. A systemic inflammatory disease associated with extra-articular diseases including pulmonary diseases. Because of a higher rate of cigarette smoking, pulmonary emphysema and chronic obstructive pulmonary diseases are more common in RA compared with other connective tissue diseases. Rheumatologists should take care of lung cancer and various pulmonary infections, including COVID-19, specifically in patients treated with immunosuppressive disease-modifying antirheumatic drugs. Importantly, pre-existing RA-related pulmonary diseases are risk factors for pulmonary infection and drug-induced lung injury. This session primarily focuses on RA-related pulmonary diseases and complications, both of which are important for rheumatologists. We further propose that it would be beneficial to evaluate

pulmonary manifestations by assessing chest CT and pulmonary functions.

## EL12

### Ocular complications in rheumatic diseases

Toshikatsu Kaburaki

Ophthalmology, Jichi Medical University Saitama Medical Center, Saitama, Japan

Conflict of interest: None

Ocular complications of rheumatic diseases include conjunctivitis, dry eye, scleritis (keratitis), uveitis, and uveitis includes anterior uveitis and posterior (pan) uveitis. Sjogren's syndrome and rheumatoid arthritis are prone to conjunctivitis and dry eye. Rheumatoid arthritis and polyarteritis nodosa tend to be scleritis, and Behcet's disease (BD), sarcoidosis and Vogt-Koyanagi-Harada disease (VKHD) and SLE frequently complicate uveitis. Dry eye is classified into aqueous-deficient dry eye, decreased-wetability dry eye, and increased-evaporation dry eye. Collagen diseases such as Sjogren's syndrome are those of aqueous-deficient type. Tear film is divided into oil layer, aqueous layer and mucin layer, and a decrease of any layer causes dry eye. Fluorescein staining of tear film can clarify the decreased layer and treatment is performed according to the layer. Scleritis is divided into episcleritis, anterior scleritis, and posterior scleritis, and anterior scleritis is further divided into diffuse, nodular, and necrotizing type. Attention should be paid to the risk of perforation of the eyeball in necrotizing scleritis and retina/optic disc damages in posterior scleritis. Local/systemic steroids are given, but intractable cases may require steroid pulse therapy, cyclophosphamide, and TNF inhibitors. Uveitis can also lead to irreversible visual impairment. The complication rates of uveitis are higher in VKHD (100%), BD (60%) and sarcoidosis (66%). Ocular symptoms and recommended treatments also greatly vary depending on the disease. BD often presents with panuveitis and repeated acute recurrences (ocular attacks). The treatments gradually strengthen in the order of colchicine, cyclosporine, and TNF inhibitors. VKHD develops with binocular optic disc edema and serous retinal detachment, and steroid pulse therapy is recommended at the early stage of onset. Sarcoidosis is characterized by granulomatous uveitis and treated with local/systemic steroids.

## EL13

### Why remission is not enough?

Georg Schett

FAU Erlangen Nürnberg, Germany

Conflict of interest: None

Cure is the aspirational aim for the treatment of all diseases, including chronic inflammatory conditions such as rheumatoid arthritis (RA); however, it has only been during the twenty-first century that remission, let alone cure, has been a regularly achievable target in RA. Remission is generally a more realistic treatment goal. Whilst both lead to cessation of symptoms, the underlying disease process remains active in remission but is absent in cure. This differentiation is important as remission, in contrast to cure, generally requires continuation of treatment, regular follow-ups and carries the risk of relapse, particularly if treatment is interrupted or stopped. Notably, the absence of symptoms does not differentiate between remission and cure. My lecture is aimed at addressing the obstacles to the achievement of cure in RA. The differences between remission and cure in RA are first defined, followed by a discussion of the underlying factors (referred to as drivers) that prevent the achievement of cure in RA by triggering sustained immune activation and effector cytokine production. These factors include aberrations of the adaptive immune system, changes in resident synovial cells and their inter-relationships, and factors remote from the joints, such as mucosal barrier function and neuroendocrine circuits. Any of these factors, whilst active, may prevent achievement of cure. Current and future possibilities for interventions are discussed, as well as the consequences for the design of experimental medicine studies to probe these drivers.

## EL14

### New online medical education produced by web presentation

Makoto Fukuta

CEO M.D. Ph.D., H&F Front Point Partners Co., Ltd.

Conflict of interest: None

Medical congress and medical seminar play important role for life long education for medical staff. These meeting performed not only for a platform to get updated medical information but also for a place to meet together with participants or friends. Participants talks about new project, new research... etc. Finally, motivation of medical staff goes up by participating these meetings. On the other hand, the number and scale of medical congress and seminar increased recently. Accordingly, the cost of holding meetings increased that were becoming issues for organizer. In such a situation, Pandemic of corona virus had a big impact on medical education. Words of the time changed from concentration and contact to decen-tration and non-contact. We have to study medical education in spare environment. At the sama time, system of online communication improve rapidly, we can held online small or large meeting using these systems like zoom. Accordingly, the skills of online presentation and communication were becoming important. I would like to talk about online communication and presentation skills to make your presentation successful.

## EL15

### Novel treatment of dermatological diseases

Shinichi Sato

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Conflict of interest: Yes

In Dermatology, biologics for psoriasis, including anti-TNF- $\alpha$  antibodies, have been launched one after another in the last 10 years, leading to total 10 biologics, including recently released anti-IL-23 p19 antibodies. Among these, anti-IL-23 p19 antibodies have long dosing intervals of 2-3 months and unlike other biologics for psoriasis, improved patients' convenience. In addition, since oral JAK inhibitors were also launched for psoriatic arthritis, exhibiting almost the same effect as biologics, treatment options as an oral medication increased. Such new treatment waves were also spread to atopic dermatitis with higher morbidity (about 10% in children and about 5% in adults). In particular, anti-IL-4 receptor  $\alpha$  antibody with high safety significantly changed the treatment of atopic dermatitis by reducing troublesome topical therapy. Furthermore, topical and oral medications of JAK inhibitors and a topical medication of a PDE4 inhibitor are also available for atopic dermatitis. With the increase in many new treatment options, treatment of atopic dermatitis is in progress to the new stage. In addition, with regard to systemic sclerosis, the investigator-initiated clinical trial in Japan has shown that B cell removal therapy by anti-CD20 antibody is effective for skin sclerosis. Thus, novel therapy has emerged for skin sclerosis of systemic sclerosis, for which few effective treatments were available, and further advances in treatment for systemic sclerosis are expected in the future. In this lecture, I would like to summarize the novel and latest treatment for such dermatological diseases.

## EL16

### Destructive innovation of vaccine R&D took place during COVID-19

Ken Ishii

Division of Vaccine Science, The Institute of Medical Science, The University of Tokyo

Conflict of interest: None

In 2020, the coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to the successful development of two mRNA-based vaccines, encoding the full length of the viral surface spike protein, with high efficacy and reasonable safety. However, reactogenicity, such as fever, caused by innate immune responses to the vaccine formulation remains to be improved. To overcome this potential issue, we developed a lipid nanoparticle (LNP)-based mRNA vaccine, encoding the SARS-CoV-2 spike protein receptor-binding domain (LNP-mRNA-RBD), that improved immunogenicity by removing



reactogenic materials from the vaccine formulation in mice and conferred protection against SARS-CoV-2 infection. The vaccine is filed for patent, finished for pre-clinical development, and is underway to first in human clinical trial by the end of March 2021. We will present recent data about vaccines and immunotherapeutics by immunostimulatory adjuvants for prevention and treatment of not only infectious diseases, but also cancer, allergy and other immunological disorders.

## EL17

### **Intravital multiphoton imaging dissecting bone cell dynamics in vivo - a novel trend in basic rheumatology**

Masaru Ishii

Osaka University Graduate School of Medicine

Conflict of interest: Yes

Intravital imaging of various live tissues and organs has launched a new trend in the field of biology. By using this advanced imaging technique, we first succeeded in visualizing the various dynamic phenomena within bones and joints, where various kinds of immune cells are produced and functioning although poorly analyzed by conventional methodology such as histological analyses with decalcified sections. We have so far identified the real modes of migration, differentiation and function of bone-destroying osteoclasts, special kind of macrophages responsible for bone and joint erosions. Moreover, based on the observation of pathological bone destruction, we could identify a novel subset of osteoclast specifically involved in inflammatory bone erosion. In this lecture I will show the recent updates in the field of basic rheumatology - which surely leads to development of new lines of therapeutics against rheumatic diseases and revolution of the future daily practice in clinic.

## EL18

### **Functional MRI in rheumatoid arthritis: an ideal translational tool for basic research and prediction of therapeutic outcome in the clinics**

Andreas Hess<sup>1</sup>, Jürgen Rech<sup>2</sup>, Georg Schett<sup>2</sup>

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory, autoimmune disorder of the synovium that causes severe morbidity and increased mortality. Pain is a key symptom in patients with arthritis. Although the pivotal role of TNF-alpha in RA is well documented, its role as a pain mediator is less understood. However, TNF inhibitors (TNFi) signify a major advance in RA treatment. However, treatment success initially remains uncertain as one third of patients do not respond adequately to TNFi. We hypothesized that hypernociception due to chronic TNF overexpression leads to an altered pain processing in the brain. Using functional magnetic resonance imaging (fMRI) we demonstrated that mice overexpressing human hTNF as well as RA patients exhibit more intensive and widespread prolonged brain activity upon nociceptive stimuli. Graph-theoretical analysis of fMRI data showed rewiring within the pain matrix under chronic pain conditions. Neutralization of TNF by different antibodies (Infliximab and Certolizumab) rapidly reversed this hypernociception in mice and men. This was reflected by an overall decrease of functional activity in the brain and by dissociation of the tight clustering long before peripheral anti-inflammatory effects were evident. These results suggest profound functional changes of nociceptive brain activity during arthritis in mice and men, which normalize upon TNFi. This similarity of pain related effects in mouse and man facilitates a translational approach. In human patients of particular interest was, that patients with a large response volume upon joint compression even before treatment show a higher probability of being a treatment responder to Certolizumab. First results of our PreCePRA phase 3 study will be presented validating our hypothesis. We conclude that high BOLD volumes, indicating high-level brain representation of pain in RA - but no other clinical or MRI parameter as analyzed by machine learning - predict the response to TNFi.

## EL19

### **How to use DMARDs in the viewpoint of the 2020 clinical practice guidelines for the management of rheumatoid arthritis**

Yutaka Kawahito

Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Conflict of interest: Yes

The prognosis of rheumatoid arthritis (RA) has improved dramatically in recent years due to the availability in routine clinical practice of molecular targeted agents such as biologics and JAK inhibitors in combination with methotrexate (MTX). Recent changes in therapeutic strategies based on the concept of Treat to Target (T2T) have also had a significant impact on improving the prognosis of RA. The concept of T2T strategy has been adopted into daily clinical practice. An important issue in the current treatment of RA is the methodology of drug selection and treatment intensification, considering the patient's background. The 2020 JCR clinical practice guidelines for RA provide guidelines on the sequence of use of DMARDs. It is recommended to start with csDMARDs before molecular targeted drugs, especially MTX. The problem of MTX use is that more than half of RA patients are elderly, due to improve the prognosis of the disease and to increase the age of onset. There are many cases in which MTX use is not feasible due to multiple diseases, concomitant use of multiple drugs, prolonged use of drugs for chronic diseases, decreased organ reserve (decreased renal function) which leads to overdose at regular doses and consideration of reduction in the dose of MTX, decreased adherence due to cognitive impairment and hearing loss (decreased understanding), and misuse of MTX. In addition, there are many cases in which the use of MTX itself is not feasible. Furthermore, RA patients are at high risk of developing malignant lymphoma, and the use of MTX, which has immunosuppressive effect, increases this risk, especially in the elderly. In addition, biologics and JAK inhibitors may increase the risk of infections, cardiovascular events, and malignancies, and may not be used sufficiently due to economic and other reasons. In this seminar, I review the useful use of DMARDs in the daily practice of RA, including the 2020 JCR clinical practice guidelines for RA.

## EL20

### **Latest update on periprosthetic joint infection: current status and issues**

Yutaka Inaba, Naomi Kobayashi, Hyonmin Choe

Department of Orthopaedic Surgery, Yokohama City University

Conflict of interest: None

Periprosthetic joint infection (PJI) is one of serious complications after total joint arthroplasty. Therefore, we need to update information about prevention measures, diagnosis, and treatment of PJI. As for diagnosis, there is no single test to diagnose PJI, and a combination of several tests is recommended for suspected PJI patients. The new diagnostic criteria were proposed at second International Consensus Meeting (ICM) in 2018. In these new criteria, scoring system was adopted and new category, gray zone, was created to increase both sensitivity and specificity, however, there are still difficulty in differentiation between septic and aseptic failures. In treatment, indications of one-stage revision surgery and chronic suppression therapy are reevaluated although two-stage revision surgery is gold standard. There is increasing interest in more conservative procedures such as one-stage revision surgery because of high mortality rate of PJI patients and inferior functional outcomes of two-stage revision surgery. And DAIR (Debridement, Antibiotics and Implant Retention) is considered as an effective option for early-onset PJI. In prevention of PJI, risk stratification to identify high-risk patients is important and preoperative measures should be performed for these patients. Glycemic control is vital for patients with diabetes, and nasal decolonization and skin preparation should be considered for MRS carriers. The importance of prophylactic antibiotics in the prevention has been well established. ICM recommend that the dose of peri-operative antibiotics should be based on weight and continued within 24 hours postoperatively, whereas The WHO and the CDC recommend that the prophylactic antibiotic should not be continued beyond wound closure even in the presence of a surgical drain. In this presentation, the latest update on PJI including current status and issues will be discussed.



## EL21

### Auto-inflammatory diseases in adults: focus on VEXAS syndrome

Yohei Kirino

Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine

Conflict of interest: Yes

Autoinflammatory diseases have been considered to be a group of diseases caused by congenital genetic mutations of childhood onset, and pediatricians have often been involved in their diagnosis and treatment. Although adult rheumatologists do participate in seeing patients with familial Mediterranean fever and PFAPA syndrome, we do not have much experience in genetic diagnosis because genetic testing for these diseases has not been mandatory. However, VEXAS syndrome, which was published last year, strongly suggests the need for genetic diagnosis in adult rheumatology. VEXAS syndrome is an autoinflammatory disease with a poor prognosis, characterized by relapsing polychondritis, skin rash, high-grade fever, arthritis, and myelodysplastic syndrome, and is caused by acquired somatic mutations in hematopoietic stem cells of *UBA1*, a gene involved in E1 ubiquitination. However, because of the variety of clinical presentations of VEXAS syndrome and the wide range of mosaicism of the *UBA1* gene in peripheral blood, diagnostic criteria have not yet been established. Most cases require high-dose steroid therapy, and many patients die from opportunistic infections because symptoms such as fever and skin rash flare up after steroid tapering. We used tocilizumab (TCZ) in three patients with newly diagnosed VEXAS syndrome, and found that steroid reduction was possible in two of the three patients. Measurement of serum cytokine levels before and after TCZ treatment showed that proinflammatory cytokines such as IL-18 persisted at high levels even after TCZ treatment, suggesting that TCZ may not completely control underlying inflammation. In this talk, I would like to give an overview of VEXAS syndrome and its unmet needs, and discuss the need to establish a nationwide case registry to develop optimal diagnosis and treatment.

## EL22

### Rheumatic immune-related adverse events caused by immune checkpoint inhibitors

Nobuyoshi Minemura

Division of General Internal Medicine, Mitsui Memorial Hospital

Conflict of interest: Yes

As immune-related adverse events [irAE] caused by immune checkpoint inhibitors, which has emerged as a new pillar of cancer treatment, expand day by day, it is expected that the number of situations in which not only oncologists but also rheumatologists will be involved in the management of irAEs will surely increase in the future. The situations in which rheumatologists may be involved include: 1. Consultation on the possibility of rheumatic irAE and treatment strategy for new-onset arthralgia/myalgia or hyperCKemia in cancer patients undergoing ICI treatment. 2. consultation on the management of autoimmune disease when ICI treatment is started in cancer patients with autoimmune disease, or the effect of ICI treatment on the activity of autoimmune disease, and 3. consultation on the judicious use of high-dose steroids for high-grade irAEs and how effectively and safely infliximab and mycophenolate mofetil are to be used for the management of steroid-refractory irAEs. In this lecture, we aim to prepare rheumatologists who encounter the above-mentioned situations. In 1, 1) Outline of major rheumatic irAEs (inflammatory arthritis, PMR, myositis) 2) differences from other non-rheumatic irAEs in the measures against those rheumatic irAEs 3) the possibility of overlap with irAE myasthenia and/or irAE myocarditis should be considered when encountering myositis/hyperCKemia. In 2, 1) precautions when ICI treatment is to be performed in cancer patients with rheumatoid arthritis and measures to be taken when rheumatoid arthritis worsens, 2) currently known consensus on the introduction of ICI treatment in cancer patients with pre-existing autoimmune disease. 3 focuses primarily on the management of high-grade non-rheumatic irAEs: 1) wise use of high-dose steroids for irAEs that have emerged in cancer patients. It describes how to be involved from the standpoint of rheumatologists who are proficient in steroid use, and 2) how it is appropriate to use immunosuppressive drugs.

## EL23

### Overview of Patient Safety Practice

Yoshimasa Nagao

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Conflict of interest: None

In Japan, patient safety activity has started due to the some severe malpractices which occurred in 1999. After that, various measures have been performed. From 2015 to 2016, in a scientific research supported by the Ministry of Health, Labor and Welfare, we classified the patient safety activity which should be performed in hospital to “emergency phase” and “usual phase”, and showed a picture of works in one schema (The loop of patient safety activity). In “emergency phase”, we need the following works. -Treatment cooperation which crossed departments. -Open-disclosure to a patient. -Judgement of necessity of a report to a medical accident investigation center. -Medical accident investigation and making on a report. -Explanation the result of investigation to the patient family. Some measures for recurrence preventive are leaded from the investigations. Failure of initial action in “emergency phase” leads the hospital to huge risk. In “usual phase”, we need the following works. -Collection on incident reports. -Root cause Analysis and search of a problem. -Reconsideration of rules or procedures. -Training and education. -Patrol in a site. The validity of the quality control technique in the hospital is pointed out. Appropriate utilization of a mathematical method is useful to lead a good outcome. “Usual phase” is connected with “emergency phase” complementarily. It's necessary to recognize the patient safety activity as core action, not an option, and build governance appropriate to make these something useful. Today, I'd like to explain the picture of patient safety activity while introducing some cases in detail.

## EL24

### WNT signaling in bone homeostasis and disease: Sclerostin Biology and Inhibition

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Conflict of interest: Yes

Several rare human mutations in components of the WNT signaling machinery have illustrated the essential role of this pathway in the development and homeostasis of the skeleton. One of these components, Sclerostin, is a canonical WNT signaling inhibitor secreted by osteocytes which acts as a paracrine/autocrine regulator of bone formation and bone resorption along bone surfaces. Sclerostin binds to the WNT co-receptors LRP5/6, forms a complex with LRP4, and decreases WNT signaling activity, endogenously inhibiting bone formation and favoring bone resorption. Physiologically, sclerostin expression is regulated by mechanical loading, PTH/PTHrP signaling and sex hormones. Mutations in the LRP4, 5 or 6 receptors decrease their affinity for sclerostin, favoring WNT signaling and inducing high bone mass phenotypes. Studies of sclerostin-null mice, or inhibition of sclerostin by anti-sclerostin monoclonal antibodies (romosozumab) reveal the molecular and cellular mechanisms by which sclerostin inhibition enhances bone formation and decreases resorption, leading to rapid increases in bone mass. The effects of sclerostin inhibition occur mainly through modeling rather than remodeling, whereby bone formation is induced on quiescent surfaces. Furthermore, activation of Wnt signaling induces a negative feedback loop with increased endogenous inhibitors such that the anabolic effects are limited in time. Clinical trials illustrate how the molecular mechanisms of sclerostin inhibition translate into increased bone density, improved micro-architecture and decreased fracture risk, as well as the need for sequential treatment with anti-resorptives upon cessation of treatment with romosozumab.

## EL25

### Management of osteoporosis associated with rheumatic diseases

Kosuke Ebina<sup>1</sup>, Makoto Hirao<sup>2</sup>, Yuki Etani<sup>2</sup>, Seiji Okada<sup>2</sup>

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is associated with increased bone turnover and early bone loss, which lead to increased fracture risk and progressive joint destruction. Pro-inflammatory cytokines, such as IL (interleukin)-17, TNF- $\alpha$  (tumor necrosis factor alpha), IL-1, and IL-6 induce the expression of RANKL (receptor activation of nuclear factor  $\kappa$ B ligand) from synovial fibroblasts. RANKL promotes osteoclasts differentiation and activation. According to the arrival of various new osteoporosis therapeutic agents (anti-bone resorption, bone anabolic, and dual effect agents), it is of great interest to investigate effective osteoporosis treatment strategy to prevent both fracture and joint destruction progression. In this symposium, we would like to review the past evidences and discuss about the optimum treatment strategy of osteoporosis associated with rheumatic diseases.

## EL26

### Genetic and epigenetic regulation of the rheumatic disease

Keishi Fujio

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Conflict of interest: Yes

The treatment of the rheumatic diseases has greatly advanced with the advent of molecular targeted therapy. In addition, the existence of ineffective cases of molecular targeted therapy strongly suggests that there is a group of patients with different response to treatment and thus different underlying pathology. In this context, the approach of evaluating and stratifying each patient's condition and selecting the most appropriate drug will become increasingly important in the treatment of the rheumatic diseases. The rheumatic diseases are characterized by autoimmune responses and organ damage. Recent advances in gene expression analysis, especially single-cell RNA sequencing, have greatly advanced our understanding of immune cells in peripheral blood, rheumatoid arthritis synovium, and lupus nephritis kidney. However, it is difficult to identify the genes and pathways that serve as hubs of inflammation and the networks they create by mere correlation. Combining genetic predisposition, genes and pathways associated with disease development may reveal important pathways for stratification. Therefore, if we evaluate gene expression in immune cells at the site of inflammation while combining gene polymorphism and epigenomic modification, it is expected to lead to the stratification of diseases. We constructed a functional genomic database, ImmuNexUT, from 28 immunocompetent cell subsets in peripheral blood derived from 416 Japanese patients with immune-mediated diseases and healthy controls. Using these data, we have identified the immune pathways associated with high and low disease activity in SLE, as well as the cells and immune pathways targeted by belimumab and MMF. In this talk, I will review the genetic and epigenetic regulation of the rheumatic diseases, which may lead to the patient stratification.

## Meet the Expert

### MTE1

#### Current status and tasks of Behçet's disease

Hiroto Kikuchi

Department of Internal Medicine, Teikyo University School of Medicine

Conflict of interest: None

Behçet's disease (BD) is a syndrome with major symptoms of recurrent oral aphthous ulcers (OU), cutaneous involvements, genital ulcers, and ocular involvements. The condition develops into a chronic disease after repeated acute inflammation. This year marks the 50th anniversary of the BD research group, which was organized by the Ministry of Health, Labour and Welfare in 1972. At its inception, the research group prepared diagnostic criteria for BD, and these are still used for diagnosis after slight revisions. As seen in these criteria, research data and effects of treatment for BD in various organs have been accumulated for many years, despite the lack of specific tests. The "Behçet's Disease Treatment Guidelines 2020" were published based on this accumulated information to allow the many findings and experiences of Japanese experts on BD to be shared. Preparation of the guidelines was difficult due to the limited evidence for diagnosis and treatment of BD, since it is a rare disease, and some findings differed from those in overseas studies. The present BD registry was started through a collaboration between the BD research group and the Japan Agency for Medical Research and Development (AMED). A large-scale clinical database will be established in several years, and this will enable us to obtain answers to the questions that we have today. In recent years, some multiple sclerosis cases have been diagnosed as neuromyelitis optica (NMO), and treatment for NMO has been provided in such cases. In BD, disease susceptibility genes have been identified for individual groups based on the results of cluster analysis. Thus, it is likely that improved treatment methods will become available through more precise identification of targets for diagnosis and treatment of BD. Several years will be required for this work, but we would like to show the latest findings we have obtained to date in this lecture.

### MTE2

#### Treatment of WoCBA Patients in Rheumatic Diseases - Based on the Rheumatoid Arthritis Treatment Guidelines 2020

Mikako Goto

The Japan Drug Information Institute in Pregnancy, National Center for Child Health and Development, Tokyo, Japan

Conflict of interest: None

Last year, the Rheumatoid Arthritis Clinical Practice Guideline 2020 was published, and the section on perinatal pharmacology was considerably more extensive and more comprehensive than the 2014 edition. The perinatal section of the guideline is much larger and more comprehensive than the 2014 edition. Not only is there a section on how to treat rheumatoid arthritis (RA) in patients who want to become pregnant and pregnant women, but there are also new sections on how to treat pregnancy in the partners of male RA patients and on RA treatment and breastfeeding, making the guideline more practical. Compared to the other sections, the perinatal section is more narrative. There is a lack of studies with a high level of evidence due to the difficulty in conducting interventional trials on pregnant women. In this MTE, I would like to explain the basics of pregnancy and medication to understand the guidelines and more in-depth information that could not be included in the guidelines. Physicians who see patients with collagen diseases often treat women of childbearing age on an ongoing basis. However, many of them may feel uncomfortable because they have few opportunities to gain knowledge about pregnancy. Nowadays, it is common to use medications that can be administered if necessary to suppress disease activity, rather than discontinuing medications once pregnancy is detected, so I would like you to have some basic knowledge. I hope that this lecture will help you eliminate your dislike of pregnancy, lactation, and the field of medicine and that it will be helpful in your practice tomorrow.

## MTE3

### Steroid Today

Hirotohi Tanaka<sup>1,2</sup>

<sup>1</sup>Department of Biochemistry and Integrative Biology, Keio University School of Medicine, <sup>2</sup>Department of Rheumatology, Kitasato University Kitasato Institute Hospital

Conflict of interest: None

Although steroids have been clinically used for 70 years, they are still important therapeutic agents in a wide variety of rheumatoid diseases. Notably, steroids are indicated for COVID-19 and Duchenne muscular dystrophy. So far, the science of steroids has made remarkable progress by the advanced science of each era, such as identification of steroid receptor GR, elucidation of mechanism of action and side effects of steroid, etc. GR is a member of the nuclear receptor superfamily, and it was revealed that the essential mechanism of steroid action is GR-mediated regulation of gene expression. That is, the essence of steroid therapy is nothing but “artificial gene expression control targeting GR”. However, we clinicians can hardly realize that the steroid science has been clinically fed back. Moreover, there is a tendency to avoid steroids more than necessary without scientific evidence and to rush to reduce or discontinue the dose. After 70 years, the confusion in the clinical setting of steroids is being promoted. However, recently, there have been developments that can be called “second impact” in the field of steroid research. Research utilizing the latest omics analysis and bioinformatics is rapidly closing the gap between basic steroid research and clinical practice. Rather, the clinician’s perspective and question-raising are essential in these studies. In this lecture, I would like to select and introduce recent topics related to steroids based on the keyword “from science to clinical practice” and discuss with you about the significance and problems of steroid therapy.

## MTE4

### A primer of statistical analysis for clinical researches using SAS On-Demand for Academics

Hisashi Noma

The Institute of Statistical Mathematics

Conflict of interest: None

In modern medical researches, many advanced statistical techniques have been commonly used, e.g., logistic regression, Cox regression and propensity score analyses, and we cannot understand clinical evidence from these research papers unless we have sufficient knowledge about these methods. In addition, we cannot write clinical research papers if we cannot use statistical software properly. However, most of these software packages require certain programming skills and expensive charges. In this session, I conduct a hands-on seminar using a statistical software SAS OnDemand for Academics (SAS Institute, Cary, NC), which can be used without usage charge. SAS is a well-known statistical software that has been widely used in clinical researches published in international medical journals, and has rich and reliable functions for data analyses. In addition, I will provide a short tutorial of propensity score analysis using SAS.

## MTE5

### Basic knowledge for clinical use of musculoskeletal ultrasound in rheumatology

Tadashi Okano

Department of Orthopedics, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

Conflict of interest: None

Recently, the usefulness of ultrasonography has been widely recognized in the management of rheumatoid arthritis. The ultrasound examination is useful in all situations such as diagnosis, the evaluation of treatment efficacy and management under remission, but the most useful is at the time of early diagnosis and differential diagnosis. However, it is also true that the ultrasonography is an examination whose result may be affected by the settings of the equipment and the sonographer’s skills. In order to maximize the potential of ultrasound examination, it is necessary to understand the standard settings such as frequency of the probe in grayscale and

power Doppler, gain and focus. An most important scanning skill is to take an image while keeping the gel layer without pressing the probe against the skin, particularly in a shallow part from the body surface such as a peripheral small joint or a tendon enthesis. This skill is very important in order not to underestimate synovial thickening and power Doppler signals that increased inside and/or outside of the joint. Furthermore, pathological findings in ultrasonography are not only intra-articular synovitis, but also include multiple findings including tendon and ligament enthesitis, tenosynovitis and calcification in the cartilage and cartilage surface. It is essential knowledge for differential diagnosis to understand how these pathological findings are seen in which disease, and that it may or may not be diagnosed only by ultrasound findings. In order to understand these things efficiently, this seminar is planned to give a lecture with live demonstration by using real ultrasound machine. I would be pleased that who want to start ultrasonography from now join this seminar.

## MTE6

### Approach to Fever or Inflammation of Unknown Origin 2022: Difficult “seronegative”, “periodic” cases

Noboru Hagino

Division of Rheumatology, Teikyo University Medical Center in Chiba

Conflict of interest: None

Rheumatologists sometimes serve as a “last resort” for the diagnosis of difficult, prolonged and/or periodic fever. The concept of fever of unknown origin (FUO) was first reported by Petersdorf and Beeson (1961), then re-classified by Durack and Street (1991), although its etiology has substantially changed thanks to the development of serological and imaging diagnostic modalities. “Autoinflammatory syndrome” by Kastner et al (1999) has deepened our insight into periodical, sometimes seronegative fever/inflammation of unknown origin. This MTE session aims to reflect our practice of the approach to prolonged fever or inflammation, mainly from rheumatologist’s point of view.

## MTE7

### Better understanding of rehabilitation and custom orthotic interventions in treatment of patients with rheumatoid arthritis useful or rheumatologist of physician

Jun Hashimoto

Department of Rheumatology, Collagen Disease and Allergy, National Hospital Organization, Osaka Minami Medical Center

Conflict of interest: Yes

Treatment modalities for rheumatoid arthritis (RA) that contains education for understanding the disease and managing daily living, pharmacological treatment, surgical treatment, rehabilitation and care should be timely informed and performed to patients with RA. There are several important notes for rehabilitation and custom orthotic interventions. The first is having both viewpoints of joint protection/energy conservation and improvement of physical activity. Joint protection/energy conservation is to remove the burden on inflamed/damaged joint. Typical examples are using a wrist orthosis for joint stabilization or using proximal large joints and both extremities for heavy physical work. It is important to restrict a use of cane in case of walking disability, since it could cause the physical destruction in wrist and shoulder joints of non-weight bearing joint. Walking disability of patients with RA should be treated with accurate diagnosis of disturbance in gait and surgical intervention if necessary. This is the time for rheumatologist of physician to consult the rheuma-foot and ankle surgeon, spine surgeon or joint surgeon. As to improvement of physical activity, ring splint for swan-neck or button-hole deformity of finger, and adjustment of footwear and insole interventions for forefoot deformity are helpful. The second is that rehabilitation and custom orthotic interventions are standard approach for improvement of physical activity of the patients with RA through his/her life-span. EULAR recommendation mentioned that physical activity interventions are standard care and include the behavioral change techniques self-monitoring, goal setting, action planning, feedback and problem solving with strength of recommendation A and category of evidence 1A. Recently SARAH randomized controlled trial showed that a tailored exercise regimen for hand and upper limb is effective in restoration and retaining of hand function. The third is improve-

ment and reinforcement for provision of information regarding surgical intervention for physical activity improvement. Multidisciplinary information could provide the patients with informed and *voluntary decision making* from several therapeutic alternatives and contribute his/her long life-plan in the era of centenarians.

## MTE8

### Key points in the diagnosis and treatment of IgG4-related diseases

Hiroki Takahashi

Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan

Conflict of interest: Yes

IgG4-related disease (IgG4-RD) has been established in the 21st century as a novel systemic disease which is characterized by elevated levels of serum IgG4 and various lesion formation consisting of dense infiltration of IgG4-positive plasmacytes with fibrosis. The most common sites for IgG4-RD are the lacrimal glands, salivary glands, and pancreas. In addition, multiple organ involvement, including kidney, bile duct, and retroperitoneum, et al. form diverse clinical features in synchronous and metachronous course. Thanks to increased awareness of IgG4-RD as a new disease concept, it is easy to diagnose an IgG4-RD in a case presenting with bilateral swelling of the lacrimal and salivary glands and elevated levels of serum IgG4. On the other hand, it is often difficult to diagnose in a case with lesions not frequently affected organs such as ovary and pleural effusion. Inflammatory factors such as fever, elevated CRP, and severe weight loss are not characteristic of IgG4-RD. Patients with such clinical features are rare except for cases with IgG4-related hypophysitis / periaortitis, and are strongly suspected of being IgG4-RD mimickers. In this lecture, I would like participants to understand the basic clinical pictures of IgG4-RD based on actual cases. Next, participants should learn how to use Japan's comprehensive diagnostic criteria for IgG4-RD, and organ-specific diagnostic criteria (lacrimal gland / salivary gland), and ACR / EULAR classification criteria. Finally, I would also like to mention the points that distinguish IgG4-RD mimickers. With regard to the treatment of IgG4-RD, it is often difficult to determine the treatment indication and the timing of treatment start because of the synchronous and metachronous course and the spontaneous remission. I would like to discuss the actual treatment with the participants, referring to the findings of long-term observations in our department.

## MTE9

### Behavioral economics in the medical field

Kei Hirai

Graduate School of Human Science, Osaka University

Conflict of interest: None

Many healthcare professionals have difficulty with patients who cannot be “decided” no matter how many times they explain the purpose of treatment, its effects, side effects, etc., or who want to get treatment methods with high risk and uncertain effects at the end of life. Behind this “miscommunication” of communication between the patient and the healthcare professional, the decision-making that both the healthcare professional and the patient are rational and that the correct decision can be made if the correct information is available. It is considered that there is a system design that presupposes such rationality. Behavioral economics is a discipline that unravels the “framework of irrational thinking when a person makes a decision” (bounded rationality), and solves problems related to human decision-making on the premise of that. In medical communication, there are various types of behavioral economic biases in both the medical staff and the patient, which are the causes of the above-mentioned miscommunication between the patient and the medical staff. Therefore, it is possible to identify and correct it from the viewpoint of behavioral economics. What is important in this correction is the concept of libertarian paternalism. The mechanism for promoting decision-making and behavior change is called NUDGE. Many efforts to create a small opportunity to encourage the other person's behavior by utilizing the mechanism of Nudge are included in the actual communication in the clinical setting. In this lecture, I will explain Nudge as a mechanism to promote decision-making and behavior change based on the existence of a specific bias

in order to make communication in the current medical situation smoother and more productive, using actual cases, including ethical issues in the theory and implementation.

## MTE10

### Tips of Risk Management for Infectious Diseases. Think from a Viewpoint of Clinical Immunology

Hirofumi Shoda

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Conflict of interest: Yes

Risk management for infectious diseases is important in the treatment strategy of rheumatic diseases. Infectious diseases not only affect the prognosis, but also often prevent the continuation of immunosuppressive treatment. Therefore, risk management for infectious diseases should be taken to provide the best practice in rheumatology. To perform infectious disease risk management neatly, it is necessary for the rheumatologists to have a good understanding of clinical immunity. High quality risk management would result in better clinical outcomes. In this lecture, I will explain the outline, method, and practice of risk management for infectious diseases based on an understanding of clinical immunity. Also, as a topic today, I will provide some information about COVID-19 risk management in the patients with rheumatic diseases. 1. Overview of the immune system: innate immune system, adaptive immune system, immunodeficiency and infectious diseases 2. Immunological Targets of Immunosuppressive Therapy 3. How to know the immune status of a host?: Genetic background, biomarkers, immune phenotyping 4. Practice of infectious disease risk management in patients with rheumatic diseases 5. COVID-19 in patients with rheumatic diseases

## MTE11

### Current status of the clinical practice on autoinflammatory syndrome Part 2

Ryuta Nishikomori

Department of Pediatrics and Child Health, Kurume University School of Medicine

Conflict of interest: Yes

Autoinflammatory syndromes are hereditary diseases in which inflammation is the main pathology. Familial Mediterranean fever is a rare disease with a prevalence of approximately 1 in 100,000, while other autoinflammatory syndromes are extremely rare with a prevalence of about 0.1 in 100,000. However, it is important for rheumatologists to know the existence of autoinflammatory syndromes because early diagnosis can prevent complications of organ damage and improve patient QOL. In this Meet the expert session, we will focus on the diagnosis of autoinflammatory syndromes, especially genetic testing, which is not familiar to rheumatologists, and discuss various aspects of autoinflammatory syndromes, including treatments and information on newly identified autoinflammatory syndromes. This year's talk will be a continuation of last year's talk, but this time I will include explanations and updates on relatively common autoinflammatory syndromes that you may encounter in the clinics, as well as some updates on new diseases.

## MTE12

### Welcome to the world of statistical genetics

Yukinori Okada<sup>1,2</sup>

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Conflict of interest: None

Statistical genetics is a research field that evaluates causality of human genetic variations on diseases, using statistical and bioinformatics approaches. Genetic backgrounds contribute to onset and prognosis of rheumatic diseases (= high heritability), and genome-wide association studies (GWAS) have identified a number of disease risk loci. However, little is



known regarding how to develop methodology to integrate large-scale human genome data with diverse biological resources, to which statistical genetics should contribute. We have developed such methods and applied to a pioneering example of large-scale genetic association studies on a variety of human complex traits, including immune-related diseases, clinical biomarkers, and past medical records. Tran-layer omics analysis identified the cell types and microbiomes implicated in disease biology. Network analysis between the disease risk genes and the drug target genes could identify novel candidates of drug repositioning. Integration of cell type-specific gene expression profiles estimated from GWAS with compound perturbation databases can pinpoint novel therapeutic targets and compounds. Application of the machine learning methods into population genome data can classify the samples without prior biological information. Further, we demonstrated utility of deep learning in human population genomes, such as in silico estimation of HLA gene variants. Polygenic risk score (PRS) integrating genetic risk of the genome-wide variants can stratify the samples based on disease risk, and can also identify causal factors for human longevity. These results should empirically show the value of statistical genetics to dissect disease biology, novel drug discovery, and personalized medicine. Finally, we would like to introduce our activity on young researcher developments ("Summer school of statistical genetics" in Osaka University).

### MTE13

#### Robotic surgery in total joint arthroplasty

Nobuhiko Sugano<sup>1</sup>, Masaki Takao<sup>2</sup>, Wataru Ando<sup>1</sup>, Hidetoshi Hamada<sup>1</sup>, Keisuke Uemura<sup>2</sup>

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Conflict of interest: Yes

The longevity of artificial joints has been drastically improved due to the advanced materials, design, implant manufacturing, and surgical techniques. The issues of implant fracture, loosening and wear of bearing couples in the past have been quite resolved. Nowadays, the issues of instability, dislocation, and edge loading due to implant mal-alignment have become a major concern for total hip arthroplasty. To solve these, the use of a large diameter femoral head or dual mobility construct is not perfect and a personalized proper cup alignment with consideration of the individual pelvic tilt is needed. Robotic surgery has been proven to be most accurate for cup placement and its clinical benefits to reduce the rates of dislocation and reoperation are expected to be proven. In total knee arthroplasty, navigation has shown to be effective to obtain neutral mechanical alignment (NMA), but it has not been successful to increase the rate of patient satisfaction. On the other hand, kinematic alignment with the use of image-based surgical template failed to show a better functional score than NMA. Functional alignment (FA) has been recently proposed to restore the native plane and obliquity of the joint, as dictated by the soft-tissue envelope. This technique aims to execute individualized physiological limb alignment and achieve patient-specific knee kinematics while limiting any soft-tissue releases. To achieve FA, the use of robotic technology is wide spreading. At this moment, personalized proper preoperative planning is made or fine-tuned by the experienced surgeons and the plan is precisely executed with the use of robotic assistance. The big data of their postoperative radiographic and functional outcome evaluation can be used for AI deep learning to reveal what is the real proper preoperative plan in each case. Then, it can be used to develop AI automated proper preoperative system which can be used to train inexperienced surgeons.

### MTE14

#### Total elbow arthroplasty; how to use Unlinked or Linked for lifelong strategy

Mitsuyasu Iwasawa<sup>1</sup>, Masashi Naito<sup>1</sup>, Satoru Ohashi<sup>1</sup>, Tetsuro Yasui<sup>2</sup>, Sakae Tanaka<sup>3</sup>

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Conflict of interest: None

The destruction of large joints in rheumatoid arthritis (RA) is decreasing with the progress of drug therapy. There is a concern that it will be difficult to acquire adequate treatment and surgical techniques of upper limbs in the future, because the number of total joint arthroplasty of the upper limbs is extremely small compared to that of the lower limbs. Total elbow arthroplasty (TEA) is an effective mean to achieve therapeutic goals for range of motion, pain relief, and stability. Surgical techniques are more diverse than those of other joint arthroplasties. In many models, the radio-humeral joint, which is the main load transmission in the extended position, is not constructed, so it has been required to devise measures against joint instability and difficulty in applying the load. Although the Linked type does not cause joint instability, it requires a longer stem length, humeral anterior flange and cement fixation due to its higher constraint, and the stem shape and structure have also been improved to avoid breakage and loosening. On the other hand, the Unlinked type is small size due to its low stress, but due to its low constraint, it is necessary to ensure stability by soft tissues. In Unlinked type, accurate implant fixation and reconstruction of soft tissues are required more than those in Linked type. Lifelong strategy with an eye on revision surgery is required in TEA, especially for younger patients. It is desirable to use the Unlinked type, which allows more bone preservation in the primary surgeries, than the Linked type. We believe that it is important to make TEA a general surgery that is not limited to experienced surgeons. In this lecture, appropriate surgical indications and surgical techniques will be explained.

### MTE15

#### Antinuclear antibodies: novel nomenclature of the fluorescence patterns, clinical relevance and their roles in pathogenesis

Tetsuo Kubota

Department of Medical Technology, Tsukuba International University

Conflict of interest: None

Since the 1970's, the standard antinuclear antibody (ANA) assay has been performed by indirect immunofluorescent test on HEp-2 cells, and it is still one of the indispensable clinical test items. However, richness in nuances of the morphological patterns requires renovation of nomenclature and classification of the staining patterns. International Consensus on Antinuclear Antibody Patterns (ICAP) workshop has been committed to discuss this issue and released the first outcome in 2015 (Front Immunol 6:412). This novel classification included 14 nuclear, 9 cytoplasmic, and 5 mitotic staining patterns, which was uploaded on the ICAP web site, and translated later into many languages to facilitate the discussion and prevalence. The same as last year, this lecture will introduce this novel classification of ANA, adding the latest information. On the other hand, ANAs are probably involved in pathogenesis of various autoimmune diseases. Since more than four decades ago, internalization of ANAs by living cells has been observed. Their pathogenic roles are gradually revealed owing to the progress of studies on endocytosis and natural immunity, and improvement of confocal microscopy and other technology. For example, ANAs can form immune complexes with DNA or RNA and be internalized into innate immune cells, resulting in interaction with Toll-like receptors or other nucleic acid sensors and production of pro-inflammatory cytokines including IFN- $\alpha$ . Recent progress in this research field will also be discussed.

### MTE16

#### Diagnosis and management of axial spondyloarthritis

Naoto Tamura

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine

Conflict of interest: Yes

Axial spondyloarthritis (axSpA) is a group of SpA in which arthritis is predominantly seen in sacroiliac joints and spine. axSpA often develops in young men with inflammatory back pain, and strongly associated with *HLA-B27* gene. Primary site of the inflammation is enthesitis at the attachment of the ligaments. Over the course of the years, bone erosion and its repair are followed by new bone formation, seen as syndesmophytes leading to spinal ankylosis. axSpA comprises radiographic ax SpA, which meets the modified New York criteria for ankylosing spondylitis (AS) in a

plain X-ray of the sacroiliac joints (almost the same population of AS), and non-radiographic axial SpA (nr-axSpA) that does not meet the criteria, although it seems to lack the objectiveness. Although nr-axSpA often does not progress to radiographic axSpA, the patient's disease burden is the same as that of AS. Early diagnosis and intervention are required for axSpA to improve the patient's QOL, however, early diagnosis of axSpA is frequently challenging. Most important in the diagnosis of axSpA is the presence of non-infectious sacroiliitis. ASAS (Ankylosing SpondyloArthritis International Society) criteria must be used for cases already diagnosed with axSpA, and it should not be applied to the initial diagnosis. It is necessary to familiarize yourself with the characteristics of axSpA, and careful observation is needed before making a diagnosis. In the treatment of axSpA, patient education, including smoking cessation and encouragement of exercise, is important. In drug therapy, non-steroidal anti-inflammatory drugs (NSAIDs) are used at first. There is no evidence of efficacy of methotrexate for both axial and peripheral symptoms. In addition, systemic glucocorticoid is not normally used. If NSAIDs are inadequate, TNF inhibitors or IL-17 inhibitors are used. Switching to other TNF inhibitors is also useful in case of secondary failure of a TNF inhibitor. These drugs are expected to have an inhibitory effect on new bone formation, but have not been clarified yet. In this MTE, I would like to outline and discuss diagnosis and management of axSpA.

## MTE17

### Management of elderly patients with rheumatoid arthritis

Hideto Kameda

Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

Conflict of interest: Yes

In Japan, approximately 30% of the population is over the age of 65. The impact of the super-aged society on the management of rheumatoid arthritis (RA) includes: difficulties in diagnosis due to a clinical picture resembling polymyalgia rheumatica; rapid decline in physical functions due to accelerated frailty; difficulties in treatment due to renal dysfunction or infection risk qualifying for cautious administration of methotrexate; and the strain on the medical economy due to molecular targeted therapy with reduced co-payments. Controversies in treatment often include whether to include corticosteroids in the initial treatment, whether to use multiple synthetic anti-rheumatic drugs in addition to multiple treatments for complications, and the indication and selection of molecularly targeted drugs in consideration of complications. In addition to atherosclerotic cardiovascular disease, which are important in other countries, osteoarthritis and spondylosis, respiratory diseases such as interstitial pneumonia and pneumocystis pneumonia, and hematological diseases such as lymphoproliferative diseases and myelosuppression are particularly important in Japan. Furthermore, it has recently been noticed that elderly patients are at risk for infections due to impaired systemic barrier function, as well as abnormalities in immune cell responses, and that persistent production of proinflammatory cytokines, known as "inflammaging", is observed in elderly patients. There is no doubt that the knowledge gained from clinical practice in Japan, the world-leading super-aged society, will make a significant contribution to the future treatment of RA in overseas countries.

## MTE18

### The knack in physical examination of children including juvenile idiopathic arthritis patients

Naomi Iwata

Department of Infection and Immunology, Aichi Children's Health and Medical Center

Conflict of interest: None

Physical examination is an important procedure for physicians to understand patients' conditions by looking at, touching, and listening with a stethoscope. Although the same is true for pediatric rheumatologists, we value physical examination much more. Children may be unable to express themselves due to young age or fear of examination. In juvenile cases, the informant in medical interviews may be a patient's guardian. Guardians cannot feel a patient's pain as same as they can their own. For this reason, pediatric rheumatologists determine a patient's medical condi-

tion by physical examination and make a diagnosis by adding information from guardians. Hence, I would like to share with you some tips about how pediatric rheumatologists examine pediatric patients.

## MTE19

### Interstitial Lung Disease: Up to date

Yasuhiro Kondo

Department of Respiratory Medicine and Allergy, Tosei General Hospital

Conflict of interest: Yes

Interstitial lung disease (ILD) is a general term for diseases in which the interstitium of the lung is the primary pathological lesion. In connective tissue disease (CTD), the frequency of respiratory diseases is high regardless of the disease, and various pathological lesions occur in the airway, interstitial, blood vessels, and pleural membrane. Among them, interstitial lung disease is an important prognostic factor in rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM / DM), and mixed connective tissue disease (MCTD). In this Meet The Expert session, after understanding the basic knowledge on idiopathic interstitial pneumonia, you will understand the significance of ILD on CTD and learn the treatment strategy through case-based discussion. Then, you will find out how to formulate a treatment strategy for CTD-ILD from the viewpoint of the underlying disease and histopathologic classification of ILD. In addition, a treatment strategy for IPAF that assumes interstitial pneumonia due to an autoimmune mechanism but does not meet the diagnostic criteria for CTD will be discussed. You will understand the timing of judgment of PF-ILD, a phenotype that exhibits progressive fibrosis even with standard treatment and management, and the actual treatment intervention on a case-by-case basis. Moreover, the roles and effects of anti-inflammatory and anti-fibrotic drugs and the significance of their combined use will be another issue. Finally, you will learn the significance and problems of early diagnosis and early intervention, the practice of acute to chronic management, and the management of various complications as well as comorbidities. We will discuss the significance and approach of rehabilitation, ACP, and palliative medicine. I hope you can improve your comprehensive management ability for patients with CTD-ILD by participating in this session.

## MTE20

### Total shoulder arthroplasty update (from anatomical to reverse shoulder arthroplasty)

Yuichi Nagase<sup>1</sup>, Masashi Naito<sup>2</sup>, Sakae Tanaka<sup>3</sup>, Kazuya Tamai<sup>4</sup>

<sup>1</sup>Department of Rheumatic Surgery, Tokyo Metropolitan Tama Medical Center, <sup>2</sup>Department of Orthopaedics, Sagami Hospital, <sup>3</sup>Department of Orthopaedics, The University of Tokyo Hospital, <sup>4</sup>Department of Orthopaedics, Toho Bunkyo Hospital

Conflict of interest: None

The characteristics of rheumatoid shoulder was rotator cuff insufficiency or tears owing to the invasion of synovitis and osteoclasts into a bare area. Arthroscopic rotator cuff repair for patients with RA may increase with tight control era of RA. Anatomical total shoulder arthroplasty (TSA) in the destructive rheumatic shoulders with cuff insufficiency usually gives patients pain relief but never gets good satisfaction of range of motion. Therefore, the treatment for destructive rheumatic shoulders with cuff insufficiency bothers orthopaedic surgeons for ages. Reverse shoulder arthroplasty (RSA) was invented in 1986 by Paul Grammont and it enables patients with cuff tear arthropathy (CTA) to recover use of the deltoid muscle through the medialization of the center of rotation and lengthening of the deltoid muscle. The long-term outcomes of RSA for cuff tear arthropathy (CTA) showed satisfactory results. We reported that mid-term outcomes of RSA in patients with RA using patient specific outcome measure (Shoulder36) and RSA improved pain relief, flexion, abduction, general health, and quality of life. The case of RSA for proximal humeral fractures with destructive rheumatic shoulders may increase with aging society. Early design of the Grammont type RSA have minor complication such as scapular notching. The next generation device was invented to have lower neck-shaft angle to decrease scapular notching and can lateralize humerus to use internal and external muscle effectively and choose glenoid inferior offset to decrease scapular notching. 3D templating for

glenoid, patient specific instrument, and intraoperative navigation were recently used. Recent advances in the treatment of RA have increase treatment options for rheumatic shoulder and that will make improvement of ADL and QOL if that kind of options were gradually recognized among rheumatologist and orthopaedic surgeon.

## **MTE21**

### **Differential diagnosis of arthritis in the elderly**

Mitsumasa Kishimoto

Department of Nephrology and Rheumatology, Kyorin University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

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, especially focusing on the elderly population, 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.

## **MTE22**

### **Difficult-to-treat RA**

Eiichi Tanaka

Division of Rheumatology, Department of Internal Medicine, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

The sufficient methotrexate use and the introduction of biological DMARDs (bDMARDs) and/or targeted synthetic DMARDs (tsDMARDs) such as JAK inhibitors has resulted in significant advances in treatment strategies for rheumatoid arthritis (RA). In the IORRA cohort, the proportion of the patients who achieved DAS28 remission increased from 8.4% in 2000 to 60.8% in 2020, and most recently approximately 80% of the RA patients are well-controlled. On the other hand, despite these advances in RA treatment, 20% of the RA patients with moderate or high disease activity have not reached their therapeutic goals. Appropriate treatment of these patients is considered to be unmet needs. Since uniform terminology and a clear definition for these patient groups are lacking, a EULAR Task Force was established to derive comprehensive recommendations addressing unmet needs in the management of difficult-to-treat (D2T) RA. The EULAR definition of D2T RA was proposed in 2020. At this Meet the Expert seminar, we will first share the process of making the EULAR definition of D2T RA and the content of this definition. In addition, I would like to explain various issues that may contribute to D2T RA including (1) treatment for the RA patients who cannot use methotrexate, (2) treatment for multi-drug-resistant RA, especially inadequate response to bDMARDs, (3) treatment for RA patients with various types of complications, and (4) treatment for elderly RA patients, using data from clinical trials and registries such as the IORRA cohort.

## **MTE23**

### **Learn about advances in SLE treatment**

Kazuhisa Nakano

Department of Rheumatology, Kawasaki Medical School, Kurashiki, Japan

Conflict of interest: Yes

Systemic lupus erythematosus (SLE) exhibits a diverse clinical course and organ damage due to its complex pathology. The goals of treatment for

patients with SLE are to ensure long-term survival, achieve the lowest possible disease activity, prevent organ damage, minimize drug toxicity, improve quality of life, and educate patients about their role in disease management. In the actual treatment of SLE, we rheumatologists refer to the EULAR treatment recommendations updated in 2019 and the guidelines for SLE treatment in Japan formulated in the same year. After comprehensively evaluating complications such as disease activity, major organ damages, infectious diseases, and heart diseases, hydroxychloroquine (HCQ), a standard treatment, is started and the initial dose of corticosteroids and the type of immunosuppressive agents is determined. After the start of treatment, the drug will be adjusted regularly with the target of the disease activity index according to the Treat-to-target (T2T) algorithm. In recent years, advances in omics research have promoted an understanding of the etiology and pathophysiology of SLE, and at the same time, the development of cell-targeted and molecular-targeted drugs has also progressed. Belimumab, a human anti-BLyS monoclonal antibody, was covered by insurance in Japan in 2017, and Anifrolumab, a human anti-type I IFNAR1 monoclonal antibody, has been approved in 2021. Increasing treatment options are good news for SLE patients and rheumatologists. It is necessary to minimize corticosteroids by optimizing the use of these drugs, including those that are expected to be launched in the near future. In this meeting, we will confirm the precautions for basic treatments for SLE, and based on the results of recent translational research, we will work with participants to think about optimizing new treatment options and practicing better SLE treatment.

## Luncheon Seminar

### LS1

#### Recent Advances in Understanding the Pathogenesis of Rheumatoid Arthritis~focus on filgotinib targeting the immunopathology~

Kimito Kawahata

Division of Rheumatology and Allergology Department of Internal Medicine, St. Marianna University School of Medicine

Conflict of interest: Yes

While there have been significant steps forward in the treatment outcomes of rheumatoid arthritis thanks to advances in treatment strategy and the development of new drugs, there are still issues that remain unaddressed by current treatments. Alongside the development of medicines that are shown to be more effective and safe, solutions need to be developed for patients who have various comorbidities and complications. JAK inhibitors differ from biologics in many aspects. They function as signal inhibitors that include multiple cytokines or cytokines not targeted by conventional medicines, and have various characteristics, such as being a low-molecule compound that targets molecules within the cell, which allows patients to take them orally. Clinically, it has shown rapid clinical effects such as the improvement of symptoms, the inhibition of joint destruction, efficacy as monotherapy and efficacy in cases where various biologics are ineffective. It is becoming an important option to address a number of the previously mentioned unmet needs. It is thought that there is diverse involvement of the JAK-STAT system in the pathogenesis of rheumatoid arthritis. In this lecture, I want to focus on the issues with current treatments for rheumatoid arthritis, the latest findings with regard to pathogenesis, and an overview of filgotinib, which is attracting attention as a JAK1 inhibitor.

### LS2-1

#### Challenges in difficult-to-treat rheumatoid arthritis with JAK inhibitors

Shingo Nakayamada

First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: Yes

In the treatment of rheumatoid arthritis (RA), early and appropriate therapeutic intervention with conventional synthetic antirheumatic drugs (csDMARDs), such as methotrexate (MTX), and biological antirheumatic drugs (bDMARDs) has made clinical, structural, and functional remission a realistic goal. However, even with these treatments, the existence and characteristics of a treatment-refractory patient group, difficult-to-treat RA (D2T RA), are becoming clearer. Janus kinase (JAK) inhibitors are synthetic molecularly targeted anti-rheumatic drugs (tsDMARDs) that target JAK, an intracellular kinase that mediates cytokine signaling. Because of their multi-target effect on innate and acquired immune systems, JAK inhibitors have the potential to meet unmet needs of conventional therapies. The efficacy and safety of upadacitinib has been shown in multiple phase III trials (SELECT clinical trial program) and this drug was approved for insurance coverage for RA in 2020. Upadacitinib has been shown to be effective in patients with inadequate response to bDMARDs, thus is expected to be effective in D2T RA. On the other hand, there is no less concern about the safety of JAK inhibitors than bDMARDs. In particular, the incidence of herpes zoster is high, and it is important to consider vaccines, provide information to patients. The safety profile of upadacitinib is consistent with previous reports and stable over the long term, but long-term safety in real-world clinical practice is an important issue. Although it is a highly convenient oral drug, it should be used appropriately with adequate screening and monitoring. In this seminar, we would like to discuss the remaining issues in the treatment of RA such as D2T RA and outline the expectations for JAK inhibitors.

### LS2-2

#### Various honor achievements derived from upadacitinib-monotherapy in RA-clinical setting ~RA-treatment also favor the target, 'Simple is the best'~

Kenta Misaki

Department of Rheumatology, Kita-Harima Medical Center

Conflict of interest: Yes

One decade has passed after first-publication of RA-EULAR recommendation. We rheumatologists have experienced many paradigm shifts concerned with RA diagnosis and treatment during this 10 years, moreover can actually implement those to RA patients in clinical setting. ACPA is approved in medical insurance in terms of RA-diagnosis, however the diagnosis of seronegative RA has been become a major topic of discussion also in this new decade. The approval of musculoskeletal ultrasound examination (MSKUS) is also noteworthy for RA-diagnosis as one of the imaging procedures. MSKUS make it possible to depict the real-time pathological findings without harm nevertheless no findings by physical examination, and make a huge contribution to early seronegative RA-diagnosis. JAK inhibitors (JAKi) have been shared the spotlight with biologic agents since 2013 in our country. Upadacitinib (UPA) is a next-generation JAKi selective for JAK1 and has many novel RCTs. Especially the evidence of UPA-monotherapy is innovative and totally considered not only the clinical and structural remissions but also patient reported outcomes (PROs). Additionally, it is strongly expected that UPA-monotherapy is going to resolve the current issue about RA poly-pharmacy in this new era. Further, some concerns in terms of the safety of JAKi are noted, however it is possible to manage sufficiently by using various approach based on the strategy of UPA-monotherapy. In this session, I'm going to discuss about the strategy of UPA-monotherapy and real time RA evaluation by using MSKUS with our original summary under the treatment of UPA focused on both efficacy and safety including provisions for herpes zoster and malignancy.

### LS3

#### Recent Topics and Medication for Osteoporosis

Yukio Nakamura

Shinshu University School of Medicine

Conflict of interest: None

At present, approximately 12.5 million patients suffer from osteoporosis in Japan. The number of fragility fractures ensued from osteoporosis, especially those of the proximal femur, is increasing yearly and drastically reduces healthy life expectancy. Better prevention of osteoporosis and proximal femoral fractures is therefore urgently needed. The adequate intake of bone-related minerals and vitamins, including the three important nutrients for bones (calcium, vitamin D, and vitamin K), in addition to appropriate exercises and activities that stimulate bones are very important for preventing osteoporosis. I would like to discuss these bone-related minerals and vitamins as well as introduce our newly developed program, "Exercise to increase bone mineral density". Recently, such new osteoporosis drugs as denosumab, romosozumab, teriparatide, ibandronate, and minodronate have been approved in Japan. These advances have expanded the drug choices for osteoporosis and increased our knowledge on the relationships with lifestyle-related diseases and secondary osteoporosis. Our group has already reported on numerous cases of drug treatment in post-menopausal osteoporosis, pediatric osteopenia with multiple fractures, post-pregnancy osteoporosis, osteoporosis associated with dialysis and diabetes, and osteoporosis in super-elderly patients. In this lecture, I would like to cover the following points: 1. Recent topics in osteoporosis 2. Importance of nutrition and exercise for the skeleton and skeletal muscles 3. Various efforts to extend healthy life expectancy in Nagano Prefecture (measures against osteoporosis and locomotive syndrome, etc.) 4. Topics on the bones and teeth 5. Pharmacological treatments of osteoporosis based on the latest data from Shinshu University and its related hospitals It is my desire for us to carefully consider the importance and future directions of osteoporosis prevention together.

### LS4

#### Verify the efficacy and safety of tofacitinib again

Shigeto Tohma

President, National Hospital Organization, Tokyo National Hospital

Conflict of interest: None



Development in rheumatoid arthritis (RA) treatment are also evident in the NinJa registry analysis. In fact, the biggest contributors to that progress are the launch of biologics and JAK inhibitors. With the advent of these new anti-rheumatic drugs in addition to existing drugs, the expansion of treatment options has made it possible to aim for remission. In this seminar, I will introduce various medical information on patients with rheumatoid arthritis in the NinJa registry, as well as the administration status of JAK inhibitors. Furthermore, I will take up and verify efficacy and safety once again of tofacitinib, which first appeared as a JAK inhibitor and has accumulated various data. The anti-rheumatic effect of tofacitinib is undisputed, but in recent years the results of a large clinical study on the potential risk of MACE, thrombosis, and malignant disease in RA patients at risk for CV have been reported. Although it cannot be said to be definitive because some clinical research reports have different analysis results, it is necessary to continue to pay close attention to these potential risks. I think that the most reliable risk mitigation at this time is factor measures that have been shown to be involved in these adverse events. In other words, it is important to reduce the total risk by quitting smoking, good blood pressure control, correction of dyslipidemia, good diabetes control, etc., and to make an early diagnosis by regular examinations. As is common to all drug treatments, to make the proper use of JAK inhibitors more robust, we decided to use them while sharing the accumulated information on the efficacy / safety of the drug with patients. At the same time, appropriate follow-up after administration is required. Currently, JAK inhibitors have been introduced for a relatively short period of time, so medical economics or long-term safety are being questioned. However, I considered the efficacy and future potential of JAK inhibitors in the treatment of RA. At that time, I think there is no doubt that both the medical side and the patient side are expecting the possibility after fully understanding the characteristics and safety of this drug.

## LS5

### Updates of treatment strategy for microscopic polyangiitis and granulomatosis with polyangiitis

Masayoshi Harigai

Division of Rheumatology, Department of Internal Medicine, Tokyo Women's Medical University School of Medicine

Conflict of interest: Yes

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) is characterized by the presence of antineutrophil cytoplasmic antibody (ANCA) in the sera of patients and various organ involvements due to damage to small vessels (i.e., capillaries, venules, and arterioles). Guidelines from Japan and overseas recommend combination of high-dose corticosteroid and either rituximab or cyclophosphamide as a standard remission induction therapy in patients with organ-threatening disease. The most important adverse drug reaction during remission induction therapy is infections and glucocorticoids are considered as a significant risk factor of infections. Glucocorticoids are also known as a risk factor of osteoporosis and cardiovascular events. Hence, a therapeutic regimen with reduced-doses of glucocorticoids or even glucocorticoid-free regimen have gathered strong attention and have been under development. Avacopan, a small molecule which specifically blocks binding of C5a and C5 receptor, has been approved in September 2021 for MPA and GPA in Japan. In the preclinical development program, avacopan ameliorated anti-myeloperoxidase antibody-induced necrotizing crescentic glomerulonephritis in mice (J Am Soc Nephrol 2014;25:225-31). In the phase 3 clinical trial, ADVOCATE, patients with active MPA or GPA received either 30 mg avacopan twice daily or prednisone on a tapering schedule in combination with rituximab or cyclophosphamide (followed by azathioprine). The trial met its two primary endpoints: avacopan showed non-inferiority to prednisone for achieving remission at week 26 (avacopan, 72.3%; prednisone, 70.1%;  $p < 0.001$  for non-inferiority) and superiority for maintaining remission at week 52 (65.7% for avacopan, 54.9% prednisone,  $p < 0.001$  for non-inferiority and  $p = 0.007$  for superiority) (N Engl J Med 2021;387:599-609). In this seminar, molecular targeted therapies for MPA and GPA will be reviewed and updates of treatment strategy for these diseases will be discussed.

## LS6-1

### Tocilizumab treatment in patients with rheumatoid arthritis

Shuji Asai

Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: Yes

The efficacy of tocilizumab (TCZ) has been demonstrated in monotherapy as well as with concomitant methotrexate (MTX) in patients with rheumatoid arthritis (RA). The SURPRISE study, a randomized controlled study conducted in Japan, demonstrated that combination therapy with TCZ plus MTX was more rapidly suppress inflammation than TCZ alone, providing superior prevention of joint destruction in RA patients. We previously reported that, in TCZ treatment, concomitant MTX use was associated with an increased remission rate in patients with high disease activity. Thus, concomitant MTX use is preferable at least until patients achieve treatment targets during treatment with TCZ, although TCZ monotherapy has been demonstrated to be effective. MTX is an important anchor drug for RA patients and is used alone (monotherapy) or in combination with targeted disease-modifying anti-rheumatic drugs. However, some patients discontinue MTX due to toxicity, including gastrointestinal symptoms. In addition, the use of MTX may lead to the development of adverse events such as pneumonia and cytopenia. Thus, de-escalation of MTX while maintaining a favorable disease activity state-a challenge in RA clinical research-may be beneficial from the perspective of reducing adverse events. We examined the possibility of discontinuing MTX in RA patients who maintained low disease activity with TCZ plus MTX combination therapy. Our study demonstrated that discontinuation of concomitant MTX is clinically feasible for maintaining low disease activity, and may be beneficial from the perspective of reducing gastrointestinal symptoms in RA patients treated with TCZ.

## LS6-2

### Safety conscious strategies for the treatment of Rheumatoid Arthritis (Latest evidence of tocilizumab)

Yukitaka Ueki

Rheumatology and Collagen Disease Center, Sasebo Chuo Hospital

Conflict of interest: Yes

IL-6 inhibitor therapy has been recommended as a first-line biologic agent in the 2013 European League Against Rheumatism (EULAR) Recommendation and the 2015 American College of Rheumatology (ACR) Guidelines, as well as anti-TNF inhibitors. The 2016 EULAR recommendation clearly states the superiority of IL-6 inhibitors in the absence of methotrexate (MTX) and other conventional anti-rheumatic drugs (csDMARDs), further increasing their importance. TCZ is unique in that, unlike other biologics, it does not require concomitant use of MTX to achieve its therapeutic effects. TCZ has become an important therapeutic option for pregnant women, patients with end-stage renal failure, and elderly patients with various complications, etc. TCZ is expected to play an even more important role in future rheumatoid arthritis treatment strategies for the aging population. In this article, we will introduce the evidences on TCZ obtained in our registry and report on the usefulness and safety of TCZ.

## LS7

### Pulmonary arterial hypertension associated with connective tissue diseases - a typical algorithm / atypical complexity -

Yuichiro Shirai

Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

Conflict of interest: Yes

Although connective tissue disease (CTD) can affect various organs, pulmonary arterial hypertension (PAH) is one of the most devastating organ involvements. Three selective pulmonary vasodilators have been developed for PAH, and their efficacy and safety have been verified in clinical trials. In addition, large-scale PAH registries such as REVEAL in the United States and ASPIRE in Europe were launched, and prognosis was

analyzed. The results showed that selective pulmonary vasodilators improve symptoms, exercise capacity, hemodynamics, and long-term prognosis in PAH patients. Based on these backgrounds, risk assessment and treatment algorithms have been proposed as the framework for PAH management. The former half of the treatment algorithm is the initial treatment. Once PAH is diagnosed, a risk assessment is performed, and if the risk is low or intermediate, upfront combination therapy with oral agents is recommended. Several clinical trials have recently been reported as evidence of initial upfront combination therapy. The AMBITION trial showed that the combination of tadalafil and ambrisentan reduced the risk of clinical worsening compared to each monotherapy. The OPTIMA trial showed that the combination of tadalafil and macitentan improved hemodynamics at follow-up compared to ones at baseline, particularly lowering pulmonary arterial pressure. Thus, the effectiveness of initial upfront combination therapy with PDE-5 inhibitors and endothelin receptor antagonists has been clarified. The latter half of the treatment algorithm is risk assessment at follow-up after initial treatment and treatment intensification if low risk is not reached. Regarding treatment intensification, a sub-analysis of the GRIPHON trial has shown the efficacy of adding selexipag to PAH patients with background therapy of PDE-5 inhibitors and endothelin receptor antagonists. In addition, a real-world data from Germany showed that add-on use of selexipag reduced pulmonary arterial pressure during follow-up. Recently, oral prostacyclin-pathway agents have been paying attention, and a consensus by experts has proposed clinical scenarios in which the agents are used in CTD-PAH. In this talk, I will introduce the evidence of clinical trials and data in clinical practice related to CTD-PAH and discuss optimal therapeutic strategy.

## LS8

### Biosimilars for the treatment of rheumatoid arthritis

Hiroaki Matsuno

Matsuno Clinic for Rheumatic Diseases

Conflict of interest: Yes

Since the advent of biological products as medications for rheumatoid arthritis (RA), dramatic progress has been made in RA treatment. The goal of the drugs existing prior to the introduction of biological products was to prevent exacerbation of RA and maintain the status quo. Biological products have allowed us to aim for various remission states (clinical, structural, functional, quality of life outcome, serological, and immunological etc.). However, the prices of biological products are prohibitive, such that not all patients with RA are able to afford treatments by these drugs. Biosimilars are drug products whose efficacy and safety have been experimentally and clinically proven to be equivalent to preceding biological products, and their prices are lower than those of the preceding drugs. Currently, the development and sale of biosimilars for treating RA are being promoted worldwide. This lecture meeting reviews the actual status of biosimilars for RA, provides new evidence of differences in adverse events in some cases where biosimilars are switched, regardless of appropriate efficacy, and describes the future prospects of biosimilars.

## LS9

### RA-ILD ~Approach from etiology to clinical care~

Yutaka Kawahito

Inflammation and Immunology, Kyoto Prefectural University of Medicine

Conflict of interest: Yes

The prognosis of rheumatoid arthritis (RA) has improved with the use of biologics and JAK inhibitors in addition to methotrexate, and the average age of RA, including those with elderly onset RA, is getting older. In addition to malignancies, cardiovascular events, and infections, which are frequent causes of death in the general adult population, interstitial lung disease (ILD) accounts for about 10% of deaths and is an important organ complication in prognosis. Connective tissue disease related interstitial pneumonia also occurs in diseases other than RA, but its etiology, mode of progression, and severity vary depending on the disease. The diagnosis, prognosis, and treatment of progressive fibrosing-ILD (PF-ILD), which accounts for about 30% of ILD in systemic sclerosis and RA, is a very important clinical issue for prognosis. It has been suggested that smoking, which is an environmental factor in the development of RA, and various

immunological phenomena in the lungs may contribute to the etiology of RA-ILD. There are several types of RA-ILD, including usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). The pathological findings of these ILDs show the presence of lymphoid follicles, suggesting that the progression of RA-ILD to PF-ILD may be due partly to the residual immune response in active RA. Although steroid and immunosuppressive agents have been the main treatment for RA-ILD, anti-fibrotic agents have recently been approved, and treatment to inhibit fibrosis progression has become possible. In this seminar, I will review the etiology of RA-ILD, risk factors for PF-ILD and its treatment, based on the evidence to date, and the management of RA-ILD in daily clinical practice.

## LS10

### Usefulness of measuring matrix metalloproteinase-3 (MMP-3) in patients with rheumatoid arthritis (RA)

Satoshi Ito

Department of Rheumatology, Niigata Rheumatic Center

Conflict of interest: Yes

MMP-3 is a proteinase which is secreted from fibroblasts, synovial cells, or chondrocytes. In RA patients, MMP-3 is produced by synovial cells and directly involved in the destruction of cartilage<sup>1)</sup>. Elevated MMP-3 level in RA patients predicts progression of joint destruction but the level decreases with successful drug treatment<sup>2-3)</sup>. MMP-3 dose not elevate in patients with OA, but elevates in patients with SLE, PsA, PMR, or glomerulonephritis<sup>4)</sup>. Careful judgement is required as MMP-3 elevates with steroid and with renal dysfunction<sup>4)</sup>. MMP-3 is a good marker of the effectiveness of IL-6 inhibitors while C-reactive protein and erythrocyte sedimentation rate are not<sup>5)</sup>. With MMP-3, we can estimate clinical remission (CR), normalization of the physical function, the effect of iguratimod when it is added on biological disease-modifying antirheumatic drugs, and the effectiveness of adalimumab and abatacept<sup>6-8)</sup>. We have reported that we were able to extend interval of intravenous tocilizumab (spacing) after achieving CR<sup>9)</sup>, and the normalization of MMP-3 could be a marker of spacing<sup>10)</sup>. We have also reported that MMP-3 is a good marker for differentiating the diagnosis of seronegative RA, non-specific arthritis or OA<sup>11)</sup>. When we set a high cut off index of MMP-3, we were also able to differentiate PsA or PMR in men<sup>11)</sup>. I will talk about the importance of measuring MMP-3 in the field of connective tissue disease and rheumatoid arthritis in this seminar. 1) Ribbens C, et al. Ann Rheum Dis 2002, 2) Hattori Y, et al. Mod Rheumatol 2017, 3) Umehura Y, et al. Rinsho Byori, 2015 (in Japanese), 4) Yamanaka H, et al. Arthritis Rheum 2000, 5) Hattori Y, et al. Mod Rheumatol 2018, 6) Funahashi K, et al. Mod Rheumatol 2009, 7) Tocai N, et al. PLOS one 2018, 8) Hattori Y, et al. Mod Rheumatol 2017, 9) Takemoto T, et al. Clin Exp Rheumatol 2020, 10) Ito S et al., J Chubu Rheum Assoc 2016 (in Japanese), 11) Ito S. JCR2017, 12) Kurosawa Y, et al. JCR 2020

## LS11-1

### The role of shared-decision making on choosing appropriate medications-Reports from Web-based survey-

Mitsumasa Kishimoto

Department of Nephrology and Rheumatology, Kyorin University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

Shared decision making (SDM) is a collaborative process through which a clinician supports a patient to make decisions that are right for them. Although the proportion of patients with rheumatoid arthritis (RA) using biologic disease-modifying antirheumatic drugs (bDMARDs) has increased steadily, the relationship between patient background and preference for bDMARDs has not been fully investigated. We conducted a web-based questionnaire survey among patients aged >20 years with RA receiving bDMARDs. Participants were recruited through an internet research company in Japan. Study endpoints included factors affecting the preferred bDMARD treatment mode, namely in-hospital intravenous infusion (infusion), in-hospital subcutaneous injection (in-hospital injection), or self-administered subcutaneous injection (self-injection), and discrepancies between the current and preferred treatment mode. Of the 400 pa-

tients surveyed for preferred treatment mode, 15.3% preferred infusion, 18.0% preferred in-hospital injection, and 66.8% preferred self-injection. A preference for infusion (odds ratio [OR]: 2.218 and 6.165) and in-hospital injection (OR: 4.735 and 6.026) vs. self-injection was significantly associated with higher current frequency of hospital visits and anxiety or other hurdles related to self-injection. Flexible administration setting was significantly associated with a preference for self-injection vs. infusion (OR: 0.401) and vs. in-hospital injection (OR: 0.445). Further, age (<40 years vs. > 60 years) was significantly associated with a preference for self-injection vs. in-hospital injection (OR: 0.120). Many patients reported no discrepancy between their current and preferred treatment mode (patients receiving infusion, 68.0%; in-hospital injection, 71.2%; and self-injection, 94.0%). However, over 90% of patients responded that they would change their current mode in the future following a recommendation by a medical professional, aging or a change in RA symptoms. This web-based survey showed that patient preference for bDMARD treatment mode was significantly associated with age, frequency of hospital visits, flexible administration setting, and anxiety or other hurdles to self-injection. Changes in patient background which affect the preferred treatment mode should be considered in shared-decision-making process for RA therapy especially with bDMARDs.

## LS11-2

### Multidisciplinary management for patients with rheumatoid arthritis to maintain good QOL in the long term

Isao Matsushita

Department of Rehabilitation Medicine, Kanazawa Medical University, Ishikawa, Japan

Conflict of interest: Yes

In recent years, drug treatment of rheumatoid arthritis (RA) has rapidly progressed, and it has become possible to achieve comprehensive remission, but it is necessary to implement multidisciplinary management in order to maintain a good QOL over the long term. Although early pharmacological intervention and tight control are the main principles of RA management, a certain percentage of RA patients still suffer from progressive joint damage. In addition, with the aging of patients, osteoarthritis may also occur, resulting in functional disability. According to the algorithm for non-pharmacological and surgical treatment in the Rheumatoid Arthritis Clinical Practice Guidelines 2020, conservative treatment such as orthosis, lifestyle guidance, and joint injections are recommended when joint dysfunction is confirmed. Surgical treatment is recommended in cases that are refractory to these conservative treatments. When functional impairment and deformity are severe, evidence-based surgery should be selected for each joint and performed at the appropriate timing. On the other hand, sarcopenia, a common complication of RA, is a major problem that progressively reduces the ADL and QOL of patients. There is a lot of evidence that exercise therapies improve HAQ and muscle strength as well as subjective assessment in patients with RA. In the Clinical Practice Guidelines 2020, exercise therapies are strongly recommended as a treatment method, with a high level of agreement of 8.50 (on a 9-point scale). Occupational therapies have also been shown to improve HAQ, AIMS-II, and grip strength, and are strongly recommended in the same way as exercise therapies in Guideline 2020 (Level of agreement: 8.50). Rehabilitation treatment is necessary when aiming to maintain a good QOL over the long term. In this lecture, I would like to discuss the multidisciplinary management of RA to maintain good ADL and QOL in the long term, presenting the recommendations and evidence.

## LS12

### Update on Rheumatoid Arthritis Treatment Strategy

Tsutomu Takeuchi

Keio University

Conflict of interest: Yes

The practice of rheumatoid arthritis (RA) has changed drastically in recent years, and this change was also the result of a reconsideration of the series of processes from diagnosis to treatment toward achieving goals, clinical remission, and improvement of outcome. The revision of the classification criteria and remission criteria, the development of treatment

strategy for achieving the target and the revision of the treatment guideline were carried out all at once. This was driven by innovative advances in therapeutic agents and the impact of biologics is significant. Then, oral JAK inhibitors appeared, and the therapeutic options to achieve the treatment target were further expanded. On the other hand, there are refractory RA that are difficult to achieve the treatment target. EULAR newly defined these populations as Difficult-to-treat rheumatoid arthritis (D2TRA). It is expected that appropriate treatment strategies will be further investigated in the future. There are currently 5 JAK inhibitors indicated for the treatment of RA in Japan, but upadacitinib (UPA) strongly inhibits JAK1 and exerts anti-inflammatory effects by inhibiting the signaling of cytokines involved in RA pathology. The Phase 3 SELECT Study evaluated the efficacy and safety of UPA in subjects with diverse background RA and demonstrated the benefit of UPA in combination with csDMARD including MTX, or as monotherapy. In addition, UPA is the only JAK inhibitor that has been directly compared to biologics in different patient backgrounds (in patients with an inadequate response to MTX or biologics), and these results are of interest when considering the positioning of JAK inhibitors in the treatment of RA. As for safety, although the results of the pooled analysis of clinical studies revealed an increased risk of herpes zoster, etc., it is necessary to carefully consider the measures to be taken based on the results of all-case post-marketing surveillance in Japan in the future. In this seminar, we would like to discuss the clinical significance of UPA based on the latest evidence and the positioning of JAK inhibitors in RA treatment strategies.

## LS13-1

### A long-term strategy for treatment in patients with systemic lupus erythematosus -Utility of belimumab in remission induction therapy for active lupus nephritis-

Yoshiyuki Arinuma

Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Conflict of interest: None

Systemic lupus erythematosus (SLE) is one of the systemic and chronic autoimmune diseases characterized by the presence of autoantibodies based on excessive and abnormal autoimmunity. The disease activity of SLE is always fluctuating occasionally when severe organ damage is required for strong immunosuppression by corticosteroids (CS) with other immunosuppressants. Even though it is mild to moderate, we need to aim for "remission" or "low disease activity" as a treat to target and have to maintain them without flare-up continuously normalizing autoimmune disorders whole through patients' life. Conventionally, we have been controlling disease activity by repeatedly tapering and increasing CS with the combination of hydroxychloroquine and immunosuppressants. However, long-term use of these medicines can cumulatively cause organ damages in addition to those by SLE activity and can reduce the quality of life as well as prognosis in patients with SLE. Molecular-targeting therapy has brought a great advance even in the treatment of rheumatic diseases which play an important role to elucidate the pathogenesis of the diseases, and we have been able to aim remission without CS use as a realistic goal which is bringing paradigm shift even in SLE treatment. BLISS-NEA demonstrated the scientific evidence that belimumab (BEL) introduction can certainly reduce disease activity and can taper CS, especially in patients during the maintenance phase without activity in major organs. These results are very important in terms of reducing long-term organ damages in patients receiving conventional maintenance therapy. Besides, BLISS-LN indicated the possibility of BEL for improving renal prognosis in patients with active lupus nephritis even by additional introduction on the standard of care during the remission induction phase. In the future, we hope the efficacy of BEL on use for inception cases or newly caused organ damage as primary medicine. In this seminar, I would like to present management for long-term prevention in organ damages in patients with SLE and summarize the results from BLISS-LN, referring to our data.

## LS13-2

### The role of belimumab in the treatment of Systemic lupus erythematosus based on the current evidence

Yusuke Miyazaki

The First Department of Internal Medicine, School of Medicine, Universi-



Conflict of interest: Yes

Systemic lupus erythematosus (SLE) treatment involves glucocorticoid (GC) therapy with various immunosuppressive drugs. The initial GC dose and selection of immunosuppressive drugs are based on several factors, including SLE disease activity, presence or absence of major organ involvement, and complications. However, these drugs are nonspecific, and their long-term use can increase the risk of organ damage and adversely affect the quality of life and prognosis of patients. Belimumab (BEL) is a fully human monoclonal antibody against B-cell activating factor, which is a member of the tumor necrosis factor family (BAFF). BEL was the first biologic approved for SLE treatment, but it may result in its own clinical effects given that BEL inhibits autoreactive B-cell survival. Based on studies examining the efficacy, safety and preventing the progression of organ damage of BEL in patients with SLE, BEL is recommended for patients with SLE with moderate disease activity on standard therapy according to the 2019 update of the European League Against Rheumatism (EULAR) recommendations for SLE management. However, the long-term efficacy and safety of BEL in patients with SLE in the real-life clinical setting remain unclear. According to the treat-to-target strategy for SLE, 'lupus maintenance treatment should aim for the lowest GC dosage needed to control disease, and if possible, GCs should be withdrawn completely'. In real-world clinical practice, reducing or discontinuing drugs in patients with SLE can be challenging. From the LOOPS registry, a database of SLE patients in our department, we will analyze the long-term efficacy and safety of BEL in clinical practice. In addition, we will determine which SLE patients have the potential for GC dose reduction or discontinuation, and investigate the optimal patient profile for BEL in the treatment of SLE.

## LS14-1

### The pathophysiology and treatment of osteoporosis in patients with rheumatoid arthritis

Tadashi Okano

Department of Orthopedics, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

Conflict of interest: None

It is well known that patients with rheumatoid arthritis (RA) are more likely to have osteoporosis. The cause is related to the disease activity of RA, the decrease in physical activity associated with joint destruction, the postmenopausal osteoporosis, and the use of steroids. Since RA is a disease that causes joint destruction, it is not difficult to imagine that osteoclasts are activated locally in the joints, but it has a great effect on bone metabolism not only joints but also whole body. Inflammatory cytokines and osteoclast activation are closely related, and it is possible that controlling inflammation and disease activity may be effective for osteoporosis in RA. The control of disease activity in RA has improved dramatically. Controlling the disease activity can be prevented the decrease of bone density, but it cannot be expected to significantly increase bone density. Therefore, for osteoporosis associated with RA, it is necessary to use therapeutic drugs for osteoporosis in combination with anti-rheumatic drugs. To date, the concept of difficult to treat RA, in which disease activity cannot be well controlled, has been proposed, and the definition of difficult to treat RA includes the patients that glucocorticoid cannot be reduced. It is well known that glucocorticoid use is a risk factor for osteoporosis, but since osteoporosis due to glucocorticoid is also associated with deterioration of bone quality that cannot be evaluated by bone density. It is necessary to evaluate the risk by using the scoring in the management and treatment guidelines for glucocorticoid-induced osteoporosis and use appropriate osteoporosis therapeutic drugs in RA patients with glucocorticoid use. RA cannot be cured, so it is necessary to continue treatment, and it is also necessary to continue treatment for osteoporosis. In this session, the pathophysiology, and the points of treatment strategies for osteoporosis in RA.

## LS14-2

### The mechanisms and countermeasure of bone and joint destruction associated with rheumatoid arthritis -the significance of regulating RANKL-

Kosuke Ebina<sup>1</sup>, Makoto Hirao<sup>2</sup>, Yuki Etani<sup>2</sup>, Seiji Okada<sup>2</sup>

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is associated with increased bone turnover and early bone loss, which lead to increased fracture risk and progressive joint destruction. Pro-inflammatory cytokines, such as IL (interleukin)-17, TNF- $\alpha$  (tumor necrosis factor alpha), IL-1, and IL-6 induce the expression of RANKL (receptor activation of nuclear factor  $\kappa$ B ligand) from synovial fibroblasts. RANKL promotes osteoclasts differentiation and activation. According to the arrival of various new osteoporosis therapeutic agents (anti-bone resorption, bone anabolic, and dual effect agents), it is of great interest to investigate effective osteoporosis treatment strategy to prevent both fracture and joint destruction progression. In this lecture, I would like to review the past evidences and discuss about the significance of regulating RANKL in the treatment of RA.

## LS15-1

### How to treat elderly-onset rheumatoid arthritis?

Masataka Kuwana

Department of Allergy and Rheumatology, Nippon Medical School

Conflict of interest: Yes

Management of rheumatoid arthritis (RA) has made great strides in the last 20 years. A therapeutic strategy to prevent the progression of joint destruction and to maintain functional ability has been established by aiming for remission by early diagnosis and intervention. On the other hand, a term "difficult-to-treat RA" has drawn attention recently, and one of the factors contributing to this condition is age-related comorbidities that prevent treatment intensification. The age of RA onset has been getting older, and its speed is prominent in Japan. RA patients who developed the disease over the age of 60 are regarded as elderly-onset RA (EORA), which occurs in the acute to subacute course with involvement of large joints and impaired activity of daily living. The current treatment strategy of RA is to intervene promptly before joint destruction occurs and to adjust the treatment frequently. However, in the elderly, it is often difficult to pursue treat-to-target treatment algorithms due to impaired physiological functions, aging of immunity, and multiple complications. Sustained disease activity further promotes the frailty cycle, resulting in irreversible exercise incapacity, cognitive decline, and susceptibility to infection. Therefore, EORA is a "medical emergency", and its treatment is an extremely difficult mission to complete. Challenges to treat EORA include which DMARDs to be selected as an initial treatment, whether corticosteroids should or should not be used, how to maintain drug adherence, and how to manage risks for major cardiovascular events and malignancy that are common in the elderly. This lecture features relevant topics in the treatment strategy of EORA, which is an urgent issue.

## LS15-2

### Treatment strategy for elderly-onset rheumatoid arthritis

Motomu Hashimoto

Department of Clinical Immunology, Graduate School of Medicine, Osaka Metropolitan University

Conflict of interest: Yes

With the aging of the society, elderly-onset RA (EORA) is increasing. EORA develops rapidly with the highly inflammatory states. Earlier reports suggested that bone erosions do not progress in EORA compared with young onset RA (YORA). However, recent real-world evidences revealed that bone erosions progress more rapidly in EORA than in YORA. IL-6 signaling is involved with both the highly inflammatory state and the rapid progress of bone erosions in EORA. Therefore, IL-6 inhibiting therapies are suitable for the treatment of EORA. In the real-world data from the ANSWER cohort, drug retention rates of IL-6 inhibitors were superior to TNF inhibitors in EORA. Thus, IL-6 inhibiting therapies will be a good treatment option for EORA in place of glucocorticoids, which is the most frequently used drugs for EORA. In this seminar, the treatment strategy for EORA will be discussed including the efficacy of IL-6 inhibiting therapies.



## LS16-1

### Etanercept Clickwise- Aiming for rheumatic care that meets patient needs

Mie Fusama

School of Nursing, Takarazuka University

Conflict of interest: Yes

Biologic agents via subcutaneous self-injection for patients with rheumatoid arthritis (RA) has been used in Japan. However, challenges for adoption of self-injection, such as “fear of needles”, “fear of incorrect administration”, and “difficulty in using self-injection devices”, still remain. Many of these concerns can lead to a lack of patient self-confidence and adversely affect adherence. These are also thought to be addressed or mitigated by improvement of injection device [1]. The characteristics of the device that patients consider most important include “use without assistance”, “ease of administration”, “ease of operation”, and “ease of grip” [1]. Since Etanercept was approved in Japan in 2008 as a vial formulation for subcutaneous injection, the device has been improved as syringe and pen formulations. Furthermore, in view of patient needs, Clickwise, an automated device, has been developed to solve unmet needs and to administer drugs more appropriately. Its features are; simple injection procedure using the included display, ergonomic easy-to-grip shape, invisible needle design, no need to pinch the skin during injection, speed selection function during drug injection, injection history and injection schedule setting, and more compact size, etc. As for the operation, when the syringe is adhered to the skin, the liquid crystal display displays “press button”, so that the patient can easily confirm the adhesion to the skin. Once the injection button is pressed, the patient can monitor the injection status of the drug solution on the display, and, at the end, the message “remove from the skin” appears. So, even patients who are not confident in their self-injection skills can accurately inject while following the procedure and checking the status. In addition, patients can adjust the injection speed of the drug solution in 3 steps, probably leading to reduction of the drug injection pain. Clickwise may be used for patients who could not be introduced to conventional devices, and since the procedure is displayed, it can be expected to shorten the self-injection instruction time from medical professionals. Introduction of Clickwise will enable patients with RA to use etanercept self-injection more smoothly, probably leading to improvement of adherence and QOL.

## LS16-2

### Impact of Etanercept on RA Treatment ~Along with 17 years of history of Etanercept~

Eiichi Tanaka

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Conflict of interest: Yes

The introduction of biological DMARDs (bDMARDs) has resulted in significant advances in treatment strategies for rheumatoid arthritis (RA). Achieving and maintaining clinical remission is a realistic therapeutic goal and “Beyond remission” is being considered as a treatment strategy. These advances in the treatment of RA have not been made instantaneously, but are based on accumulating solid evidences step-by-step from daily practice. Etanercept (ETN), a bDMARD approved in Japan in 2005, has played a central role in RA treatment for the past 17 years. ETN is the first drug designated for the Japanese National Health Insurance system to pay for the guidance and management fee for self-injection at home, and DAS28 as disease activity score was used in a post-marketing surveillance for the first time. A review of the abundant evidence of ETN accumulated reveals that the treatment with ETN has evolved with changes in the treatment of RA. The TEMPO study (2004) evaluated the efficacy of ETN and MTX used in combination. The JESMR study (2010), the JERA study (2013), and the ENCOURAGE study (2015) have provided important evidence from Japan. As represented by the PRESERVE study (2013) and the SEAM-RA study (2020), there is an increasing number of reports focusing on “Beyond remission” treatment strategies. In 2021, an electronic new autoinjector for ETN, named “CLICWISE” was approved. CLICWISE may have functions that meet previously unmet needs. I believe that knowing the history of ETN, a bDMARD that has had a significant influence on the RA treatment, is useful in considering future medical care and pursuing research. In this seminar, I would like to explain the impact of ETN on RA

treatment with their history.

## LS17-1

### Potential of baricitinib for the treatment of rheumatoid arthritis

Shuji Asai

Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: Yes

The goals of rheumatoid arthritis (RA) treatment are to prevent structural joint damage and normalize physical function by achieving and sustaining clinical remission. Patient global assessment (PGA) is a major limiting factor for achieving clinical remission. Thus, adequate improvement of patient-reported outcomes (PRO), including PGA, is one of the unmet needs in current RA treatment. Baricitinib, a selective Janus kinase (JAK) 1 and JAK2 inhibitor, inhibits the signaling of multiple JAK-dependent cytokines including IL-6, IFN- $\gamma$ , and GM-CSF. In RA-BEAM, baricitinib was associated with significant clinical improvements compared to adalimumab in patients with RA who showed inadequate response to methotrexate. In particular, significantly greater improvements were found in pain and PGA as well as serum CRP levels, an objective marker of inflammation, in patients treated with baricitinib relative to those treated with adalimumab. These results raised the question as to whether baricitinib improves PRO solely via its effects on inflammation. In RA-BEAM, patients treated with baricitinib tended to demonstrate consistent pain relief independent of levels of inflammation control. Moreover, our study based on data from a multicenter registry showed significant decreases in PGA in patients treated with baricitinib who did not achieve adequate inflammation improvement. These findings suggest that the superiority of baricitinib over biologics in improving PRO cannot be solely attributed to differential effects on inflammation. The 2020 update of the JCR clinical practice guidelines for the management of RA recommends if the treatment target is not achieved with methotrexate treatment, addition of a biologic or a JAK inhibitor; current practice would be to start a biologic because of the long-term experience compared with JAK inhibitors. Long-term safety data of JAK inhibitors are awaited, especially regarding cardiovascular events and malignancies.

## LS17-2

### Therapeutic strategy for rheumatoid arthritis with chronic kidney disease

Hironari Hanaoka

Keio University School of Medicine

Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects joints, but also involves extra-articular organs. Approximately one-fourth of patients with RA develop chronic kidney disease (CKD), a higher rate than that of healthy individuals. The causes of kidney diseases in RA vary, but most cases can be categorized into two types: chronic inflammation, including secondary renal atherosclerosis and amyloidosis, and drug-induced kidney diseases. Since it is difficult to increase the dose of methotrexate in RA patients with CKD for its toxicity, adding other disease-modifying anti-rheumatic drugs is sometimes necessary in clinical settings. Since a number of studies have addressed CKD is one of the risk factors for severe infection, careful attention needs to be paid for preventing CKD progression in clinical practice of RA. Janus kinases (JAKs) are multidomain non-receptor tyrosine kinases that have pivotal roles in cellular signal transduction. The targeting of JAK-associated pathways through the use of JAK inhibitors has rapidly entered the clinical arena for a wide array of disease states, including RA. Often, JAK inhibitors are combined with background methotrexate, but some trials evaluated monotherapy and additional studies have been done in patients previously untreated with methotrexate. Since most of the patients with CKD could not take high dose of methotrexate because of the safety issue, monotherapy of JAK inhibitors is one of the ideal therapeutic strategies. Furthermore, JAK inhibitor which is mostly eliminated by glomerular filtration or kidney tubule active transportation needs to be avoided for patients with renal impairment. Therefore, JAK inhibitors which was verified for efficacy and safety for dose reduction of methotrexate and JAK inhib-

itor should be selected for such cases. Here, we discuss therapeutic strategy and positioning of JAK inhibitors for RA patients with CKD.

## LS18

### Drug treatment and safety measures for refractory RA

Hiroki Takahashi

Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan

Conflict of interest: Yes

The therapeutic goal of rheumatoid arthritis (RA) is to improve and normalize the patient's quality of life. Surrogate markers in daily clinical practice are composite measures reflecting disease activity to achieve tight control. To achieve and maintain clinical remission is the current treatment strategy for RA according to Treat to Target (T2T). Because many molecular targeted drugs (MTD) such as TNF inhibitors have been clinically introduced since the 21st century, and drugs with different mechanisms of action (MOA) have become available, T2T has become a realistic goal for RA treatment. The impression that arthritis control is getting feasible compared to the past seems to be the consensus of rheumatologists involved in RA treatment. However, most of MTD that suppress synovitis could manipulate immune system in the human body, tight control of RA using these drugs is often concerned about the induction and exacerbation of infection and malignant diseases, and it is necessary to consider the balance between risks and benefits for selecting MDA carefully. On the other hand, when MDA such as biologics could not be applied for economic reasons, administration of glucocorticoids have to be selected due to limited treatment options, and complications such as infections are often experienced. In recent years, the concept of difficult to treat RA (D2T RA) whose disease activity cannot be controlled by using two or more MDA has been proposed, and intervention for D2T RA is an urgent issue. However, the actual problem in daily practice is how to deal with refractory RA at the level before D2T RA, where MDA cannot be introduced due to comorbidities such as interstitial lung disease or socioeconomic reasons. Considering these circumstances, I would like to explain that rheumatologists must pay attention to the safe and effective use of anti-rheumatic drugs including MDA and the devices that can be used in daily clinical practice.

## LS19

### Toward heavy-boned treatment for osteoporosis: Better drugs for initial and sequential treatment

Yuji Hirano

Rheumatology, Toyohashi Municipal Hospital

Conflict of interest: Yes

Osteoporosis (OP) is a pathological condition in which fracture risk is increased because of low bone strength. There are two kinds of OP- primary OP and secondary OP. Rheumatologists encounter many kinds of OP, including glucocorticoid-induced OP, OP concomitant with rheumatoid arthritis, and OP due to hyperparathyroidism; thus, it is important for rheumatologists to understand these various types of OP. An update of the American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guideline for the Diagnosis and Treatment of Postmenopausal OP was published in 2020. According to this guideline, the risk of fracture should be evaluated after a diagnosis, and base treatment consists of correction of Ca/vitamin D deficiency along with education on lifestyle measures, fall prevention, and risks of medication. The initially recommended medications for high-risk patients are alendronate, risedronate zoledronate (ZOL), and denosumab (DMB). Abaloparatide, DMB, romosozumab (ROMO), teriparatide (TPD), and ZOL are recommended for very-high-risk patients. Although the aims of OP treatment are a T-score >-2.5 or a risk reduction of fracture (as measured by the FRAX) according to goal-directed treatment, the aim of using the T-score in clinical practice is realistic. Even though a continuous increase in BMD is necessary to achieve the goal, effective sequential treatment is required, as it is difficult to achieve the treatment goal using a single drug. The efficacy of bisphosphonate (BP) reached the ceiling several years ago. However, there are many options for sequential treatment after BP, including DMB, TPD, and ROMO. This is one reason why BP is the preferred

initial drug for OP. DMB or BP can be recommended after TPD or ROMO. The most preferable drugs after DMB remain a challenging problem. Several studies have examined ZOL, the strongest BP, for use after DMB.

## LS20-1

### Possibility of IL-23 inhibitor treatment for arthritis coexisting with skin diseases

Shigeyoshi Tsuji

Department of Orthopedic Surgery, Nippon Life Hospital, Osaka, Japan

Conflict of interest: Yes

A representative of arthritis coexisting with skin diseases is psoriatic arthritis (PsA). psoriasis is a typical disease of inflammatory keratosis, which occurs in 0.34% in Japan. PsA, which is characterized by arthritis, spondylitis, dactylitis, and enthesitis, develops in about 10 to 15% of psoriasis and is associated with metabolic syndrome (obesity 26%, hyperuricemia 43.9%, diabetes 15.1%, compared to psoriasis alone). Hyperuricemia 20.9%, hypertension 23.2%, hepatic enzyme abnormality 29.2%) are common, and it is new to remember that comorbidities and related conditions have been added to the GRAPPA 2021 guidelines. Another important point is that about 30% of psoriatic arthritis is associated with spondylitis, which, without early and appropriate intervention, causes ankylosis and significantly impairs the patient's quality of life. Is that there is a possibility of doing. Another skin condition you should be aware of is Palmoplantar pustulosis (PPP). PPP caused by focal infection occurs in 0.12% in Japan. About 10 to 40% of PPPs develop arthritis/enthesitis centered on the anterior chest wall, which is called PAO (Pustulotic arthro-osteitis) or Sonozaki disease. The principle of treatment for PPP is a therapeutic approach to the appropriate lesion by searching for the focal lesion (dental lesion, focal tonsil, etc.). Drug treatment is recommended if clinical symptoms persist after-treatment of the focal infection. In 2010, bDMARD became covered by insurance in Japan for psoriasis and PsA. As a result, psoriasis / PsA treatment has changed dramatically and has contributed to improving the QOL of patients. In addition, in 2018, Tremfya, a human anti-IL-23p19 monoclonal antibody preparation, was added to psoriasis and PPP for insurance coverage. In this talk, I would like to talk about the positioning and potential of Tremfya for arthritis coexisting with psoriasis and PPP from an orthopedic perspective.

## LS20-2

### Significance and Potential of IL-23 in Psoriatic Arthritis from a Dermatologist's Perspective

Yukari Okubo

Dermatology, Tokyo Medical University

Conflict of interest: Yes

Psoriasis is a chronic and refractory inflammatory skin disease characterized by erythema, infiltration, thickening, and scaling. The prevalence of psoriasis is reported to be 0.34% in Japan. Psoriatic arthritis (PsA) is reported to occur in 6-34% of patients with psoriasis, and early diagnosis and treatment are required because PsA causes irreversible joint destruction with functional disability, and patients experience severe pain that interferes with daily life. It has been suggested that activation of T cells and type 3 innate lymphocytes by IL-23 may promote inflammation, bone formation, and remodeling in the pathogenesis of PsA. The clinical manifestations of PsA include 60% of cases preceded by skin symptoms, 20% preceded by joint symptoms, and 20% coincidental cases. Predictors of PsA in cases preceded by skin symptoms include nail, scalp, buttocks/perianal area, and umbilicus. PsA is also classification of peripheral spondyloarthritis, which is characterized by adhesions and phalanges, and is caused by mechanical stimulation of the adhesions and an immune response via activation of IL-23. In addition, proliferation of mesenchymal stem cells and differentiation of osteoblasts are induced, resulting in osteogenesis. Although TNF inhibitors are recommended as the first-line treatment for PsA according to national and international guidelines, IL-17 and IL-23 inhibitors have also been recommended in recent years. In addition, oral JAK inhibitors have been approved, increasing the number of treatment options. In this session, we will introduce the approach to PsA from the perspective of a dermatologist.

## LS21-1

### Treatment strategies for women of child-bearing age (WoCBA) RA patients

Kensuke Oryoji

Center for Rheumatic Diseases, Matsuyama Red Cross Hospital

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by polyarthritis. It has been reported that the fibroblast-like synovocytes (FLS) in the synovium can be modified in various ways to become hyperplastic, multilayered, and refractory if appropriate treatment is delayed. In such in the synovium, secondary lymphoid tissue-like education of lymphocytes occurs locally, and cytokines such as IL-7 and IL-15 are released from the hyperplastic FLS. In the presence of high levels of IL-7 and IL-15, abatacept, a CTLA-4 Ig, has been reported to be insufficient in its role of regulating T cells. In the early stages of RA, it is advisable to treat the disease intensively before synovial hyperplasia develops. Once RA is diagnosed, methotrexate (MTX) should be started as soon as possible unless there are contraindications, which is in line with the EULAR recommendation 2019 update and the 2020 edition of the Japanese Rheumatoid Arthritis Treatment Guidelines. However, the placebo arm of the C-OPERA trial, which included all patients with anti-CCP antibody-positive RA, showed that the proportion of patients who achieved SDAI remission with the upper limit of MTX alone was about 30%. On the other hand, in the main arm of this study, MTX and certolizumab pegol (CZP) was used from the beginning, and the percentage of SDAI remission reached 60% in this arm. This means that 30% of patients with positive anti-CCP antibody, which is one of the poor prognostic factors of RA, require TNF inhibition in addition to MTX from the beginning. In this lecture, I will outline the importance of early remission with TNF inhibitors in the clinical practice of WoCBA RA, and the need to consider remission induction therapy separately from remission maintenance therapy.

## LS21-2

### The characteristic of WoCBA-RA and importance of the induction and maintenance of remission

Isao Matsumoto

Division of Rheumatology, Department of Internal Medicine, University of Tsukuba

Conflict of interest: Yes

The treatment strategy mainly focusing on the pregnancy and delivery management are highlighted on older age of the pregnancy in the rheumatoid arthritis (RA). It is reported that it tends to be hard to become pregnant within high disease activity in RA, but there is the teratogenicity in methotrexate which is anchor drug of the treatment, and the JAK inhibitor is contraindicated in a pregnant woman. Thus, it is necessary to consider discontinuation of these drugs after remission induction, or start with other treatment without using them. Beneficial cast with biologics, shared decision making is necessary for the benefit to give biologics during the pregnancy exceed a disadvantage. In addition, the TNF inhibitor shifts to a fetus to a child born, and attention is necessary at inoculation time of the live vaccine, but certolizumab pegol (CZP) and etanercept are proved that there are few shifts to a fetus. In this seminar, I will explain the knowledge of RA condition of a patient within pregnancy period, and gather up the basic characteristic of CZP and characteristic of the biologics through the compact MRI in our example in the joint local site.

## LS22

### We have to understand the importance of MTX as an anchor drug

Toshiaki Miyamoto

Rheumatology, Seirei Hamamatsu General Hospital

Conflict of interest: Yes

RA is a systemic chronic inflammatory autoimmune disease of unknown cause with the joint synovium. Previously, the treatment goal of RA was short-term QOL improvement (care). However, with the advent of bDMARD represented by TNF inhibitors in addition to methotrexate (MTX), long-term improvement (cure) such as completely stopping the

progression of joint destruction, dysfunction and improving the prognosis of life has become achievable. Treatment strategies are also advancing to achieve such treatment goals, and treatment strategies based on treat to target (T2T) are absolutely necessary. Anti-rheumatic drugs are used to control the disease activity of RA patients. Anti-rheumatic drugs are classified into sDMARD represented by MTX, bDMARD represented by TNFi, and tsDMARD represented by JAKi. The treatment algorithm in the Rheumatoid Arthritis Guideline 2020 states that when diagnosed with RA, the use of MTX should be considered immediately unless there are any contraindications. MTX has been its position as an anchor drug even in the era of bDMARD and tsDMARD. While various new drugs have appeared in recent years, position of MTX might be slightly neglected. I'll explain the significance of MTX and its best use. We will also discuss the possibility of MTX dose reduction after achieving the treatment goal. Although MTX has been an important drug in RA treatment, we need to be careful to minimize its adverse reactions. It is known that Japanese RA patients are getting elderly, and that the frequency of complications of LPD and interstitial pneumonia is higher than that in other countries. And we should consider contraindications, age, renal function and complications of patients. It is also necessary to decide starting dose, and timing of dose escalation corresponding to the individual patient. I'd like to explain the major adverse events of MTX that should be noted and measures for prevention in order to use safely and to maximize its efficacy.

## LS23-1

### Management of rapidly progressive interstitial lung disease associated with polymyositis/dermatomyositis

Masaru Kato

Rheumatology and Nephrology, Hokkaido University Hospital

Conflict of interest: Yes

Rapidly progressive interstitial lung disease is a fatal manifestation in patients with polymyositis/dermatomyositis. Testing for Anti-MDA5 antibodies and the combination therapy with glucocorticoids, tacrolimus and cyclophosphamide have improved its diagnosis, treatment and prognosis. However, there are still unmet needs in its management, such as cases refractory to intensive immunosuppressive therapy, opportunistic infections, development in anti-MDA5 negative cases. To avoid rapid progression, early administration of immunosuppressive therapy is sometimes prioritized over confirming autoantibodies in patients with hypomyopathic manifestations, vasculopathic rash (inverse Gottron's sign, purpura and ulcer), and specific chest CT findings (subpleural consolidation with contraction). By using whole-body MRI, we have demonstrated that myofascial-dominant involvement, compared to muscle inflammation, is a risk factor for developing rapidly progressive interstitial lung disease in patients with dermatomyositis (Karino K, et al. Rheumatology (Oxford) 2020). In this seminar, we introduce our recent works to improve the prognosis of rapidly progressive interstitial lung disease associated with polymyositis/dermatomyositis.

## LS23-2

### Pathogenesis and Treatment Strategies of Lupus Nephritis

Kunihiro Ichinose

Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: Yes

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease caused by immune abnormalities caused by T cells and B cells. Among them, lupus nephritis (LN) is complicated in 20-40% of SLE patients. For a long time, it has been recognized that LN is clinically unique among SLE and may develop even in the absence of systemic symptoms. From this point of view, both the 2019 EULAR (European Society of Rheumatology)/ACR (American College of Rheumatology) SLE classification criteria allow for classification as SLE when histological findings characteristic of LN and antinuclear antibodies or other autoantibodies are positive. The pathogenesis of LN involves a complex interaction of abnormally activated immune cells, renal localized cells, autoantibodies, and inflammatory mediator production. One of the mechanisms is that immune



complexes (ICs) derived from the necrotizing material released from apoptotic cells are deposited in the kidney, activating innate immune cells through the complement pathway, and forming neutrophil extracellular traps (NETs), which damage renal parenchymal cells. Although many cases of LN can be controlled with existing therapies, there are cases of poor response to treatment and relapse during maintenance. The goal of the treatment of LN is to maintain normal renal function in the long term. For this purpose, reliable induction of remission and prevention of relapse is essential. In Japan, biologics such as tacrolimus, mycophenolate mofetil, belimumab targeting B cell activation factor belonging to TNF, and hydroxychloroquine with immunomodulatory effects have been approved for the treatment of SLE and LN. They are expected to improve the life prognosis of SLE patients. However, even in patients receiving immunosuppressive therapy, chronic irreversible lesions have been observed in renal biopsies of LN patients. In treating LN, it will be necessary to optimize the balance of therapeutic risks and benefits, from treatment selection and timing to tapering and withdrawal. In this presentation, we will discuss the pathogenesis of LN and therapeutic strategies to achieve low disease activity and remission.

## LS24

### Hepatitis B Virus Reactivation during Immunosuppressive Therapies in Patients with Rheumatoid Diseases

Satoshi Mochida

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Conflict of interest: Yes

Liver injuries develop as a result of immune response against HBV, and clinical courses of patients with HBV infection are classified into immune tolerant, immune clearance and low proliferation stages, and a part of patients move to the remission stage in which serum HBs-antigen are undetectable. Thus, patients with previously resolved HBV (prHBV) infection are classified into those after transient HBV infection and HBV carriers at the remission stage. In these patients, liver injuries do not occur. During immunosuppressive therapies, however, minor HCV strains possibly showing active proliferation capacity may appear in the sera leading to development of liver injuries. The study group supported by the Ministry of Health, Labour and Welfare, revealed that the cumulative rate of HBV reactivation defined as serum HBV-DNA levels of 20 IU/mL or more was 3.2% at 6 months following the initiation/modification of immunosuppressive therapies, and HBV reactivation seldom developed then later. Thus, the Japanese guideline was revised in 2013 and serum HBV-DNA measurements are recommended to be done every month within 6 months following the initiation and/or modification of the therapies, but the duration of examinations can be prolonged up to 3 months then later. Considering economic issues, the study group is now conducting the prospective study to apply HBs-antigen measured by a high-sensitive method instead of HBV-DNA for monitoring of HBV reactivation. Also, the project to increase serum anti-HBs levels in patients with rheumatoid diseases by HBV vaccination has been on going. However, fatal cases with acute liver failure due to HBV reactivation were still enrolled in the nationwide survey by the study group until 2019. Enlightenment activity for HBV reactivation should be done in all field of clinical medicine including rheumatology and applied immunology.

## LS25-1

### Pathogenesis of rheumatoid arthritis induced by IL-6

Kunihiro Ichinose

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Conflict of interest: Yes

The pathogenesis of rheumatoid arthritis (RA) is thought to be a multi-step process. First, an interaction between genes and environmental factors disrupts tolerance to autoantigens, including citrullinated proteins generated by post-translational modifications. Second, this disruption of tolerance induces an immune response of antigen-specific T cells and B cells that contain citrullinated antigens. Then, starting with synovitis in the

joints, systemic inflammation is promoted by positive feedback. In this context, interleukin (IL)-6 plays a central role in the pathogenesis of rheumatoid arthritis. In immune cells, IL-6 promotes the differentiation of B cells into immunoglobulin-producing plasma cells and supports plasma cell survival. Plasmacytes and plasmablasts produce anti-citrulline protein antibodies. IL-6 stimulates the differentiation of naive CD4<sup>+</sup> T cells into Th17 and inhibits their differentiation into Treg cells, thereby shifting the Th17/Treg balance to Th17 dominance and promoting inflammation. IL-6 also induces the differentiation of follicular helper T cells (T<sub>fh</sub>) cells, necessary for B cell responses. Locally in the joint, IL-6 acts on vascular endothelial cells and induces vascular endothelial growth factor (VEGF), which directly or indirectly promotes vascular leakage, causing synovial effusion, joint swelling, and synovial proliferation. IL-6 also stimulates osteoblasts and synovial cells to produce receptor activators of NF- $\kappa$ B ligand (RANKL), which activates osteoclasts, causing osteoporosis and joint destruction. In terms of systemic manifestations, IL-6 rapidly induces the production of acute-phase proteins, C-reactive protein (CRP), serum amyloid A, complement C3, fibrinogen, hepcidin, and thrombopoietin, and decreases albumin and cytochrome p450. As a result, it causes systemic diseases such as secondary amyloidosis and cardiovascular events. IL-6 receptor inhibitors and JAK inhibitors are involved in IL-6 signaling. They have been shown to regulate systemic immune responses and inhibit bone destruction through modulation of the local joint, immune cell responses, and osteoclast-osteoblast signaling. In this talk, I would like to discuss the pathogenesis of rheumatoid arthritis through the local and systemic immune response to IL-6.

## LS25-2

### Current Status, Potential, and Expectations for IL-6 Receptor Inhibitors

Yuji Nozaki

Department of Hematology and Rheumatology, Kindai University Faculty of Medicine

Conflict of interest: Yes

It is widely accepted that the Cytokine Signaling Pathway in Rheumatoid Arthritis (RA) is upstream of Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and downstream of Interleukin (IL)-6. The idea of TNF- $\alpha$  as upstream and Interleukin (IL)-6 as downstream is widely accepted and is important when considering RA treatment strategies. However, there are many cases in daily practice in which IL-6 receptor inhibitors are effective in TNF- $\alpha$  naïve patients, and Cytokine Signaling Pathway is complicated by the influence of clinical and genetic factors such as age and gender. There is no one-size-fits-all treatment for RA. After RA diagnosis, methotrexate (MTX) is the first drug considered for initiation of treatment, but with the aging of RA and the aging of RA patients, dose adjustment is necessary for the reasons mentioned above. The therapeutic effect of MTX is enhanced when it is used in combination with all biologic agents (bDMARDs), and it should be used in bDMARDs therapy whenever possible. However, MTX dose reduction or withdrawal is often necessary when bDMARDs monotherapy is the only option. Among bDMARDs, anti-IL-6 receptor inhibitors have been reported to be effective in the absence of MTX, and I myself use them in my daily practice in patients without MTX. In recent years, real-world data have been reported mainly from various cohort studies, and the results are attracting attention. Sarilumab, the most recently approved anti-IL-6 receptor inhibitor, has been reported to be highly effective with or without MTX in real-world data, but the difference in best use between sarilumab and other bDMARDs or JAK inhibitors as a second anti-IL-6 receptor inhibitor has not yet been fully discussed. However, the difference in best use between bDMARDs and JAK inhibitors as second-line anti-IL-6 receptor inhibitors has not been fully discussed. In this presentation, we will discuss the challenges of RA treatment in Japan's aging population, the differences in patients suitable for anti-IL-6 receptor inhibitors and JAK inhibitors, and the current best use of the anti-IL-6 receptor inhibitor sarilumab for RA treatment, which is becoming clearer based on real-world data, as well as its potential and expectations in the future. Translated with [www. DeepL. com/Translator](http://www.DeepL.com/Translator) (free version)



## LS26

### Unmet Medical Needs and Further Progresses in Treatment for Rheumatoid Arthritis

Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan

Conflict of interest: Yes

Treatment for rheumatoid arthritis (RA) has evolved dramatically in the last two decades. Symptomatic therapy with steroids and NSAIDs was the primary treatment method in the 20th century. The advent of biologics and Janus kinase (JAK) inhibitors, which effectively suppresses immunological abnormalities, has led to the induction and maintenance of clinical remission and prevention of functional disability. On the other hand, the economic burden of such an expensive medicine has emerged and there are not a few patients with an inadequate response to the biologics and JAK inhibitors. To address the economic burden and unsatisfactory symptom management, new therapeutic strategies for effective usage of the evolutionary medicines are required in clinical practice. Specific issues for consideration include effective use of various drugs and research on tailor-made medicine, predictors of aggravation and poor prognosis. Furthermore, after inducing remission, maintaining safe and adequate treatment is required for a long period. Therefore, withdrawal, dose reduction, or spacing of expensive medicines after remission could lead to a reduction in medical costs. Another issue is how to respond to patients' dissatisfaction with medical treatment. For example, patients strongly want to eliminate their existing symptoms, whereas physicians tend to think that controlling structural damage to the joints is the most important treatment target. As a result, the patient's attitude about treatment may not always agree with the physicians. Especially, pain and fatigue, which are invisible and subjective expression, are often difficult to understand. To bridge this gap, it is important to scientifically evaluate patient-reported outcome and effectively use it in clinical trials and daily clinical practice. In this seminar, these unmet medical needs in RA treatment are reviewed. In the latter half of the seminar, further progresses in treatment for RA will be introduced.

## LS27-1

### Role of abatacept in the treatment of rheumatoid arthritis

Kimito Kawahata

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Conflict of interest: Yes

The involvement of the adaptive immune system as well as the innate immune system in the pathogenesis of rheumatoid arthritis has been clarified. Abatacept is a typical biological anti-rheumatic drug that targets this acquired immune system. Abatacept is a recombinant protein in which the extracellular domain of human CTLA-4 and the Fc portion of IgG1 are bound. Since CTLA-4 binds more strongly to CD80 / CD86 than to CD28, abatacept competitively inhibits the binding of CD28 and CD80 / CD86 in T cells. While it has the same clinical effectiveness as other biologics, the frequency of serious infections is considered to be slightly lower than that of other biologics and it can be used as monotherapy. In this luncheon seminar, its various basic and clinical aspects will be discussed.

## LS27-2

### Anti-modified protein antibodies in rheumatoid arthritis and their clinical significance

Takao Fujii

Department of Rheumatology and Clinical Immunology, Wakayama Medical University, Wakayama, Japan

Conflict of interest: Yes

In rheumatoid arthritis (RA), anti-citrullinated protein antibodies (ACPA) are not only important for their diagnosis and prediction of joint damage, but also may be associated with the efficacy of biological disease modifying anti-rheumatic drugs (Courvoisier DS, *et al. Rheumatology*, 2020). Recently, many reports regarding autoantibodies against post-translational modified proteins (anti-modified protein antibodies, AMPA) other

than ACPA, have been published. Anti-carbamylated protein antibody (Anti-CarP) is an autoantibody against a protein in which a lysine is replaced with a homocitrulline residue. It is found in 45% of RA and is positive even in 30% of ACPA-negative patients. Bone destruction may progress in such cases (Shi J, *et al. PNAS*, 2011). The combination measurement of rheumatoid factor, ACPA, and anti-CarP is useful for differentiating RA from other diseases and predicting the progression from pre-RA to RA (Verheul MK, *et al. A&R*, 2018). Notably, it is suggested that anti-CarP is associated with RA-interstitial lung disease (Castellanos-Moreira R, *et al. ARD*, 2020) and may define a different subset from ACPA-positive RA patients. In addition, anti-acetylated vimentin antibodies (Anti-AcVim) have been reported (Juarez M, *et al. ARD*, 2016). RA relapse is frequent in patients with a large number of these AMPA (Figueiredo CP, *et al. ARD*, 2017). There are still many unclear points about AMPA production mechanisms other than ACPA, and it is difficult to measure in daily practice. In addition, there are many types of modified antigens such as vimentin, fibrinogen, and  $\alpha$ -enolase. It is conceivable that their clinical immunological significance is different. In this lecture, clinical significance and the related T / B cells in association with AMPA in RA will be discussed.

## LS28

### Therapeutic strategy for elderly patients with rheumatoid arthritis

Hironari Hanaoka

Keio University School of Medicine

Conflict of interest: None

The number of elderly patients with rheumatoid arthritis (RA) is increasing as life expectancy increases, and new strategies are needed to optimize therapy in this population. Limited data are available regarding the treatment of RA in individuals aged 65 years and older due to age-based selection criteria or because such patients often have comorbidities, factors which restrict their inclusion in intervention studies. Furthermore, management of RA in elderly individuals is challenging owing to comorbidities and frailty, requires appropriate tailoring of the aggressiveness of the therapeutic approach. Frail patients and patients with comorbidities (including cardiovascular disease, cancer, infection) and associated polypharmacy might require a tailored approach to therapy. Most of the elderly patients have problems in drug metabolism includes decline in renal function and impaired digestion and absorption. Consequently, the half-life of drugs is prolonged, and the serum concentrations of drugs are maintained at a higher level as compared with that in younger patients. Therefore, frequent follow-up and close monitoring are needed, and drugs that do not interact with other drug metabolism are preferable in clinical settings. Peficitinib is a pan-JAK inhibitor that inhibits JAK1, JAK2, JAK3, and TYK2 and it primarily undergoes metabolism, but approximately 10% is excreted in the urine in the unchanged form. Additionally, the plasma concentration-time profile of peficitinib was similar between individuals with normal and impaired renal function. Therefore, peficitinib is one of the drugs which can be used in elderly patients with renal dysfunction. The guidance in Japan for dosing in adults recommends 150 mg orally once daily after a meal, which can be reduced to 100 mg once daily depending on the patient's condition. Here, we discuss therapeutic strategy for elderly RA patients.

## LS29-1

### Update on management of psoriatic arthritis

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Conflict of interest: Yes

Psoriatic arthritis (PsA) is associated with decreased quality of life. As delayed diagnosis may lead to progressive joint destruction and long-term disability, the key clinical features of PsA should be recognizable to a wide range of clinicians for early diagnosis. In addition to assessment and identification of skin and nail lesions, which occur in up to 85% of those with musculoskeletal manifestations, clinicians should be aware of both the peripheral and axial manifestations of musculoskeletal disease reviewed

here. Meticulous history-taking and physical examinations, and familiarity with appropriate imaging studies is often necessary to distinguish axial-PsA from other differential diagnoses. Swift diagnosis and treatment are necessary to control PsA disease, as well as mitigate the risks of the many associate comorbidities that may accompany it. In this session, at first, we aim to review the new information in PsA including T2T, co-morbidity, the clinical features of PsA especially focusing on Axial PsA. Secondly, the treatment guideline and recommendation for PsA is changing constantly with the advent of new therapies in the EULAR, ACR, and GRAPPA internationally, and I would introduce a current treatment strategy “T2T” and its limitation. Furthermore, therapeutic strategies of how to set the treatment target should be determined through a shared decision making between physicians and patients in consideration of the disease activity and the characteristics (presence or absence of complications) of each patient.

## LS29-2

### The state and issue of diagnosis/treatment in axial spondyloarthritis

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Conflict of interest: None

Axial spondyloarthritis (axSpA) encompasses both radiographic axSpA (r-axSpA), that is, ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA). The state and issue of diagnosis/treatment in axSpA is the followings: (1) epidemiology of axSpA, understanding of natural course from inflammatory back pain (IBP) to axSpA and pathogenesis. (2) even now delayed diagnosis, and significance and issue of early diagnosis. (3) point of early referral to specialist. (4) the diagnosis of axSpA relies on the recognition of a clinical pattern of the disease, based on clinical, laboratory and imaging features, but not by ASAS classification criteria. (5) significance and difficulty of differential diagnosis (DISH, OCI, SAPHO, infection and malignancy, etc), (6) reconfirm of treatment (1st line is NSAID and physiotherapy) is important, and initiation of biologics should be deliberated. (7) usual care vs. tight control care (from TICOSPA study) (8) possible drug withdrawal or tapering after clinical remission?, etc. In this section, we review these current states and would like to discuss future issues with rheumatologists.

## LS30-1

### The utility of Baricitinib focused on the inhibition of radiographic progression in RA-clinical setting ~The awareness of the novel phrase “Time is bone” for treatment strategy of RA~

Kenta Misaki

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Conflict of interest: Yes

The adaptation of Biologics (Bio) for RA has caused the paradigm shift, and it has also been approved under the medical insurance in Japan since 2003. Bio make it possible to improve the RA prognosis as a clinical remission, however we often encounter the cases unfortunately led to drastic radiographic destruction after achieving clinical remission, and those refractory to multiple Bio. It is suggested that good outcome is only brought to the RA patients triggered by particular cytokine as we expected because the target of Bio is just for one-focused cytokine. As it is still difficult to apply the RA-tailored medicine in clinical setting, the treatment of Bio sometimes causes poor cost-effective results and unexpected bone destruction during the Bio switching. JAK inhibitor (JAKi) induces the efficacy for RA under the mechanism of working in upper RA inflammatory pathway, inhibiting the multiple cytokine- signaling. JAKi has been also available in Japan since 2013, it is noteworthy JAKi was approved all the same time in all over the world. Five kinds of JAKi including Baricitinib (BAR) are now available and focused as one of the novel therapeutic strategies. Fortunately, JAKi is conditionally recommended as well as Bio in phase II strategy in Japanese RA-treatment guideline in 2020. RA-treatment strategy is not only the administration of Bio/JAKi, but also the achievement of sustained radiographic remission. One of the useful procedures for monitoring the RA disease activity is musculoskeletal ultrasound (MSKUS). Recently MSKUS is shared the spotlight as a pivotal non-inva-

sive examination tool as well as Bio/JAKi. The collaboration between MSKUS and Bio/JAKi will enable early diagnosis, early treatment induction, early achievement of remission and finally reduce various DMARDs. I'll introduce the utility of BAR and MSKUS, especially focused on the validation about radiographic outcomes of BAR in clinical trials with current topics and evidence in this session.

## LS30-2

### Therapeutic Strategies to Prevent Patients from Developing Difficult-to-treat Rheumatoid Arthritis: An Update on the Efficacy and Safety of Baricitinib

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Conflict of interest: Yes

Difficult-to-treat RA (D2T RA) refers to patients with RA whose disease activity is uncontrolled despite the use of two or more biologics or JAK inhibitors (b/tsDMARDs) with different mechanisms of action, accounting for 5-20% of all patients. Recent studies have shown that D2T RA is more common in seropositive patients with high disease activity and pulmonary involvement at baseline. It has also been reported that the time to initiation of b/tsDMARDs in D2T RA patients was significantly longer than that in non-D2T RA patients. Therefore, patients who are predicted to be D2T RA may require earlier therapeutic intervention with b/tsDMARDs. In the EULAR recommendations 2019 update, JAK inhibitors are endorsed as one of the therapeutic options in RA patients who show an inadequate response to MTX and exert their efficacy by inhibiting intracellular signaling of multiple inflammatory cytokines. Baricitinib, a JAK1 and JAK2 inhibitor, has been proven to be non-inferior and superior to adalimumab in the RA-BEAM study in terms of ACR20 after 12 weeks of treatment (Taylor PC, et al. N Engl J Med. 2017). In addition, baricitinib was also shown to improve patient-reported outcomes (PROs) and inhibit joint destruction. What is the optimal therapeutic strategy for preventing patients from developing D2T RA? And what should we do if patients are D2T RA? In this seminar, I will overview the latest reports on D2T RA and explain the role of JAK inhibitors in its prevention and treatment, including data from the ANSWER cohort. In addition, I will discuss the long-term safety of baricitinib, including an integrated analysis of clinical trials with a maximum of 9.3 years and a median of 4.6 years, as well as safety information on 4731 cases in Japan with fixed data up to 24 weeks after the start of treatment.

## LS31

### Challenge to Pulmonary Hypertension by Rheumatologists

Hideyuki Okada

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Conflict of interest: None

When pulmonary hypertension (PH) is found, can you immediately come up with a subsequent examination, treatment plans, prognosis for PH and drug side effects? We rheumatologists often encounter Group 1 pulmonary arterial hypertension (PAH). Diagnosis of PH is made by right heart catheterization (RHC). At present, the diagnosis criteria for PAH in Japan is that mean PAP  $\geq 25$  mmHg, mean PAWP  $\leq 15$  mmHg, PVR  $\geq 3$ WU. However, even if these criteria are met, it may be Group 3 PH associated with interstitial lung disease (ILD). Needless to say, connective tissue disease (CTD) often results in ILD. It is a characteristic of CTD-PH that it cannot be clearly declared as Group 1 PH like idiopathic PH. In CTD, not only ILD but also myocardial lesions, pericardial lesions and pulmonary thromboembolism may be complicated at the same time. All conditions occur and are complicated, including Group 2 due to left heart disease, Group 3 due to ILD, Group 4 due to CTEPH, and furthermore Group 5 due to chronic hemolytic anemia, etc. In this way, CTD-PH is often caused by multiple factors, it is difficult to make treatment plans such as selection of therapeutic drugs and administration orders. On the other hand, few rheumatologists will perform a RHC on their own to diagnosis PH. In many case, we have to ask a cardiologists for a RHC to diagnosis PH, not only the diagnosis, but also the restudy after treatment. Because

CTD presents with various symptoms, the contact point is not fixed, and sometimes department of oral surgery and ophthalmology are the contact points for the first visit. Furthermore, patients who develop symptoms of PH do not always go to a core hospital, but may go to a clinic responsible for community medical care. In order to receive appropriate medical care without delay and suffering any disadvantages for such patients, we rheumatologists need to work with doctors from multiple departments in the community and hospitals to treat PH on a daily basis.

## LS32

### Latest topics on EGPA

Yoshinori Komagata

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Conflict of interest: Yes

EGPA was defined by the 2012 International Chapel Hill Consensus Conference as “Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present”. In the conference, the name of the disease was also changed from Churg-Strauss syndrome. Most patients have adult-onset asthma or rhino-sinusitis, and it takes several years to develop EGPA after the onset of asthma. Severe eosinophilia causes peripheral neuropathy, cardiac and gastrointestinal diseases by infiltration of eosinophils. Thus, early diagnosis and early treatment are very important. Only one-third of the patients have ANCA, and their presence seems to differentiate between two phenotypes of EGPA, with different clinical characteristics, genetic background, and etiology. In Japan, Research Committee on Intractable Vasculitides of MHLW has released a new treatment guideline of EGPA in 2021. In patients with non-severe disease, they conditionally recommend GC only or plus cyclophosphamide for remission induction. In patients with active severe EGPA or who have relapsed, they conditionally recommend adding mepolizumab. On the other hand, ACR/Eular also released the treatment guideline almost at the same time. In the guideline, they conditionally recommend a treatment by RTX for remission induction of EGPA, which is not covered by health insurance in Japan. They recommend Mepolizumab for treatment of active non-severe EGPA. There are several differences between Japanese and ACR/Eular guidelines, which will be discussed in this session.

## LS33

### Pathophysiology of pneumococcal disease and Importance of vaccination for preventing infection in patients with autoimmune diseases

Shigeki Nakamura

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Conflict of interest: Yes

Pneumonia is the fifth leading cause of death in Japan in 2019 and has a high clinical impact. *Streptococcus pneumoniae* is the most frequently isolated causative pathogen of community-acquired pneumonia, often developing to invasive pneumococcal diseases (IPD), with an extremely high fatality rate of 20 to 30%. According to the age distribution of IPD, it is common in children under 5 years old and elderly people over 60 years old, so children under 6 years old are routinely vaccinated with 13-valent pneumococcal conjugate vaccine (PCV13), and elderly people aged 65 years and over are routinely vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23). Recent report examining the risk ratio of IPD by chronic underlying disease such as chronic lung, heart, liver disease, and diabetes mellitus etc. have a high risk of developing IPD even if they are less than 65 years old. Infectious diseases are extremely important as a cause of death in patients with autoimmune diseases, and pneumonia is reported to account for 15 to 25%. According to reports using medical receipt data from the United States, the prevalence ratios of pneumococcal pneumonia and IPD in patients with autoimmune diseases were 4.4 and 7.1, respectively, even in aged 18 to 49 years compared to healthy subjects. The autoimmune diseases are high risk of infection due to the immune abnormalities caused by the disease itself and the effects of immunosuppressive agents in use. The risk-based preventive strategy is

important and the vaccination should be promoted for all ages with risk of pneumococcal disease. In Japan, “Concept of pneumococcal vaccination for high-risk persons aged 6 to 64” was published from the Japanese Respiratory Society, the Japanese Association for Infectious Diseases, and the Japanese Society for Vaccinology under the agreement of 5 academic societies specializing in clinical practice in March 2021. In this time, I will overview about the pathophysiology of pneumococcal disease and importance of vaccination to prevent infection in patients with autoimmune diseases.

## LS34

### Significance of TNF-inhibition therapy from the viewpoint of suppressing the progression of joint destruction

Kazuhisa Nakano

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Conflict of interest: Yes

Understanding the pathophysiology of rheumatoid arthritis (RA) has made great strides in recent years. The control of disease activity and longevity in the majority of RA patients is significantly improved compared to previous generations. Although several factors may have contributed to the dramatic improvement in RA management during this period, the greatest contributor is TNF inhibition therapy with biopharmaceuticals approved about 20 years ago. In this seminar, we will focus on the effect of suppressing joint destruction, and reconfirm the therapeutic effect and risk factors of b/tsDMARD+/-MTX in various clinical trials so far. In addition, we will also reconsider the central involvement of TNF $\alpha$  in pannus formation from synovial biology, which has made remarkable progress in recent years due to advances in synovial biopsy and analysis technology at the single-cell level. In addition, I will introduce some studies that evaluated treatment responsiveness and molecular changes before and after treatment with b/tsDMARD+/-MTX for RA. We would like to take this opportunity to consider the current positioning of TNF inhibitors that have been the driving force behind RA treatment.

## LS35-1

### Use of tocilizumab (TCZ) to patients with rheumatoid arthritis (RA)

Satoshi Ito

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Conflict of interest: None

TCZ was approved for RA in 2008. It works for TNF inhibitor non-responders without methotrexate (MTX)<sup>1)</sup>, and it makes it possible to reduce steroids and MTX<sup>2,3)</sup>. Since it masks signs and symptoms of infection, it should be used with caution in elderly patients. We reduced the number of the lethal cases to zero by the early introduction of TCZ, education of the masking to their young family, and establishing the emergent admission system to the local general hospitals<sup>4)</sup>. Recently, we started to use TCZ for elderly patients in a good condition, since rejuvenation of the elderly people<sup>5)</sup>, role of IL-6 in elderly RA patients<sup>6)</sup>, and safe and effective use of TCZ in elderly RA patients were reported<sup>7)</sup>. We have reported “spacing” of TCZ after achieving clinical remission (CR)<sup>8)</sup>, effectiveness of intravenous use of TCZ in heavy patients<sup>9,10)</sup>, adding iguratimod<sup>10)</sup>, and transient use of steroid when TCZ was switched from etanercept<sup>11)</sup>. Weekly use of subcutaneous TCZ was approved in 2017 but we have to be careful since one lethal patient was reported in the clinical trial<sup>12,13)</sup>. However, in real world, weekly TCZ was reported safe and effective, and spacing was also possible<sup>14,15)</sup>. We also used weekly TCZ and confirmed its effectiveness and safety. 1) Emery P, et al. Ann Rheum Dis 2008, 2) Nishimoto N, et al. Mod Rheumatol 2010, 3) Kremer JM, et al. Arthritis Rheumatol 2018, 4) Ito S, et al. Rheumatology 2015 (in Japanese), 5) Ouchi Y, et al. Geriatr Gerontol Int 2017, 6) Pers YM, et al. Joint Bone Spine, 2015, 7) Ito S, et al. Rheumatology 2020 (in Japanese), 8) Ito S et al. J Chubu Rheum Assoc 2016 (in Japanese), 9) Kobayashi D et al. Rheumatology 2016 (in Japanese), 10) Ito S, et al. Clin Rheumatol Rel Res, 2017, 11) Ito S, et al. Rheumatology 2016 (in Japanese), 12) Ogata A, et al. Mod Rheumatol. 2018, 13) Ito S. Mod Rheumatol 2018, 14) Murata M, et al. Clin Rheumatol Rel Res 2020 (in Japanese), 15) Hattori Y et al. J Chubu Rheum Assoc 2020 (in Japanese).



## LS35-2

### Life stage of rheumatoid arthritis patients and IL-6 inhibition

Kensuke Oryoji

Center for Rheumatic Diseases, Matsuyama Red Cross Hospital, Ehime, Japan

Conflict of interest: None

In the absence of contraindications, rheumatoid arthritis treatment should be initiated with methotrexate, followed by biologics or JAK inhibitors in cases of inadequate efficacy or having poor prognosis factors. It has been shown that IL-6R inhibitors have a recommendation in biologics, especially when csDMARDs such as methotrexate cannot be used concomitantly (Ann Rheum Dis. 2017;76:960-). On the other hand, factors such as methotrexate-associated lymphoma and impaired renal function make the use of methotrexate more difficult in elderly rheumatoid arthritis patients. Patients with rheumatoid arthritis in Japan are aging (45% aged 70 years or older, according to the JCR Guidelines for Rheumatoid Arthritis Treatment 2020), and in our hospital, 48% are aged 70 years or older. There are two types of aged RA: Elderly RA and Elderly-onset RA (EORA), and the phenotypes of these two types differ significantly, especially in the case of seronegative (or nearly seronegative) EORA. We have reported that the genotype of HLA-DRB1 determines the efficacy of other drug (Ann Rheum Dis. 2018;77:1234-), while tocilizumab shows little difference in efficacy by genotype (Arthritis Rheumatol. 2017;69 suppl 10). In this presentation, we will discuss the appropriate use of tocilizumab according to the heterogeneity of rheumatoid arthritis.

## Evening Seminar

### ES1

#### Contemporary clinical strategies for managing rheumatoid arthritis and preventing structural joint damage: the role of filgotinib

Peter C Taylor<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>

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Conflict of interest: Yes

On behalf of Gilead Sciences K. K. and Eisai Co., Ltd, please join us for a dynamic virtual presentation by Profs Peter Taylor and Tsutomu Takeuchi. The presentation will be focused on contemporary management strategies for rheumatoid arthritis (RA), including the use of Janus kinase (JAK) inhibitors in clinical practice, and current international guidance on their use. It will also discuss the latest clinical data for filgotinib - a once-daily oral JAK inhibitor approved for the treatment of RA, including the prevention of structural joint damage in patients who have had an inadequate response to conventional therapies. Prof Takeuchi will review recent EULAR recommendations and JCR guidelines for the management of RA and highlight the importance of early intervention with effective therapies to prevent structural damage and achieve treatment goals, in line with the treat-to-target strategy in clinical practice. He will also discuss the therapeutic advancements in RA, including the role of JAK inhibitors in clinical management of RA. Prof Taylor will focus on the use of JAK inhibitors, including filgotinib - recommended by NICE for use in the management of moderate RA in England - and the summary of key clinical data for filgotinib. He will discuss the clinical evidence for the efficacy of filgotinib 200 mg in combination with methotrexate (MTX) in achieving clinical remission, preventing structural damage, and improving physical function in MTX-IR patients, and highlight the importance of early intervention with filgotinib + MTX. Data will also be presented about the safety of filgotinib, from the clinical trials and ongoing long-term safety studies, that have demonstrated no noticeable dose-dependent increases in the rates of adverse events of interest. The presentation will provide an understanding of patient groups who may be good candidates for receiving filgotinib therapy, and the importance of shared decision-making.

### ES2

#### Further improvement in outcomes of RA therapy: Treatment optimization based on real world evidence

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Conflict of interest: Yes

Having chronic destructive arthropathy as a presenting symptom, rheumatoid arthritis (RA), is an autoimmune disease that causes joint deformities and physical problems. Since about 20 years ago, there has been a paradigm shift in RA therapy from intermittent low-dose methotrexate treatment, to biological products that inhibit inflammatory cytokines and lymphocytes, which play pivotal roles in the pathogenesis of RA, and Janus kinase (JAK) inhibitors, which inhibit intracellular signaling pathways. The continuous advances in therapy have significantly improved the prognosis. With proper treatment, about 60% of patients can now achieve clinical remission and about 20% can achieve low disease activity. However, there are still patients who cannot attain remission, and the rate of remission seems to have peaked out in recent years, suggesting that there is still room for further efforts. Many have voiced concern that Japan also faces issues associated with its aging population, for example, patients with long-standing disease and adults with a first episode later in life. Currently, it is a major clinical challenge to manage RA patients with complications. Since the rates for elderly RA patients who have comorbidities related to age or RA itself, such as reduced renal function, interstitial pneumonia, and chronic infection, are high, selection of treatment and management for RA require special considerations, including increasing incidence



of adverse drug events, management of organ damage other than that due to RA, and polypharmacy. During treatment, consideration also needs to be given to infectious diseases due to drug-induced immunosuppression and characteristic adverse drug reactions. So, what kind of RA therapy is needed in Japan, where aging of the population is unprecedented in human history? In our presentation at the seminar, we will discuss optimization of pharmacotherapy aiming at further improving the outcomes of RA treatment based on real world evidence.

### ES3-1

#### Current status of spondyloarthritis treatment

Hiroaki Dobashi

Kagawa University Hospital

Conflict of interest: Yes

Spondyloarthritis (SpA) can be broadly classified into those with axial lesions and those with peripheral lesions. Ankylosing spondylitis (AS) is most common form of an axial lesion. Psoriatic arthritis (PsA), on the other hand, is a typical example of spondyloarthritis with peripheral lesions. However, in PsA, axial lesions are also observed and are considered to be important therapeutic targets. More recently, non-radiographic axial spondyloarthritis (non-radiographic SpA) has been recognized as a new disease category. SpA features are important in the diagnosis of SpA. SpA features, which are various extra-articular lesions, can be seen in both axial and peripheral SpA. Early diagnosis of SpA is an important issue, but differential diagnosis is crucial for the diagnosis of SpA that requires therapeutic intervention. Particular attention should be paid to the diagnosis of non-radiographic axial SpA. In the treatment of these SpA, advances in clinical immunology and the results of clinical trials of novel therapeutic agents have led to treatment strategies based on the cytokine taxonomy, and a variety of options now exist. In this context, TNF- $\alpha$  inhibitors were the first biologic agents to be covered by insurance for AS and PsA, which had a significant impact on physicians and patients. Subsequent advances in basic and clinical research related to the pathogenesis of SpA have led to the development of drugs that inhibit IL23-IL17axis and JAK inhibitors in addition to TNF $\alpha$  inhibitors. Among these drugs, IL-17 inhibitors have been demonstrated to be effective one after another. However, the optimal use of these many biologics has not yet been fully determined. In this lecture, I would like to discuss the importance of SpA diagnosis and the necessity of therapeutic intervention with examples of my own experience.

### ES3-2

#### Responsiveness of power Doppler ultrasound in psoriatic arthritis to demonstrate continued improvement in synovitis and enthesitis with secukinumab: Results from the ULTIMATE study

Maria Antonietta D'Agostino<sup>1</sup>, Georg Schett<sup>2</sup>, Corine Gaillez<sup>3</sup>, Carlos Gamez<sup>4</sup>, Petra Hanova<sup>5</sup>, Tomas Cazenave<sup>6</sup>, Maria S Stoenoiu<sup>7</sup>, Marina Backhaus<sup>8</sup>, Gaël Mouterde<sup>9</sup>, Maarten Boers<sup>10</sup>, Anne-marie Duggan<sup>11</sup>, Punit Goyanka<sup>12</sup>, Philip G Conaghan<sup>13</sup>

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Conflict of interest: Yes

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory arthritis characterized by the association of peripheral arthritis and periarticular inflammation. Power Doppler ultrasound (PDUS) is a sensitive im-

aging tool to visualize a wide range of articular and periarticular inflammation in PsA. ULTIMATE (NCT02662985) is the first large RCT that used ultrasound with Global OMERACT ultrasound synovitis score (GLOESS) as the primary endpoint, to demonstrate early benefits of secukinumab on synovitis in patients with PsA through 12 weeks. This was a 52-week study with a 12-week double-blind placebo-controlled treatment followed by 12-week open-label treatment and 6-month open-label extension treatment in all patients. Synovitis and ultrasound enthesitis response were measured by GLOESS and Global OMERACT enthesitis Score at patient level, respectively. Other assessments across key PsA manifestations of joints (ACR responses), enthesitis, (SPARCC), skin (PASI responses), dactylitis (LDI) and physical function (HAQ-DI) were also evaluated. A total of 166 patients were enrolled, of which 90% [75/83] of secukinumab and 83% [69/83] of placebo-secukinumab participants completed 52 weeks. A continued improvement in GLOESS was observed in both secukinumab and placebo-secukinumab group after switch to active therapy at Week 12 through Week 52. A similar trend of improvement in Global OMERACT enthesitis score was observed up to 52 weeks in both groups. Sustained clinical response rates were observed across multiple facets of disease and physical function up to 52 weeks in both groups findings. ULTIMATE confirmed the rapidity of response of secukinumab and demonstrated the responsiveness of ultrasound on both synovitis and enthesitis outcomes in PsA supporting its use in clinical trials.

### ES4-1

#### Challenges in the treatment of elderly rheumatoid arthritis

Takahiko Sugihara

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine

Conflict of interest: Yes

The prevalence of rheumatoid arthritis (RA) in the elderly is increasing in line with the increasing life expectancy, and the attending physicians often take into account age-related changes such as sarcopenia, decreased physiological function, and decreased immune function, as well as multi-morbidities. The treatment goals of RA are to control disease activity, reduce the progression of joint destruction, improve physical function, allow patients to continue to work and enjoy their hobbies, and improve long-term prognosis, while in the elderly, the treatment goals may be to prevent the progression of physical frailty and extend healthy life expectancy. Pulmonary complications and chronic kidney disease (CKD) are more frequent in the elderly, and maintenance of pulmonary and renal function is one of the therapeutic goals of elderly RA. In the 2020 Japanese College of Rheumatology Clinical Practice Guidelines, a systematic review of the treatment of older rheumatoid arthritis (Sugihara, T., et al., Systematic review for the treatment of older rheumatoid arthritis patients informing the 2020 update of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis. Mod Rheumatol. Online Ahead of Print) was conducted and recommendations for the older patients were given. Although the basic treatment strategy is the same as for younger patients, it is clear that the proportion of adverse events, including infections, is higher in elderly patients than in younger patients, and the predictive factors of safety influenced the choice of treatment. In this seminar, we would like to discuss how to initially treat elderly patients with RA and the issues necessary to maintain low disease activity or remission while managing subsequent complications.

### ES4-2

#### Therapeutic strategies for elderly RA patients-focusing on sarcopenia-

Motomu Hashimoto

Department of Clinical Immunology, Graduate School of Medicine, Osaka Metropolitan University

Conflict of interest: Yes

Rheumatoid arthritis (RA) patients, in particular elderly RA patients, have an increased risk for sarcopenia due to inflammatory cytokines or joint pain and deformity. Needless to say, diet and exercise are important to prevent sarcopenia. In addition, drug therapies for RA should be carefully determined considering their effect for sarcopenia. Glucocorticoids,

frequently used drugs for elderly RA patients, have the risk to promote sarcopenia via steroid myopathy. On the other hand, bio- and ts-DMARDs have the potential to improve sarcopenia by inhibiting the catabolic cytokine signaling such as TNF and IL-6. Especially, IL-6 signaling plays a critical role for elderly onset RA (EORA), which develops rapidly and frequently falls into frail and sarcopenia. Thus, active use of bio-DMARDs such as IL-6 inhibitors instead of glucocorticoids will be considered for the treatment of EORA in the future. In this seminar, therapeutic strategies for elderly RA patients will be discussed with the special focus on sarcopenia.

## ES4-3

### Issues in early diagnosis and actual treatment for elderly patients with rheumatoid arthritis

Shigeki Momohara

Keio University / Hakkeikai Incorporated Medical Institution

Conflict of interest: Yes

The cause of rheumatoid arthritis (RA) is still not fully understood, but it is understood as a disease in which joints are damaged due to immune abnormalities. Since the use of glucocorticoids in 1948, drug therapy has been the mainstay of treatment. A variety of anti-rheumatic drugs (DMARDs) have emerged over the years. The breakdown of DMARDs includes conventional synthetic DMARDs, biological DMARDs, and bio-similar agents to prior biopharmaceuticals. In addition, JAK inhibitors were introduced under these circumstances. With the introduction of these DMARDs, remission has become a realistic goal for treatment. However, there are still many unmet needs in the treatment of RA, and treatment strategies for refractory RA (D2TRA) have recently come into focus. Among these, the treatment of elderly patients has become a major issue as the number of patients increases, and it is urgent to address this issue. The problems with RA for the elderly are: 1) the definition of the elderly is unclear, 2) there is little data on the elderly, 3) there are many complications: hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, etc., 4) the general condition of the elderly is poor, and 5) there is a lack of data on the elderly. 4) problems with general health: cognitive impairment, depression, malnutrition, sensory limitation, motor limitation (frailty, sarcopenia), incontinence, etc., 5) caution with medications: multiple medications, increased risk of drug interactions, etc. In addition, elderly patients are less likely to achieve remission, their risk of infection increases with age, and they are at higher risk of cardiovascular events such as myocardial infarction, stroke, and even cancer. First of all, it is important to diagnose and start treatment as soon as possible, before the condition becomes more complicated. Depending on the age of the patient, it may be necessary to reduce the dose of DMARDs and sometimes use glucocorticoids. In addition, efforts should be made to avoid fractures due to osteoporosis and to prevent the onset of dementia. With a good understanding of these points for elderly patients, total management that goes one or two steps higher is now required.

## ES5-1

### Treatment for the patients with rheumatoid arthritis, considering their life events ~We shall get complete remission by utilizing ultrasonography and we shall look to the bright future~

Yasuhiro Tani

Orthopedics, Nagato General Hospital

Conflict of interest: None

We can target the clinical remission in rheumatoid arthritis (RA) treatment with the benefit of drug development, Biologics, Jak-inhibitors, csDMARDs, etc. In addition, we should try to target the structural remission and physical remission. These days, the patients assessment has been focused on the estimation of the RA activity by themselves. Considering RA disease from patients side aspect, patients have various problems, for example, working, marriage, child birth, parenting, retirement, golden age, etc. Patients have not only symptoms (pain, swelling, stiffness, joint disability, etc) but also emotional problems, (stressful, disappointment, sad, etc). As a result, patients maybe change the life styles, and fall into the situation loosing their social position. Therefore, Reumatologists have to relieve patients from the crisis of their social life, and I think it's the ulti-

mate mission in RA treatment to promise the bright future. It goes without saying, we have to treat patients with RA based on the recommendations and tight control to target the aim deep remission, moreover I suggest the assessment with ultrasonography (US). So, we should estimate the joint arthritis activity and prevent the joint destructive by US. And we estimate the joint disability, sometimes use the ultrasound to support injection guide. Generally, there is no enough consensus yet for US in the treatment assesment, however, in my opinion, I think it's impotant to utililize the US. Now, we have been trying to utilize not only estimation of joint arthritis activity but also rehabilitation to improve the joint function by judgging the soft tissue movement of joints and around the joints by dynamic US. Thanks to US, we have shared the patients disease activity and various problems in life events. US is essential tool for the clinical doctor to target more higher level remission for each individual patients. We discuss the ultimate strategy of RA treatment for targeting the happiness and bright future in life events.

## ES5-2

### Art the rheumatology therapy ~Tips for improving medical skills and usefulness of Golimumab~

Taichi Hayashi

Clinic QUEST for Rheumatology & WELL-BEING

Conflict of interest: Yes

Many drugs have appeared in the clinical practice of rheumatoid arthritis, and it has become possible to construct various treatment strategies that meet the wishes of patients. On the other hand, the concept of Difficult treat to RA (D2T-RA) has been proposed, and it has been pointed out that the remission rate has reached a plateau in many registries. Various factors are associated with D2T-RA, and it seems difficult to resolve them. From a different perspective, when we consider the “factors” of “factors”, we understand that the essence of the problem lies in the physician-patient relationship based on informed consent (IC) and the practice that excessively emphasizes EBM. Many problems can be resolved by adopting a narrative treatment strategy that goes beyond the guidelines based on appropriate setting of treatment goals and shared decision making (SDM), and sustainable management that always depends on patients' wishes can be realized. Medicine is a work of art created together. The goal should always be the best. However, there are many different approaches and paths, and there are multiple scenarios for different patients personality, preferences, living standards and knowledge levels, and desired outcomes. The best works are born when not only the director or the screenwriter, but also all the leading patients and staff exert their individual abilities with a common goal. It may be possible to select a scenario in which patients can perform vividly by themselves and create it with occasional ad-lib. Golimumab is characterized by a high level of utility and is one of the important items for induction and maintenance of remission in various situations. In this seminar, as a treatment strategy for rheumatoid arthritis from a patient's journey, we will outline a treatment strategy for rheumatoid arthritis that is highly sustainable throughout the entire life of patients. In addition, we will introduce some of the specific skills of clinicians as scientific information for clinicians.

## ES6

### The current role of standard use of TNF inhibitors in rheumatoid arthritis

Masato Okada

Immuno-Rheumatology Center, St. Luke's International Hospital

Conflict of interest: Yes

Rheumatoid arthritis is a chronic inflammatory disease, which mainly involves peripheral joints with large range of motions. Conventional disease modifying anti-rheumatic drugs still play a major role in treatment of rheumatoid arthritis. Combination therapy, particularly conventional synthetic disease modifying anti-rheumatic drugs and biologic disease modifying anti-rheumatic drugs, has been used as the standard of care. In the non-erosive era, it is imperative to treat rheumatoid arthritis to target, and timely adjustment of medical treatment should not be postponed. Early escalation of disease modifying anti-rheumatic drugs dose and initiation of disease modifying anti-rheumatic drug combination therapy can be a rea-

sonable approach. TNF inhibitors have been intensively studied and the effectiveness on prevention of joint damage, and long-term safety data has been established. With the accumulation of the clinical experience, rheumatologists are well-versed in the routine pre-administrative screening, dose adjustment, evaluation of the efficacy and necessary monitoring for some adverse effects, which is mostly preventable. In addition to the effect on musculoskeletal system, tumour necrosis factor alpha is an important proinflammatory cytokine, abundantly expressed in synovitis in rheumatoid arthritis. It is of demonstrated importance in unstable atherosclerotic plaques. Premature mortality of patients with rheumatoid arthritis has been improved with intensive anti-inflammatory treatment and vigilant infectious surveillance.

## ES7-1

### Treatment of psoriasis and psoriatic arthritis from the standpoint of a dermatologist

Ryuhei Okuyama

Department of Dermatology, Shinshu University School of Medicine

Conflict of interest: Yes

In psoriasis, erythema with thick scales is often spread over a wide area on the skin, and the rash is conspicuous, which greatly reduces the patient's QOL. Dermatologists have used a combination of steroid ointment, vitamin D3 ointment, ultraviolet light therapy, oral retinoids, and intermittent cyclosporin to control the rash. On the other hand, it was often difficult to stably control dermatitis for a long period of time. However, with the advent of biologics, which selectively suppress TNF, IL-23, or IL-17, and phosphodiesterase 4 inhibitors, the number of out-of-control cases has decreased. However, the significant shift in immunity by the powerful therapeutics means that the correct diagnosis is more important when initiating administration. In a case of biologics administration, there is a great risk that the therapeutic drugs themselves will make the diagnosis more difficult if the diagnosis is incorrect. Careful skin examination is important because we do not have useful biomarkers for diagnosis. It is now widely known that psoriasis often causes inflammation not only in the skin but also in various tissues. Especially in psoriatic arthritis where inflammation occurs mainly in the entheses, not only rash but also joint symptoms bother the patient and further lower the QOL. Accurate diagnosis and appropriate treatment are important. However, it is occasionally difficult to make a diagnosis of psoriatic arthritis or other spondyloarthropathies when skin symptoms are inconspicuous, or when eruptions appear later than arthritis. From the standpoint of a dermatologist, I would like to comment how we approach the treatment of psoriasis and psoriatic arthritis, especially in terms of skin symptoms.

## ES7-2

### A multifaceted treatment strategy for psoriatic arthritis from Rheumatologist

Masamitsu Natsumeda

Rheumatoid Center, Mabi Memorial Hospital

Conflict of interest: Yes

Psoriatic Arthritis (hereinafter referred to as PsA) refers to a condition in which a skin disease, is accompanied by symptoms such as arthritis, enthesitis, and spondylitis, and is said to account for 10 to 15% of psoriasis in Japan. Since skin symptoms precede in 70% or more of patients with PsA, it is a characteristic disease that dermatologists are often involved first, but on the other hand, rheumatologists are in daily practice. It can be said that the role involved through joint symptoms. We also play an important role in suppressing the progression of joint destruction in the future, similar to dermatologists. In addition, in order to understand the pathophysiology and treatment of PsA and to achieve the suppression of the progression of joint destruction, it's a disease in terms of differentiation from rheumatic diseases that we usually face and immunological aspects. There is also a need for an understanding-based, early intervention. However, in order to perform the early treatment intervention, a series of "medical examination - diagnosis" during facing PsA patients in the medical examination room is a very important factor. In order to realize these early diagnosis and early intervention, we are conducting medical treatment with reference to various guidelines such as GRAPPA and EULAR. We

already have anti-TNF- $\alpha$  inhibitors and anti-IL-17 inhibitors. Furthermore new treatments such as GMA and JAK inhibitors have also been added to our treatment options. With the increase in these new treatment options, it's also true that more optimal treatment strategies must be taken for each patient. In this seminar, when considering the optimal treatment strategy for each patient, we have already taken into consideration the points that rheumatologists should pay attention to in "medical examination - diagnosis" and various treatment options based on various guidelines. Based on the fact that the anti-TNF- $\alpha$  inhibitor Certolizumab pegol, which is used in treatment, was added as a new treatment option for PsA in Japan from December 2019. We want to consider it with the actual treatment at our hospital.

## ES8

### Clinical Update for Collagen Disease Pulmonary Arterial Hypertension-REPLACE Trial and Clinical Application-

Masaru Kato

Hokkaido University

Conflict of interest: None

Pulmonary arterial hypertension associated with connective tissue diseases (CTD-PAH) is different from scleroderma pulmonary hypertension (SSc: systemic sclerosis-PAH) due to differences in pathology and treatment. It is becoming subclassified as scleroderma connective tissue pulmonary arterial hypertension (non-SSc CTD-PAH). Especially in the treatment, immunosuppressive therapy centered on steroids and cyclophosphamide is performed in addition to selective pulmonary vasodilator therapy for non-SSc CTD-PAH, whereas immunosuppression therapy for SSc-PAH is performed. Only selective pulmonary vasodilator therapy is commonly used due to poor response to suppressive therapy. In addition, SSc-PAH is characterized by remodeling of pulmonary veins as well as pulmonary arteries, and often associated with left heart disease and interstitial lung disease. From a pathological point of view, it is the first + 2 Group 3 Pulmonary hypertension is increased by a complex mechanism that can be called pulmonary hypertension. We are conducting research to determine which of the first, second, and third groups is superior in each case of SSc-PAH, and we will introduce the results in this seminar. Up-front combination therapy, which is a combination of two or more selective pulmonary vasodilators, is the basis for PAH treatment, but for SSc-PAH patients who are suspected of having elements in groups 2 and 3 coexisting. Initial monotherapy (sequential combination therapy) has become popular. However, it has not been clarified which selective pulmonary vasodilator should be used with priority at that time, and this point will be discussed while introducing the results of the recently published REPLACE study. Finally, we would like to introduce our department's cooperation with medical examinations, which is working for the purpose of early diagnosis of CTD-PAH and improvement of prognosis.

## ES9-1

### Treatment Target of Systemic Lupus Erythematosus: Remission and Low Disease Activity

Yasuhiro Katsumata

Division of Rheumatology, Department of Internal Medicine, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

Conflict of interest: None

Over the past few years, it has been lively discussed how to define remission and low disease activity in systemic lupus erythematosus (SLE). In 2017, the EULAR (European Alliance of Associations for Rheumatology) Task Force proposed definitions of remission in SLE (DORIS), either 'on-treatment' or 'off-treatment' [Ann Rheum Dis. 2017;76:554]. However, durable remission was reported to be rare. Accordingly, Lupus Low Disease Activity State (LLDAS) was proposed and prospectively validated by the Asia Pacific Lupus Collaboration (APLC) [Lancet Rheumatol. 2019;1:e95]. LLDAS is defined as follows: 1) SLEDAI-2K  $\leq 4$ , with no activity in major organ systems and no haemolytic anaemia or gastrointestinal activity; 2) no new lupus disease activity compared with the previous assessment; 3) a SELENA-SLEDAI physician global assessment (scale 0-3)  $\leq 1$ ; 4) a current prednisolone  $\leq 7.5$  mg/day; and 5) well tolerated standard maintenance doses of immunosuppressive drugs and approved



biological agents. It has been shown that LLDAS attainment is associated with significant protection against flare and damage accrual in SLE. Thus, these findings validate LLDAS as an endpoint for clinical studies in SLE. Subsequently, in 2021, the EULAR Task Force recommended a single DORIS for use in clinical care, education, and research including clinical trials and observational studies: clinical SLEDAI=0; Evaluator's Global Assessment <0.5 (0-3); prednisolone  $\leq$  5 mg/day; stable antimalarials, immunosuppressives, and biologics [Lupus Sci Med. 2021;8:e000538]. In addition, the task force stated that both DORIS and LLDAS serve unique important purposes and that they felt that both DORIS and LLDAS should be used in clinical practice and research settings including clinical trials. Having said that, an Italian multi-center study reported that clinical SLEDAI=0 is the most attainable definition of remission, while displaying the best performance in predicting damage progression [Ann Rheum Dis. 2020;79:943].

## ES9-2

### Reconsideration for the goals of treatment in patients with systemic lupus erythematosus in respect to reproductive health

Kayoko Kaneko

Division of Maternal Medicine, Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development

Conflict of interest: Yes

Recent advances in medical treatment with lupus erythematosus have made it possible for people to live their own lives while coping with the disease. How will the goals of treatment for women with SLE of childbearing age change in the future? Firstly, one of the goals will be supporting patients to continue to live as independently as possible, in a way that is compatible with their values and lifestyle. In the past, many women were forced to give up pregnancy and childbirth because they had diseases. But now, with control of disease activity before pregnancy and the continuation of available drugs during pregnancy, the possibility of having a healthy baby is increasing. At the same time, however, it is important not to be bound by the stereotype that because you are a woman you must give birth, or because you are a man you must become a father. The freedom of the patient to choose not to conceive or not to carry a child to term must be respected. In collaboration with gynecologists, it will be important to support patients in respecting their reproductive health and rights. We also need to help patients with SLE prepare for a healthy transition to old age with minimal complications and disability associated with a long illness. For example, the cumulative incidence of cervical dysplasia in patients with SLE is known to be higher than in healthy individuals or in women with other autoimmune diseases. Awareness of cancer screening and HPV vaccination is essential, as is awareness of other female-specific cancers. Fragility fractures, such as vertebral fractures caused by osteoporosis, also significantly reduce the ADL of patients. Osteoporosis should be prevented through appropriate weight control, exercise, nutrition, and drug therapy, as well as by reducing the number of steroids that contribute to osteoporosis. This lecture will focus on the topic of reproductive health and discuss new treatment goals for patients with SLE of childbearing age.

## ES10-1

### Paradigm shift in RA hand surgery with joint-conserving surgery / soft tissue reconstruction

Ryo Oda

Department of Orthopaedics, Kyoto Prefectural University of Medicine

Conflict of interest: None

With the advent of the 21st century, the paradigm shift that has rushed to RA has extended to surgical treatment through early diagnosis and control of inflammation by DMARDs. RA surgery aimed at improving IADL and QOL for small joints has been performed. Even in RA, that is joint destruction disease, joint-preserving surgery has become a realistic option. Inflammation control suppresses osteochondral destruction, while degeneration of soft tissue with relapse of disease activity and instability due to poor joint compatibility. Based on this situation, the theme of the panel discussion in RA Hand Surgery 2022 is "joint-conserving surgery / soft tissue reconstruction". Dr. Natsuko Nakagawa intend to talk about the

preservation of MP joints and wrist joints from the viewpoint of leaving as much range of motion as possible, and Dr. Yoshiya Arishima may talk about the past of swan neck deformity and buttonhole deformity, through looking back on the joint-sparing technique and will mention the indications and limitations. Oda would like to present some cases of reconstruction of the thumb MP joint, which is very important functionally, and deepen the discussion with the participants. In the special lecture, Dr. Takushi Iwamoto will introduce his efforts to improve the long-term results of hand and elbow arthroplasties under the title of "Hand and elbow joint arthroplasty for RA patients in the era of biologics". Even if RA is diagnosed and treated according to the guidelines, joint deformity and dysfunction worsen over time. Examining the number of RA surgical treatments, it can be seen that the need for functional reconstruction of orthopedics has never diminished. Through this seminar, we hope that rheumatologists will build total management for consistent treatment by making full use of treatment methods including surgical treatment, and that the prognosis of RA patients will improve further.

## ES10-2

### Hand and elbow joint arthroplasty for RA patients in the era of biologics

Takuji Iwamoto

Department of Orthopaedic Surgery, Keio University School of Medicine

Conflict of interest: None

Advances in drug therapies have made it possible to control synovitis in rheumatoid arthritis (RA), and the indications for orthopedic surgery are also changing. The number of surgeries for pain relief, tendon rupture and nerve palsy has decreased, and the number of surgeries for finger function and aesthetic hand surgery has been increasing. Rheumatologists should be aware that many patients want to improve their aesthetic appearance for their hands, because the hands are exposed parts. However, it is essential to consider the patient's disease activity to determine the appropriate surgical indication. It is important to recognize that there are surgeries that should be performed in tightly controlled situations (reconstructive surgery for finger deformity) and surgery that should be performed regardless of the situation (subcutaneous tendon rupture, nerve palsy). With the progress of drug therapy, the disabilities of RA patients have improved, and participation in work and social activities has become active. In addition, since Japan is a super-aging society, it is necessary to consider appropriate surgical strategies that can achieve long-term results. For joint replacement surgery, it is important to select implants that are suitable for the future revision surgery. For elbow joints, unlinked type implant can be used, as the number of cases with severely damaged joints such as arthritis mutilans is decreasing. For wrist joints, clinical use of total wrist arthroplasty has started in Japan, and it is expected to be a procedure that preserves the range of motion instead of arthrodesis. For finger joints, silicone implant is still the gold standard treatment, but implant fracture is a main problem. In this lecture, I would like to introduce our efforts to improve the long-term results of hand and elbow arthroplasty, and show the recent progress and future challenges of rheumatoid hand surgery in the era of biologics.

## ES11-1

### Up-to-date evidence of JAK inhibitor

Gerd R Burmester

Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Germany

Conflict of interest: Yes

In the 2019 EULAR Recommendation update, JAK inhibitors were recommended to be used in phase 2 of the treatment algorithm after csDMARD. However, after FDA drug safety communication issued, some rheumatologists may be wondering whether JAK-inhibitors should be used in phase 2 or 3. Currently, regarding Baricitinib long-term efficacy/safety data and enough real-world experience are accumulating for us to be able to see which benefits this drug can bring to RA treatment, which may exceed the outcome with past treatment regimens. In this presentation, efficacy, accumulated safety evidence and proper use of Baricitinib will be discussed based on the latest evidence from clinical trials and real-world evidence. Also, I will discuss when JAK inhibitors might be used



in 1st line therapy after cDMARDs, and also the characteristics of patients who would benefit most with JAK treatment.

## ES11-2

### The role of baricitinib in the treatment of rheumatoid arthritis

Akio Morinobu

Rheumatology, Kyoto University Hospital, Kyoto, Japan

Conflict of interest: Yes

JAK inhibitors have been shown to be effective in the treatment of rheumatoid arthritis in cases of insufficient responses to MTX or TNF inhibitor refractory cases. They are recommended along with bDMARDs in the EULAR recommendations. Baricitinib was approved in 2017 as the second JAK inhibitor in Japan and has been used in many clinical settings for 4 years. Baricitinib can be orally administered thus highly convenient for patients, but it is necessary to consider liver function and renal function when administering it. PMS data from 4700 cases in Japan provided great information on the safety of baricitinib. Clinical trials conducted during the development of baricitinib have made significant contributions to the treatment of rheumatoid arthritis. First, direct comparison with a TNF inhibitor showed superiority in clinical response, implicating the potential of the JAK inhibitor. Baricitinib is a JAK inhibitor that suppresses JAK1 and JAK2, and it is presumed to exert a clinical effect by suppressing the signal transduction of IL-6 and GM-CSF, which are closely related to the pathophysiology of rheumatoid arthritis. Second, the effects of patient-reported outcomes (PRO) were extensively studied in Baricitinib programs. In addition to HAQ-DI, it has been shown to improve indicators of fatigue and pain, which has become essential outcome in subsequent clinical trials for rheumatoid arthritis. At the same time, the results raised the question of how to relate fatigue and pain to inflammatory conditions. In this talk, I will discuss the mechanism of action of baricitinib and its clinical potential in RA treatment.

## ES12

### The role of filgotinib in clinical practice for the treatment of rheumatoid arthritis and preventing structural joint damage

Peter C Taylor

Experimental Rheumatology Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK

Conflict of interest: Yes

On behalf of Gilead Sciences K.K. and Eisai Co., Ltd, please join us for an interactive, discussion-based session chaired by Prof. Yoshiya Tanaka. This session will include a short presentation from Prof. Peter Taylor followed by panel discussion with Japanese rheumatologists/orthopedic surgeons. Key topics in the session will include contemporary management strategies and guidance for rheumatoid arthritis (RA), the importance of early intervention with advanced therapies to achieve treatment goals and prevent irreversible joint damage, and the latest clinical data for filgotinib - a once-daily oral Janus kinase (JAK) inhibitor for the treatment of RA, including for the prevention of structural joint damage, in patients who have had an inadequate response to conventional therapies. In clinical trials, filgotinib, in combination with methotrexate, has demonstrated strong efficacy in preventing structural damage and achieving clinical remission in patients with inadequate response to methotrexate alone (MTX-IR patients). Exploratory and post hoc analyses that evaluated various clinical outcomes in the long-term, including patient-reported outcomes, will also be discussed. In addition, patients treated with the recommended dose of filgotinib (200 mg) did not experience noticeable dose-dependent increases in the rates of adverse events of interest such as herpes zoster and venous thromboembolism during the phase 3 trials, and ongoing long-term safety studies with filgotinib have reported similar findings, which will be reviewed during the interactive session and panel discussion. The presentation and panel discussion will also provide an understanding of ongoing patient management strategies, the patient groups who may be good candidates for receiving filgotinib therapy, and the importance of shared decision-making.

## ES13-1

### Involvement of IL-6 in the pathogenesis of rheumatoid arthritis

Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo

Conflict of interest: Yes

Several proinflammatory cytokines are known to be involved in the pathogenesis of rheumatoid arthritis (RA). The role of interleukin (IL)-6 plays in the pathogenesis of RA are as follows: (1) IL-6 acts on osteoblasts and synovial fibroblasts together with sIL-6R to induce the expression of receptor activator of nuclear factor kappa B ligand (RANKL), (2) inhibits osteogenesis by suppressing the differentiation of osteoblast progenitors into mature osteoblasts, (3) promotes cartilage matrix degradation by inducing various proteolytic enzymes in cartilage, and (4) promotes angiogenesis associated with inflammation by acting on vascular endothelial cells. Tocilizumab, a humanized anti-interleukin-6 receptor antibody has been shown to have a favorable clinical response in RA patients. In addition, tocilizumab has been shown to be effective in some patients refractory to TNF-inhibitors, suggesting that the two cytokines, IL-6 and TNF- $\alpha$ , may be involved in the pathogenesis of RA through different mechanisms. A more detailed understanding of the effects of IL-6 will further advance our understanding of the pathogenesis of RA.

## ES13-2

### The importance of REBONE and Interleukin-6 signaling inhibition related to HR-pQCT system

Georg Schett

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic and inflammatory disease characterized by joint inflammation leading to local and systemic bone loss. The appropriate identification and monitoring of bone erosions is of crucial because erosions are the central sign of progressive destructive arthritis and are associated with an impaired functional outcome. HR-pQCT can measure the change of systemic bone mass and architecture in each arthritis. Inflammatory cytokines lead to an imbalance between bone resorption and formation in RA. Proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) are the main triggers for bone erosions by inducing an imbalance of local bone metabolism. The role of cytokines in this process is only partly understood, common concepts suggesting that a combination of TNF- $\alpha$  and IL-6 are responsible for the loss of bone in RA. Current data have supported a key role of IL-6 in bone loss in RA, suggesting that IL-6 suppresses repair of damage bone in RA. This concept is based on findings that suggest that treatment with the anti-IL-6 receptor antibody tocilizumab (TCZ) induced the repair of existing bone erosions in patients with RA, while no such repair is found when inhibiting TNF- $\alpha$  with respective therapeutic antibodies on HR-pQCT. These findings point to a homeostatic role of IL-6 in bone, which is also supported by findings that show that treatment with TCZ increases systemic markers of bone formation indicating repair. Thus, apart from the anti-inflammatory action of IL-6 targeted therapies in RA, such approach also seems to restore bone homeostasis. In this symposium, I will focus on the effectiveness of HR-pQCT in arthritis, and the relationship between bone loss and inflammatory cytokine such as IL-6 in RA.

## ES14-1

### The need for preconception care and Shared Decision Making

Yuri Hiramatsu

Department of Medicine, Division of Rheumatology, Osaka Medical and Pharmaceutical University

Conflict of interest: Yes

In recent years, medical technology has dramatically improved the prognosis of rheumatoid arthritis. In addition, the number of female patients who wish to become pregnant is increasing. On the other hand, the

pregnancy age has increased remarkably in Japan. In patients with rheumatic diseases, the risk of maternal and infant risk due to the disease as well as the risk of pregnancy complications due to aging increases. With this in mind, it is necessary to make a pregnancy plan for female patients of childbearing age from an early stage. At our hospital, internal medicine and obstetrics collaborate to provide medical care to support pregnancy with rheumatic diseases. One of the problems that patients feel in clinical practice is that while patients have vague anxiety about pregnancy, they lack specific knowledge about pregnancy. According to the questionnaire we actually conducted, the reasons why the anxiety about pregnancy was strong were “vague anxiety about whether it is okay to get pregnant”, “anxiety that it is difficult to get pregnant”, and “bad pregnancy” at the pre-pregnancy stage. In addition, during pregnancy, “effects on children caused by their own illness / drugs” and “vague anxiety about childcare” were answered as patient voices. Furthermore, even after childbirth, voices of physical / mental anxiety such as “the recovery of one’s body is worse than expected” and “there are few partners / counselors who share anxiety” were obtained from the questionnaire results. In order to eliminate the anxiety of the patient, it is important for the patient to acquire knowledge about pregnancy by sufficiently conducting patient education (preconception care) before pregnancy. In addition, it is important to establish two-way communication between doctors and patients regarding future treatment plans and to make shared decision making. In order to realize them, it is important to cooperate with information sharing not only with rheumatologists but also with assisted reproductive technology and obstetrics. It is also important to collaborate with pediatrics (transitional medical care) as early education for patients with childhood onset. In women with rheumatoid arthritis, anxiety about pregnancy is large and varied. Regardless of whether or not patients wish to become pregnant at the time, it is necessary to adequately control the disease at any time and to provide patients and their families with information including general knowledge about pregnancy from an early stage.

## ES14-2

### Preconception care and decision support for reproductive women with rheumatoid arthritis

Makiko Matsuda<sup>1</sup>, Yoichiro Akiyama<sup>1,2</sup>

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Conflict of interest: None

Rheumatoid arthritis (RA) is more common in women and occasionally develops during their reproductive years. Rheumatoid arthritis often goes into remission with the advancement of medical care and the quality of life has improved. In women’s life cycle, the therapeutic duration for RA coincides with the period of pregnancy, childbirth, and childcare. Many RA patients receive treatment while facing these problems. They are concerned for a variety of issues, including when they can become pregnant, what medications can be administered during pregnancy and lactation, and concerns about worsening or flare-up of RA. Therefore, it is important to intervene from the onset of RA focusing on women’s life cycle before starting treatment. WHO states that ‘Preconception care is the provision of biomedical, behavioural and social health interventions to women and couples before conception occurs’. It aims at improving their health status, and reducing behaviours and individual and environmental factors that contribute to poor maternal and child health outcomes. Its ultimate aim is to improve maternal and child health, in both the short and long term. Especially for women and couples who reproduce with diseases, it is necessary to have knowledge and understanding of the disease as well as to take into account their future influence. It is not exaggeration to say that this medicine for women is one preventive medicine. Patients with RA in their reproductive time are sometimes asked to make decisions and treatment choices with focusing on the future of pregnancy and childbirth. We do not always know what is best from the beginning, and both RA patients and medical professionals have different values about what is important or what is good. It will be necessary to continue to find the best solution through a process (consensus building) between RA patients and medical professionals. It will be necessary to continue to search for the best solution through a process (consensus building) between RA patients and medical professionals. The nurse is a facilitator for patients with RA in reproductive age. We believe that it is necessary to intervene from the early stage of RA diagnosis through preconception care and to provide decision-making support so that patients can make treatment choices with

looking into the future.

## ES15-1

### Unsolved clinical questions and future prospects of interstitial lung disease associated with systemic sclerosis

Masataka Kuwana

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Conflict of interest: Yes

Systemic sclerosis (SSc) is an intractable condition, which is characterized by chronic inflammation, vascular remodeling, and excessive fibrosis. SSc affects many critical organ systems, including lung, kidney, heart, and gastrointestinal tract. Of these, pulmonary manifestations, including interstitial lung disease (ILD) and pulmonary hypertension, are the leading cause of morbidity and mortality. Pathogenic process of SSc-ILD includes migration of lymphocytes, macrophages and mesenchymal precursors into the lung parenchyma due to endothelial dysfunction, and subsequent differentiation of myofibroblasts, leading to accumulation of extracellular matrix and distortion of the normal lung tissue. Immunosuppressants targeting lymphocytes have been the mainstream of the treatment of SSc-ILD, based on treatment evidence showing prevention of decline in forced vital capacity (FVC) and improved patient-reported outcomes. However, survival benefit has not been shown in long-term follow-up studies of patients treated with immunosuppressants. Recently, evidence for short-term effectiveness of drugs targeting a variety of molecules involved in the pathologic process of SSc has been accumulating and resulted in expanding treatment options. In particular, the tyrosine kinase inhibitor nintedanib, which is classified as an antifibrotic drug, was shown to prevent the FVC decline over placebo in a phase 3, randomized, placebo-controlled, double-blind, controlled trial. However, there are still many unsolved clinical questions, such as in what cases, at what timing, when to use choices of the potentially effective drugs alone or in combination, or what timing of judging the therapeutic response. The updated information regarding answers to the clinical questions and the ongoing international efforts to solve them will be covered and discussed in this seminar.

## ES15-2

### Assessment and treatment of pulmonary hypertension associated with systemic sclerosis

Yuichi Tamura<sup>1,2</sup>

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Conflict of interest: Yes

Pulmonary hypertension is one of the poor prognostic factors in systemic systemic sclerosis, thus early diagnosis and therapeutic intervention are required. Furthermore, not only pulmonary artery lesions but also left ventricular dysfunction and interstitial pneumonia often complicate pulmonary hypertension, therefore, assessment to separate the components of pulmonary hypertension is necessary. In this presentation, based on data from the Japanese registry and actual medical experiences, we will discuss the peculiarities of pulmonary hypertension associated with systemic sclerosis and how to interpret it, as well as the methods and tips for therapeutic intervention in pulmonary arterial hypertension and pulmonary hypertension associated with left heart disease.

## ES16-1

### Diagnosis and treatment of psoriatic arthritis focusing on enthesitis

Keita Fujikawa

Department of Rheumatology, Japan Community Healthcare Organization (JCHO) Isahaya General Hospital

Conflict of interest: None

Enthesitis is a hallmark of spondyloarthritis (SpA), including Psoriatic arthritis (PsA), and is correlated with disease activity and patient quality of life. Entheses defined as the locations where the tendon, ligament, or joint capsule inserts into the bone to facilitate joint motion, and are constantly

exposed to mechanical stress. Histologically, it is divided into a fibrous enthesis and fibrocartilaginous enthesis, and in PsA, inflammation occurs in the fibrocartilaginous enthesis. Assessment of enthesitis is important for PsA diagnosis and treatment strategies. The Leeds Enthesis Index (LEI) and Spondyloarthritis Research Consortium of Canada (SPARCC) scores have been proposed as clinical assessments of enthesitis. These indices have limitations, because subclinical inflammation cannot be assessed, mimicking conditions such as mechanical trauma and tendinitis cannot be identified, and they are overestimated in patients with fibromyalgia. Advances in imaging techniques such as MRI and ultrasound (US) have enabled to more accurately assess of enthesitis. In the US, not only structural damages in entheses (bone irregularities, bone erosions, enthesophytes, and calcification), but also inflammatory changes (Doppler signal inside and outside enthesis, and bursitis) can be assessed. However, enthesitis in the US is not PsA/ SpA-specific finding and may also be detected in crystal-induced arthritis, SLE, trauma, etc. It is difficult to diagnose PsA or SpA based on US findings alone, and it is important to make a clinical diagnosis by differentiating or excluding other diseases. In addition, various US indices for evaluating enthesis have been proposed, but dissociation from clinical indicators such as DAPSA and PASDAS has been pointed out. In this lecture, I would like to focus on enthesitis in PsA and discuss practical use of US and treatment strategies in daily clinical practice.

## ES16-2

### New treatment strategy for the axial symptom of psoriatic arthritis

Yuhō Kadono

Orthopaedic Surgery, Saitama Medical University

Conflict of interest: Yes

Psoriatic arthritis (PsA) exhibits arthritis, enthesitis, and/or spondylitis with skin and/or nail psoriasis. The pathological condition is composed of chronic enthesitis in response to mechanical stress. Once enthesitis occurs in sacroiliac joint or spine, a patient complains the inflammatory back pain (IBP). IBP is typically relieved by exercise, and worsened by rest. It is important that we ask patients by open questions, and do a medical examination appropriately to ascertain the difference with the general back pain. Because of severe IBP, patients may complain about ADL or may not get enough sleep. We should distinguish PsA from nonspecific lumbago or degenerative disease including disc herniation and spondylolisthesis. We should also distinguish it from pustulotic arthro-osteitis (PAO), osteitis condensans ilii (OCI), diffuse idiopathic skeletal hyperostosis (DISH) as well as ankylosing spondylitis (AS). We should make a diagnosis with both clinical manifestations and images, or we sometimes need to follow up clinical findings for final diagnosis. PsA exhibits syndesmophyte formation around intervertebral disk space, which sometimes leads to ankylosis like AS. Unlike marginal syndesmophytes seen in AS, non-marginal syndesmophytes seen in PsA look chunky. It is difficult to distinguish PsA from PAO with images, and required to check skin. In DISH, usually seen in elder, osteophytes look proliferative. Since PsA exhibits various symptoms, a treatment strategy depends on a targeted symptom. When effects of NSAIDs, 1st choice drug, on axial symptom of PsA is insufficient, the biologics, such as TNF inhibitor and IL-17A inhibitor, may be considered. Recently, we can use Upadacitinib, one of JAK inhibitors, for PsA. According to the results of clinical trials, Upadacitinib improves axial symptom both in csDAMRDs-IR and bDMARDs-IR patients. In this lecture, I discuss differential diagnosis and a new treatment strategy focused on axial symptom of PsA.

## ES17-1

### Treatment of Behçet's disease and QOL of the patients

Masato Okada

Immuno-Rheumatology Center, St. Luke's International Hospital

Conflict of interest: None

Behçet's disease is a multisystem vasculitis that causes oral ulcers, genital ulcers, dermatological manifestations such as papulopustular and nodular lesions, arthritis, uveitis, arterial aneurysms, and arterial and venous thrombosis and sometimes involve the central nervous system and gastrointestinal tract. Recurrent relapsing and remitting oral ulcers are often the first manifestations of Behçet's disease. Oral ulcers cause pain;

difficulty in eating, drinking, and talking; and decreased participation in routine daily activities and quality of life. Apremilast, a phosphodiesterase 4 inhibitor, prevents degradation of cyclic adenosine monophosphate, thereby reducing the production of proinflammatory cytokines and increasing the production of anti-inflammatory mediators. Apremilast has therapeutic effects in patients with Behçet's disease by means of modulation of TNF  $\alpha$ , IL-2, IL-8, IL-12, IL-17, and IFN- $\gamma$  production, all of which are up-regulated proinflammatory mediators in Behçet's disease. In a phase 2 trial, apremilast was effective in reducing the number of oral ulcers, the pain associated with oral ulcers, and overall disease activity. In a phase 3 trial, the efficacy and safety of apremilast in a larger were evaluated, geographically more diverse group of patients with Behçet's disease who had active oral ulcers that did not respond to previous treatment with at least one nonbiologic agent such as a topical glucocorticoid or systemic treatment. In patients with oral ulcers associated with Behçet's disease, apremilast resulted in a greater reduction in the number of oral ulcers than placebo but was associated with adverse events, including diarrhea, nausea, and headache

## ES17-2

### Registry study reveals discrepancies between patients' perceptions and physicians' assessment of disease activity in Behçet's disease

Yohei Kirino

Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine

Conflict of interest: Yes

Behçet's disease presents with a variety of symptoms such as oral ulcers, skin rashes, genital ulcers, and arthralgia. Although it is expected that patients' QOL will be improved if treatment targets similar to those for rheumatoid arthritis can be set, standard QOL indices and disease activity indices have not been established at present, and their development is urgent. In the Yokohama City University Registry Study, about 300 patients were followed and analyzed, and the mean value of the disease activity index BDCAF of these patients was about 2, indicating that they still had symptoms of the two Behçet's diseases. Even after one year of follow-up, the mean value of BDCAF was about 2, suggesting that it is difficult to reduce BDCAF score of 0 with the existing treatment. Of the residual symptoms, oral ulcers were the most frequent, occurring in about half of the patients with Behçet's disease. The mean score on the face scale (range 1-7 points), which indicates the patient's own perception of disease activity, was 4 points. The mean score on the physician's face scale was 3, which was significantly lower than the patient's assessment of activity. Clinical trials have confirmed that apremilast, which has been approved since 2019, significantly reduces oral ulcers and BDCAF scores. In our observational study, we found that apremilast reduced oral ulcers and BDCAF, suggesting that it is an important drug for achieving "complete remission" of Behçet's disease. In addition, a meta-analysis conducted by our department showed that in addition to the reduction of oral ulcers and BDCAF, the drug also had effects on cutaneous mucosal symptoms and joint symptoms. In this lecture, I would like to discuss the future treatment of Behçet's disease to improve the QOL of patients, including the results of our registry and clinical studies.

## ES18-1

### The diagnosis and treatment of osteomalacia

Yuichi Takashi

School of Medicine, Department of Endocrinology and Diabetes Mellitus, Fukuoka University

Conflict of interest: None

Osteomalacia is a metabolic bone disease characterized by impaired bone calcification. The patients with osteomalacia are suffered from progressive pain in their bones, joints and muscles. Therefore, we have to distinguish from other diseases, such as rheumatoid arthritis, ankylosing spondylitis and myositis. Most patients with osteomalacia show chronic hypophosphatemia. Fibroblast growth factor 23 (FGF23)-related hypophosphatemic osteomalacia is caused by overproduction of FGF23, which is a bone-derived hormone to reduce blood phosphate level. While some genetic mutations cause FGF23-related hypophosphatemic osteomalacia,



tumor-induced osteomalacia (TIO) is an acquired paraneoplastic syndrome. TIO can be cured by resection of the causative tumors. However, it is sometimes difficult to identify the culprit tumors. Furthermore, the diagnosis of TIO has been difficult because the measurement of blood FGF23 level was not available in clinical settings. Now, the measurement of FGF23 level is available, and we can treat TIO with anti-FGF23 antibody, “burosumab”. FGF23-related hypophosphatemic osteomalacia including TIO is expected to improve the outcome from the therapy with burosumab. Therefore, it is necessary to expand awareness of this disease.

## ES18-2

### Clinical significance of low ALP - common symptoms of rheumatic disease may hide a rare metabolic bone disease -

Masaru Kato

Rheumatology and Nephrology, Hokkaido University Hospital

Conflict of interest: Yes

Hypophosphatasia (HPP) is caused by mutations in the *ALPL* gene, which encodes tissue nonspecific alkaline phosphatase (ALP), and characterized by defective mineralization of bone and dental problems. Since HPP varies greatly in severity, its mild form, such as adult HPP presenting pain or bone fracture, needs to be differentiated from rheumatic diseases. Moreover, the use of bone resorption inhibitors may increase the risk of atypical femoral fractures in individuals with HPP regardless of its severity. In daily clinical practice, HPP is suspected by low serum ALP levels and referred by urinary amino acid analysis (increased urinary phosphoethanolamine), then diagnosed by genetic testing. Conversely, serum ALP levels generally increase in high-turnover osteoporosis, such as postmenopausal osteoporosis and rheumatoid arthritis, through the compensatory bone formation, being a clue to differentiate HPP from rheumatic diseases. We have identified HPP in three women with rheumatoid arthritis, polyarteritis nodosa, and early loss of permanent teeth. The second patient had a novel mutation in the *ALPL* gene. A pediatrician referred the third patient to us upon the premature loss of deciduous teeth in her children. Our recognition of low ALP as well as hospital-clinic collaboration would help to avoid the inappropriate use of bone resorption inhibitors for currently mis- or under-diagnosed HPP.

## ES19

### Spinal lesions in RA patients

Yasushi Oshima, Sakae Tanaka

Orthopaedic Surgery, The University of Tokyo Hospital

Conflict of interest: Yes

RA patients eventually present with disorders in the spine, particularly in the upper cervical spine. Although progress in surgical techniques has improved outcomes after surgical intervention, the incidence of surgery-related complications remains higher as compared with patients without RA. According to the DPC data in Japan, about 5% of all the patients who underwent spine surgery in Japan suffered from RA, which remained unchanged from 2012 to 2017. On the other hand, the proportion of patients treated by biological agents increased from 5.6% in 2012 to 7.9% in 2017, which may influence the surgical treatment in RA patients in the future. In this presentation, recent topics in the spine lesions in RA patients will be discussed.

## ES20

### Effectiveness and safety of JAK inhibitors in treatment of rheumatoid arthritis: Evidence from real-world clinical data

Shunsuke Mori

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Conflict of interest: Yes

Janus kinase (JAK) inhibitors are the newest class of disease-modifying antirheumatic drugs (DMARDs) that target the JAK-STAT (signal transducer and activator of transcription) signaling pathway. The JAK-STAT pathway is employed by a variety of cytokines, which transduces extracellular cytokine signals from cell surface receptors to the nucleus.

There are four JAK isoforms and six STAT proteins, and various different combinations of these molecules contribute to the induction of a wide range of cytokine activities. JAK inhibitors normalize an imbalance between pro- and anti-inflammatory signaling in immune-mediated inflammatory diseases such as rheumatoid arthritis (RA). While biologic DMARDs target specific cytokines and cytokine receptors in the inflammatory cascade, JAK inhibitors are multitarget drugs. To determine the optimal position of JAK inhibitors in the treatment algorithm for RA, it is important to compare differences in efficacy and safety between JAK inhibitors and bDMARDs. The efficacy and safety of JAK inhibitors for RA have been extensively evaluated in recent phase 3 or 3b/4 clinical trials. In these studies, JAK inhibitors, such as tofacitinib, baricitinib, and upadacitinib, demonstrated equivalent or even superior efficacy to adalimumab in combination therapy with MTX. In addition, upadacitinib showed superior efficacy to abatacept. Using real-world registries, we showed that tofacitinib was more likely to induce better improvement in disease activity compared with tocilizumab in bDMARD-naïve patients, but these differences were not observed in the treatment of previous bDMARD-failure patients. Despite the positive therapeutic impacts, concerns have been raised regarding the risk of venous thromboembolism. We experienced a case of massive pulmonary embolism occurring 3 months after starting baricitinib for multiple bDMARD-resistant RA. In this seminar, we focus on recent real-world evidence investigating the effectiveness, treatment persistence, and safety of JAK inhibitors in patients with RA. COI: Pfizer Co and Eli Lilly Japan K.K

## ES21-1

### Role of type I interferon in the pathogenesis of systemic lupus erythematosus

Keishi Fujio

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Conflict of interest: Yes

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease that demonstrates a variety of immune abnormalities and organ damages associated with the production of autoantibodies. Genetic predisposition analysis by genome-wide association analysis has revealed the importance of innate immune signals such as Toll like receptor (TLR) and Interferon regulatory factor (IRF). Recent functional genomic and single-cell analyses have shown that B cells are associated with genetic risk of SLE. Type I interferon (IFN) is a cytokine with diverse functions, including antiviral activity and modulation of innate and adaptive immunity. Recent genome-wide association analysis of East Asian SLE revealed that the type I IFN genes themselves are risk factors for SLE. Type I IFN signaling is associated with disease activity in SLE, and has been shown to modulate not only innate but also adaptive immune responses. Type I IFN signaling is associated with disease activity, and act not only on innate immune responses but also on adaptive immune responses associated with autoantibody production and organ damage due to cellular infiltration. In this lecture, I would like to discuss the latest findings on the pathogenesis of SLE with a focus on type I IFN.

## ES21-2

### Anti-interferon therapy as a new treatment for systemic lupus erythematosus

Tomonori Ishii

Clinical Research, Innovation and Education Center, Tohoku University Hospital

Conflict of interest: Yes

Systemic lupus erythematosus (SLE) presents with various pathological conditions, and there is no uniform treatment. Molecular-targeted therapies developed in recent years have an extremely important safety advantage in that general side effects are unlikely to occur due to the narrow range of action. However, they also have an essential drawback that no effect can be expected in a pathological condition in which the target is not affected. The understanding of the pathophysiology of SLE is insufficient. Therefore, the only way to determine the suitability of molecular targeted therapy is to proceed with development while evaluating the effectiveness



by trial and error through intervention studies. Although many candidate drugs have been evaluated, only few drugs showed significant efficacy in clinical studies. The expression of type 1 interferon (IFN) is increased in SLE, especially during its active phase, which acts on the affected cells to transmit certain intracellular signals. An SLE-like pathology that occurs during IFN treatment for viral hepatitis was also confirmed. Anifrolumab is an IFN receptor antibody that specifically suppresses IFN signals and the first drug in this class that has been successfully approved for SLE therapy. However, one of the two validation trials failed to meet the primary endpoint, confirming the difficulty of SLE clinical trials. Moreover, it is difficult to understand the difference between anifrolumab and belimumab when investigating the results of clinical trials. However, the characteristics of the drug are different from belimumab in many respects such as the extent of its effect, and it is considered that future post-marketing studies will be important for the administration of anifrolumab to target populations.

## ES22

### More deeply understanding spondyloarthritis

Masahiro Yamamura<sup>1</sup>, Tetsuya Tomita<sup>2</sup>, Sachiko Miyake<sup>3</sup>, Hideto Kameda<sup>4</sup>, Taiki Nozaki<sup>5</sup>

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Conflict of interest: Yes

Spondyloarthritis (SpA) is a group of inflammatory rheumatic diseases comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, SpA-associated with inflammatory arthritis and undifferentiated SpA. More recently, classification criteria for axial and peripheral SpA (axSpA & pSpA) have been developed by the Assessment of SpondyloArthritis international Society (ASAS); axSpA involves sacroiliitis and spondylitis, while pSpA predominantly presents with peripheral arthritis, enthesitis and dactylitis. In addition, axSpA is now divided into radiographic and non-radiographic axSpA (r-axSpA/nr-axSpA) with or without definite X-ray evidence of sacroiliitis. These interrelated disorders share clinical features and are associated with MHC class I molecules, in particular HLA-B27. Activation of the IL-23/IL-17 pathway and the TNF- $\alpha$ -derived proinflammatory cascade has been known to play an important role in the pathogenesis of SpA diseases. IL-17 is now well defined as a major factor in inducing and mediating proinflammatory responses, including osteoproliferation as well as osteoclastogenesis. Of interest, this cytokine can be produced by the cells of the innate immune system such as gdT cells, type 3 innate lymphoid cells, and MAIT cells, in addition to CD4+T cells and CD8+T cells. Clinical studies have demonstrated that SpA diseases can be greatly ameliorated by blocking the IL-23/IL-17 pathway, likely TNF- $\alpha$ , further indicating its significant role in disease development. In the seminar, experts will cover the topics in greater detail, including “the innate immune system”, “n-axSpA”, and “diagnostic imaging” in the SpA diseases.

## Workshop

### W1-1

#### Prophylaxis against pneumocystis pneumonia in rheumatoid arthritis patients treated with b/tsDMARDs: from FIRST registry

Koshiro Sonomoto, Shingo Nakayamada, Hiroko Korekoda, Hiroaki Tanaka, Naoaki Ohkubo, Yoshino Inoue, Yusuke Miyazaki, Akio Kawabe, Ayako Yamaguchi, Shunsuke Fukuyo, Kentaro Hanami, Shigeru Iwata, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan

Conflict of interest: None

[Objective] Pneumocystis pneumonia (PCP) is one of the most important infections observed in RA patients. Here we describe a systematic prophylaxis strategy against PCP in RA patients with b/ts DMARDs treatment. [Methods] Data was collected from FIRST registry. Patients were divided into two groups: group 1 (Aug 2003 to Aug 2009, N=807. Prophylaxis based on physicians' assessment), group 2 (Sep 2009 to Dec 2019, N=2980. Strategic prophylaxis based on criteria including age, coexisting lung diseases, oral glucocorticoids [GCs] use). [Results] Twenty-six PCP cases were observed. The strategic prophylaxis suppressed the PCP-incidence (/100 PY) from 0.51 to 0.22 (risk ratio=0.42). The rate of prophylaxis is increased from 14% to 51% (p<0.01). The mean dose of SMX/TMP (ST, tablets/week) decreased over time (from 5.0 in 2008 to 3.4 in 2019), however no PCP case was observed in patients receiving ST. A statistic model including age, coexisting lung disease, BMI, lymphocyte count, and IgG level efficiently predicted the PCP-development in patients without GCs (AUC 0.910), however predicted in patients with GCs in a less accuracy (AUC 0.746). [Conclusions] We developed a model to predict the development of PCP in patients receiving b/ts DMARDs. ST is preferable for prophylactic administration.

### W1-2

#### Significance and Challenges of Pharmacist Intervention Based on the Questionnaire Survey

Atsushi Sunami<sup>1</sup>, Miyuki Takemoto<sup>2</sup>, Takako Kaneda<sup>2</sup>, Yosuke Asano<sup>4</sup>, Masamitsu Natsumeda<sup>3</sup>

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Conflict of interest: None

[Objective] We aimed to evaluate the significance of pharmacist intervention in our rheumatology center. [Methods] We conducted a questionnaire survey of inflammatory joint disease (IJD) patients attending our Rheumatology Center. The content of the questionnaire included the overall satisfaction and the level of understanding of medication guidance, each of which was rated on a 4-point scale. The primary endpoint of this study was overall satisfaction. [Results] The questionnaire was administered to 361 IJD patients between May 18 and June 30, 2021, and responses were obtained from 355 patients (98%). The primary endpoint, overall satisfaction, was rated 3 or higher out of 4 by 95% of the respondents. There was a significant difference in the median age between the two groups when they were divided into two groups, those who rated 4 and those who rated 3 or less, in terms of their understanding of the adverse effects (70 vs. 72, p=0.01, Mann-Whitney U test). [Conclusions] The intervention of our pharmacist was shown to contribute to the improvement of satisfaction of IJD patients, suggesting that it is significant in team medicine. In order to improve the understanding of adverse drug reactions, it is necessary to consider repeated medication guidance, especially for elderly patients.

### W1-3

#### Consideration of time to first biological agent from the treatment initiation in rheumatoid arthritis patients using a large-scale claims database

Yuichi Shiotsuki<sup>1,2</sup>, Shiori Tsuchiya<sup>1</sup>, Daisuke Sugiyama<sup>3,4</sup>

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Conflict of interest: None

[Objective] To examine the annual transition of the period from the start of rheumatoid arthritis (RA) treatment to the starting of biological agents from JMDC claim data. [Methods] We used claim data owned by JMDC Inc. and identified patients who newly started RA treatment between 2015 and 2020. we estimated time to start of biological agents and compared survival functions stratified by RA treatment start year using Kaplan-Meier method. Observation period was 3 years from the start of RA treatment. [Results] 14,353 patients (5,547 males and 8,806 females) treated for RA were identified, of which 1,377 (430 males and 947 females) had started biological agent. The average number of days to start biological agent was 240.7 days, with a median of 147 days. Survival functions stratified by RA treatment start year were compared by the Log-rank test, the p-value was 0.0491, but the Kaplan-Meier curve was crossed at some points. [Conclusions] Although a statistically significant difference was detected, it is possible that a slight difference was detected due to the large number of cases. On the other hand, it was revealed that the start of biological agent was within 6 months more than half, which is recommended by the guideline.

## W1-4

### Analysis of characteristics elderly patients with rheumatoid arthritis using a multicenter the Kyushu area RA ultrasound prospective cohort study (KUDOS)

Chieko Kawahara<sup>1,2</sup>, Shin-ya Kawashiri<sup>1,3</sup>, Tohru Michitsugu<sup>1</sup>, Yushiro Endo<sup>1</sup>, Ayako Nishino<sup>1</sup>, Remi Sumiyoshi<sup>1</sup>, Toshimasa Shimizu<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Mami Tamai<sup>1</sup>, Tomoki Origuchi<sup>1</sup>, Atsushi Kawakami<sup>1</sup>

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Conflict of interest: None

[Background] Recently, the number of elderly patients with RA has been increasing. Since 2013, we have conducted a multicenter the Kyushu area RA ultrasound prospective cohort study (KUDOS) for RA patients introducing biologic targeted synthetic disease-modifying antirheumatic drugs. [Objective] To compare patient characteristics, drug selection, and therapeutic efficacy between young-onset RA (YORA) and elderly-onset RA (EORA) using KUDOS data. [Methods] We compared the patient characteristics and therapeutic efficacy for 246 YORA versus 174 EORA or 101 elderly YORA and 132 non-elderly YORA. [Results] There was no significant difference in the positivity of ACPA and RF between EORA and YORA. EORA had significantly more interstitial pneumonia, diabetes, and hypertension. EORA had significantly higher CRP and ESR, but no significant differences in clinical disease activity or US synovitis score. EORA had a lower rate of MTX and more rate of CTLA-4 Ig. There was no difference in treatment retention rate, clinical disease activity, or US synovitis score at 1 year of treatment between EORA and YORA. [Conclusions] Although EORA and YORA had different patient characteristics, which led to different drug selection, there were no significant differences in treatment retention and efficacy.

## W1-5

### Reasons and Risk Factors for Discontinuation of Biologic Agents in Rheumatoid Arthritis Patients

Kenya Terabe<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Yuji Hirano<sup>2</sup>, Yasuhide Kanayama<sup>3</sup>, Yuichiro Yabe<sup>4</sup>, Takeshi Oguchi<sup>5</sup>, Takayoshi Fujibayashi<sup>6</sup>, Hisato Ishikawa<sup>7</sup>, Masahiro Hanabayashi<sup>8</sup>, Yosuke Hattori<sup>9</sup>, Mochihito Suzuki<sup>1</sup>, Kenji Kishimoto<sup>1</sup>, Yoshifumi Ohashi<sup>1</sup>, Kyosuke Hattori<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Shiro Imagama<sup>1</sup>

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Conflict of interest: None

Object: This study aimed to investigate the total retention rate of biological disease-modifying antirheumatic drugs (bDMARDs) in RA patients and the risk of discontinuation of bDMARDs. Methods: A total of 564 patients with RA were included; 413 patients were aged <65 years, and 151 patients were aged ≥65 years. The primary outcome was the incidence rate of bDMARDs treatment discontinuation due to adverse events (AEs). We evaluated the effectiveness of concomitant methotrexate (MTX) with analysis using a propensity score model by inverse probability of treatment weighting (IPTW). Results: Among 564 patients, 114 had discontinued bDMARDs treatment. Discontinuation due to AEs was the most frequent cause (63.2%). The hazards ratio (HR) in the ≥65 years group was significantly higher than that in the <65 years group (HR=3.83, 95% confidence interval [CI], 1.83-8.00). We identified that the risk factors for patients ≥65 years of age were without concomitant MTX. The HRs in the concomitant MTX group were significantly lower than those in the non-MTX group in the weighted and unweighted cohorts by IPTW in the ≥65 years group (HR=0.39, 95% CI, 0.19-0.78). Conclusions: Elderly patients had a higher risk of discontinuation of bDMARDs due to AEs compared to younger patients.

## W1-6

### Clinical course of the patients who developed malignant tumors during treatment with biological agents for rheumatoid arthritis (RA)

Makiko Ikoma<sup>1</sup>, Kahori Ishida<sup>1</sup>, Takehiro Suzuki<sup>1</sup>, Takeshi Kaneko<sup>1</sup>, Takashi Hosokawa<sup>1</sup>, Koji Nomura<sup>1,2</sup>, Hiroshi Fujiwara<sup>1</sup>

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Conflict of interest: None

[Objective] To clarify the characteristics of the clinical course after the diagnosis of malignancy in patients with RA who developed malignancy while receiving biologics (Bio). [Methods] We retrospectively analyzed the clinical course of patients who were receiving Bio in January 2016, diagnosed with malignancies between January 2016 and August 2020, and still receiving Bio at the time of diagnosis. [Results] Of the 253 patients on Bio, 25 had new malignancies. Twenty patients remained on Bio at the time of tumor diagnosis. The Bio used consisted of TCZ in 7 patients, ETN in 6, ABT in 4, GLM in 2, and ADA in 1. The outcomes were survival in 11, death in seven, and unknown in two. All deaths were due to tumor progression. After diagnosis, Bio was continued in three patients, while all of them underwent radical resection. Bio was restarted in five of the 17 patients who discontinued Bio. Tumor recurrence was observed in only one patient who restarted Bio. DAS28-CRP tended to increase more in patients who restarted or continued Bio than in those who discontinued Bio. [Conclusions] Among the patients who discontinued Bio at the time of malignancy diagnosis, 29% restarted Bio due to increased RA disease activity.

## W2-1

### Immunological clustering of Behçet's disease patients by machine learning

Lisa Hirahara<sup>1</sup>, Yohei Kirino<sup>1</sup>, Yuki Iizuka<sup>1</sup>, Yutaro Soejima<sup>1</sup>, Ryusuke Yoshimi<sup>1</sup>, Yuichiro Fujieda<sup>2</sup>, Tatsuya Atsumi<sup>2</sup>, Toshihiro Tono<sup>3</sup>, Shunsei Hirohata<sup>3</sup>, Daisuke Kobayashi<sup>4</sup>, Hideaki Nakajima<sup>1</sup>

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Conflict of interest: None

[Objective] Behçet's Disease (BD) shows a various phenotype, which may be due to immune subsets. We attempted to classify patients from immunological aspects by clustering serum cytokines using machine learning. [Methods] Patients aged 18 years or older who met the International Study Group criteria or International Criteria of BD were extracted from the BD disease registry established by a multicenter study. 13 cytokine levels were measured by Cytometric Beads Assay using stored sera. Consensus Clustering and K-means were used as machine learning methods. [Results] A total of 217 consecutive BD patients were analyzed. The mean age of the patients was 49.5 years, 47.5% were males, the mean disease duration was 12.8 years. Machine learning categorized the patients into 3 groups: group1 with high expression of innate immunity, Th1 and Th17 systems, group2 with moderate expression of all cytokines, and group3 with low expression of all cytokines except MCP1. In group3, the rate of arthralgia was significantly lower. [Conclusions] Serum cytokines in BD patients were classified into 3 groups. In the future, we plan to conduct a detailed analysis by adding clinical and genetic information.

## W2-2

### Natural history of Behçet's disease focusing on remission of oral ulcers

Takafumi Tomizuka, Hirotoshi Kikuchi, Mai Okubo, Rui Nakajima, Kurumi Asako, Hajime Kono  
Department of Internal Medicine, Teikyo University School of Medicine

Conflict of interest: None

[Objective] To describe the long-term clinical course of each manifestation of Behçet's disease (BD), and to clarify the factors involved in the remission of oral ulcers (OU) using clinical information from patients with BD. [Methods] We studied 155 patients with BD who visited our hospital between 1989 and 2020. We established remission criteria for each manifestation and examined the changes in the long-term clinical course. Furthermore, classification and regression trees and multivariable analyses were performed to investigate the prognostic factors of OU; hazard ratios were used to assign scores to prognostic factors deemed significant. [Results] OU appeared earliest, with the slowest decline in prevalence observed after BD diagnosis. OU were found to be the most common factor inhibiting complete remission. Female sex, a positive pathergy test, young age at OU onset, long duration of non-treatment or symptomatic treatment for OU, and lack of central nerve involvements were prognostic factors of OU. [Conclusions] The remission criteria for each symptom determined in this study made clear that OU had the greatest impact on complete remission of BD. An analysis of factors involved in OU remission suggested that early therapeutic intervention for OU would improve its prognosis.

## W2-3

### Clinical features of 103 patients with Behçet's disease with arthritis

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University of Occupational and Environmental Health, Japan

Conflict of interest: None

[Objective] Arthritis is important in diagnosis for Behçet's disease (BD), but there is no consensus on the clinical features. We clarify the features BD with arthritis. [Methods] We compared the features in patients (pts) with BD, diagnosed by criteria of the MHLW, with arthritis (n=103) or without arthritis (n=127). [Results] 83.0% were incomplete type. Uveitis and recurrent aphthae were significantly less, nodular erythema was frequent, and women and intestinal ulcers tended to be more common in pts with arthritis (HLA-B51: 37.7, A26: 30.5, RF: 14.0 and ACPA: 1.5%). 4 pts complicated with RA, 3 of the pts had bone erosion. Mean TJC was 4.4 and SJC was 1.7 (knee 28.2, ankle 20.4, wrist 24.3, elbow 17.5, shoulder 17.5, MPJ 11.7, PIPJ 10.7, DIPJ 2.9%). No pts complicated with enthesitis and axial spondyloarthritis. Colchicine (79.9%), NSAIDs (36.9%), MTX (50.5%), GCs (28.2%), IFX (26.2%) and ADA (14.6%) were administered. In 54 pts followed over a year, TJC (3.5→0.7) and SJC (1.3→0.1) were notably decreased in each treatments. [Conclusions] Frequency of

mucocutaneous lesions and intestinal ulcers were different in pts with arthritis. Large-joint arthritis was relatively frequent, no pts complicated with enthesitis and axSpA. They were treated with Colchicine, MTX and anti-TNF rather than GCs.

## W2-4

### Clinical effects of apremilast on Behçet's disease and changes in serum cytokines

Yusuke Ushio<sup>1</sup>, Risa Wakiya<sup>2</sup>, Kiyo Ueeda<sup>2</sup>, Tomohiro Kameda<sup>2</sup>, Shusaku Nakashima<sup>2</sup>, Hiromi Shimada<sup>2</sup>, Mikiya Kato<sup>2</sup>, Taichi Miyagi<sup>2</sup>, Koichi Sugihara<sup>2</sup>, Mao Mizusaki<sup>2</sup>, Rina Mino<sup>2</sup>, Kanako Chujo<sup>2</sup>, Hiroaki Dobashi<sup>2</sup>  
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Conflict of interest: None

[Objective] To investigate the effects of apremilast on multiple lesion domains including oral ulcers and blood cytokine levels in Behçet's disease. [Methods] We analyzed the clinical effects of apremilast on oral ulcers, genital ulcers, skin lesions, and arthritis at 9 months after treatment. Changes in serum cytokines (IFN- $\gamma$ , TNF- $\alpha$ , IL-6, IL-8, IL-10, IL-23, and MIP-1 $\beta$ ) before and after treatment were measured by ELISA. [Results] Fourteen patients were included in the study. The mean age was 46.6 $\pm$ 13.0 years, and the mean disease duration was 10.2 $\pm$ 8.8 years. 5 cases of genital ulcers, 8 cases of skin lesions, 6 cases of arthritis, and 1 case of gastrointestinal lesions were observed. Oral ulcers improved in all patients except one intolerant patient. At 9 months after treatment, 100% of genital ulcers, 57% of skin lesions, and 20% of arthritis had improved. TNF- $\alpha$ , IL-23, and MIP-1 $\beta$  were significantly decreased after treatment. In the group of patients whose oral ulcers disappeared after 3 months, there was a greater decrease in IFN- $\gamma$ . In patients with arthritis, there was a decrease in IL-8. [Conclusions] Apremilast was found to be effective in domains other than the oral ulcer. Cytokines were found to be associated with lesion type and therapeutic efficacy.

## W2-5

### Anti-neutrophil Cytoplasmic Antibody (ANCA) in our Japanese Patients with Behçet's Disease

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Conflict of interest: None

[Objective] To investigate the relationship between Behçet's disease (BD) and anti-neutrophil cytoplasmic antibody (ANCA). [Methods] We enrolled 28 Japanese BD out-patients followed in our hospital, measured their MPO/PR3-ANCA during from 2013 to 2015, and analyzing the relationship between the BD's symptoms and ANCA with statistically. In the present study, all of the BD patients fulfilled the both Japanese and the international study group's criterion. [Results] The characteristics of our patients were below: male, 5; mean age (SD), 40.9 (10.9) y/o; oral aphthous ulcers: 28 (100%) patients, genital ulcers: 25 (89.3%), ocular lesions: 5 (17.9%), skin lesions: 28 (100%), positive pathergy test: 2 (7.1%), arthritis: 8 (28.6%), intestinal lesions: 4 (14.3%), neural lesions: 1 (3.6%), vascular lesions: 4 (14.3%), positive HLA-B\*51: 4 (14.3%), positive ANCA: 3 (10.7%). The both vascular and intestinal lesions of BD were tend to be related with ANCA; each *p*-value (Fisher's exactly probability test) 0.045, relative risk 8.3, 95% confidence interval 1.77-39.32. [Conclusions] In our study, ANCA tended to associated with the vascular lesions and intestinal lesions of BD. Thus, our hypothesis may be supported. It is necessary for us to collect and to analyze more cases in future.

## W2-6

### Two cases of intestinal Behçet's disease successfully treated with apremilast

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Conflict of interest: None

[Case 1] At the age of 28, he was diagnosed with Behcet's disease (BD). Colchicine was initiated for stomatitis and his symptoms were slightly relieved. Six months ago, however, intestinal involvement was confirmed by colonoscopy. He was referred to this hospital after refusing to take glucocorticoid. We suggested anti-TNF agents, but he was concerned about side effects. We next suggested apremilast, which he agreed to take. One month later, the stomatitis disappeared. The ileal ulcers had also disappeared 6 months later. [Case 2] He had intestinal BD at the age of 51. He was given salazosulfapyridine and methotrexate, however, his kept having mild abdominal pain intermittently. He did not agree to further treatment, except for apremilast. The ileal lesions had disappeared when colonoscopy was performed 6 months later. [Clinical implication] According to Behcet's Disease Clinical Practice Guidelines 2020 of JSBD, glucocorticoids and anti-TNF agents are the treatment of choice for moderate to severe intestinal BD, but there are concerns about side effects. Since the oral cavity and gastrointestinal tract have common characteristics in that they are both mucosal tissues, apremilast may be one of the treatment options for intestinal lesions of BD such as in our cases.

### W3-1

#### **Prediction of flare after discontinuation of biologics by ultrasonography in patients with rheumatoid arthritis achieving remission**

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Conflict of interest: None

[Objective] This study aimed to investigate the predictability of flare after discontinuation of biological disease-modifying antirheumatic drugs (bDMARDs) by ultrasonography (US) in patients with rheumatoid arthritis (RA) achieving remission. [Methods] We prospectively enrolled RA patients who maintained a simplified disease activity index  $\leq 3.3$  and discontinued bDMARDs and measured clinical assessment and US every 2-3 months for 2 years. The US examination was performed on 40 joints using the semi-quantitative method of 0-3 on the Grey-scale (GS) and Power Doppler (PD). [Results] Thirty-six patients were enrolled and two patients who dropped out early without flare were excluded from the comparative analyses. At baseline, the median GS score was 7, PD score was 0, and PD score was 0 in 24 patients (67%). There were no significant differences in US findings between the relapse group (20 patients) and the non-relapse group (14 patients). In the univariate Cox proportional hazards model analysis, the PD score was significant with a hazard ratio of 1.2 ( $p=0.014$ ), but not the other US findings. [Conclusions] The US findings suggests that an elevated PD score is associated with flare after bDMARDs discontinuation, although it is insufficient for the flare prediction.

### W3-2

#### **Correction of physical joint examination and prediction of joint destruction using musculoskeletal ultrasound and re-palpation in patients with rheumatoid arthritis in remission**

Jun Ishizaki<sup>1</sup>, Erika Horimoto<sup>1</sup>, Yuki Nishino<sup>1</sup>, Kenta Horie<sup>1</sup>, Daisuke Hiraoka<sup>1</sup>, Takuya Matsumoto<sup>1</sup>, Koichiro Suemori<sup>1</sup>, Hitoshi Hasegawa<sup>1,2</sup>, Katsuto Takenaka<sup>1</sup>

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Conflict of interest: None

[Objective] We analyzed the risk of joint destruction of subclinical synovitis, which was palpable and non-palpable by re-palpation after ultrasound (US) in patients with rheumatoid arthritis in remission. [Methods] In 62 patients in clinical remission, bilateral hand and finger joints were scanned using US, imaging the dorsal surface. Only the number of subclinical synovitis sites in three areas including the wrist (the radial, median and ulna side; 6 sites), the MCP (10 sites) and the first IP and 2nd-5th PIP joints (10 sites) was presented to the attending physician and

re-palpation was performed. The incidence of joint destruction after one to two years was compared between the palpable and non-palpable synovitis groups. [Results] 22 patients (36%) had subclinical synovitis in 49 sites. 26 sites (53%, wrist 16/28, MCP 8/18, IP 2/3) were palpable by re-palpation after US. The progressive joint destruction was revealed in 13 sites (27%) after one to two years, and the palpable synovitis and the presence of bone erosion at the time of US were identified as its risk factors. [Conclusions] Our analysis suggested that about half of the subclinical synovitis found using US in remission patients were palpable, and the palpable synovitis with erosion had a high risk of joint destruction.

### W3-3

#### **Association of Physical Activity with Rheumatoid Mid-Hindfoot Deformity/Destruction**

Takaaki Noguchi<sup>1</sup>, Makoto Hirao<sup>2</sup>, Shigeyoshi Tsuji<sup>1</sup>, Kosuke Ebina<sup>2</sup>, Yuki Etani<sup>2</sup>, Gensuke Okamura<sup>3</sup>, Hideki Tsuboi<sup>3</sup>, Jun Hashimoto<sup>1</sup>

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Conflict of interest: None

[Object] Even with recent improvements in medical treatment for RA, foot deformity has been often seen. Forefoot deformity generally takes a major place in surgical treatment, but it can be easy to overlook severe mid-hindfoot deformity without complaint of patients. Then, we examined the relationship between mid-hindfoot deformity/destruction and physical activity. [Methods] Radiographic findings of 101 lower limbs (59 patients) were retrospectively evaluated. Alignment parameters in the lower extremity and joint destruction grade (Larsen grade) were measured. TUG test, mHAQ, SAFE-Q, and DAS28-CRP were investigated to assess clinical status. Then we examined those relationship. [Results] Subtalar joint destruction was correlated with TUG time ( $r=0.329$ ), mHAQ ( $r=0.338$ ), and SAFE-Q: social functioning ( $r=0.332$ ). TUG time was correlated with the HKA ( $r=-0.527$ ), talo-1st metatarsal angle ( $r=0.64$ ), calcaneal pitch angle ( $r=-0.433$ ), M1-M5A ( $r=-0.345$ ), and M2-M5A ( $r=-0.475$ ). [Conclusions] Physical activity especially correlated with mid-hindfoot deformity. Even if physical activity dose not decrease for flatfoot deformity without pain, we carefully see the foot. And then, wearing arch support, foot exercise and surgical treatment should be considered from the early phase.

### W3-4

#### **Examination of the detectability of finger joint bone erosion by ultrasonography (US) ~ Comparison with HR-pQCT ~**

Hitomi Nagasaka<sup>1</sup>, Shigenori Tamaki<sup>1</sup>, Takashi Kato<sup>2</sup>, Motokazu Kai<sup>3</sup>, Kunikazu Ogawa<sup>3</sup>, Ryosuke Hibi<sup>1</sup>, Yusuke Suzuki<sup>1</sup>, Hidenao Imada<sup>1</sup>, Hiroaki Mizuno<sup>1</sup>, Hisaji Oshima<sup>4</sup>, Ikuko Tanaka<sup>1</sup>

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Conflict of interest: None

[Objective] HR-pQCT, which images peripheral joints with high resolution, is considered to be most useful for detecting bone erosion. In this study, we examined whether the bone erosion of the finger joint confirmed by HR-pQCT could be detected by US. [Methods] In 18 patients with the finger joint pain and could not confirm the bone erosion by plain X-ray and US, the finger joints were imaged by HR-pQCT. The bone erosion confirmed by HR-pQCT were detected again by US. [Results] A total of 49 bone erosions were confirmed by HR-pQCT. In MCP joints 28 erosions were confirmed (24 on the radial side, 4 on the ulnar side). In IP / PIP joints 21 erosions were confirmed (13 on the radial side, 8 on the ulnar side). In the US, a total of 41 (84%) bone erosions were detected. In MCP joints 24 erosions were detected (22 on the radial side, 2 on the ulnar side). In IP / PIP joints 17 erosions were detected (10 on the radial side, 7 on the ulnar side). [Conclusions] It was considered that the bone erosion on the side of the joint was often overlooked in the scanning from the extension side of the fingers performed by the usual US examination. On the other hand, the ability to visualize bone erosion was considered to be close to that of HR-pQCT.



### W3-5

#### Analysis of influencing factors for power Doppler remission in patients with rheumatoid arthritis

Yuka Doma<sup>1</sup>, Tadashi Okano<sup>2</sup>, Shingo Washida<sup>1</sup>, Asami Fujii<sup>1</sup>, Yuko Yoshida<sup>1</sup>, Kenji Mamoto<sup>2</sup>, Shohei Anno<sup>2</sup>, Yutaro Yamada<sup>2</sup>, Koji Mandai<sup>3</sup>, Kentaro Inui<sup>3</sup>, Tatsuya Koike<sup>4,5</sup>, Hiroaki Nakamura<sup>2</sup>

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Conflict of interest: None

[Objective] Power Doppler positive findings in rheumatoid arthritis (RA) patients are known to be predictors of joint destruction. We investigated the factors that influence power Doppler remission. [Methods] From January 2017 to August 2020, 750 RA patients who underwent ultrasound examinations were included. The definition of powered Doppler remission was defined as power Doppler Grade 0 by semi-quantitative evaluation in all sites of finger, wrist and feet. The factors that influence power Doppler remission were investigated. [Results] There were 132 cases of powered Doppler remission and 618 cases of non-powered Doppler remission. Logistic regression analysis was performed that Power Doppler remission was the dependent variable, and age, gender, RA duration, MTX use, biologics use, steroid use, CRP level, MMP-3 level, and DAS28-CRP level are the independent variables. The odds ratio for steroid use was 0.504 [95% confidence interval=0.257-0.989];  $p=0.046$ , and the DAS28-CRP level was 0.699 [95% confidence interval=0.571-0.856];  $p=0.001$ , which was found to affect the achievement of powered Doppler remission. [Conclusions] It is necessary to reduce the disease activity as low as possible without using steroids to achieve power Doppler remission in patients with RA.

### W3-6

#### Changes in the destructive hip morphology of rheumatoid arthritis during total hip arthroplasty

Hidetoshi Tsushima<sup>1</sup>, Junichi Fukushi<sup>2</sup>, Satoshi Ikemura<sup>1</sup>, Yukio Akasaki<sup>1</sup>, Toshifumi Fujiwara<sup>1</sup>, Daisuke Hara<sup>1</sup>, Takahide Sakuragi<sup>2</sup>, Satoshi Kamura<sup>2</sup>, Hisaaki Miyahara<sup>2</sup>, Hisakata Yamada<sup>1</sup>, Yasuharu Nakashima<sup>1</sup>

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Conflict of interest: None

Purpose) The purpose of this study is to perform a detailed analysis using the X-ray that has undergone THA to clarify what kind of changes are actually occurring. Methods) The subjects were RA patients who underwent Primary THA at two institutions. Patients who underwent the procedure from 1998 to 2003 were included in the early group, and 2013 to 2019 were included in the late group. The X-ray just before surgery was evaluated. The evaluated items were quantification of inward migration, the elevation of the head and compression of the head. A analysis was performed on the presence or absence of capital drops. Results) 103 patients in the early group and 87 patients in the late group were included. inward migration decreased in the late group, -7.45 mm ( $p<0.0001$ ), compared to -3.44 mm in the early group. There was no difference in the elevation and the compression of the head. The prevalence of capital drop was increased in the late group, 7.8% in the early group and 27.5% in the late group ( $p<0.0006$ ). Conclusions) The frequency of OA-like changes increased, and the degree of inward and upward migration was decreasing in the late group. It was suggested that the improvement of treatment with bioDMARDs caused great changes in the degree and mode of hip joint destruction.

### W4-1

#### Comparison of subsidence between fit-and-fill and tapered-wedge stem after total hip arthroplasty in Dorr type C femurs

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Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University

Conflict of interest: None

[Objective] To compare the degree of stem subsidence between two different femoral component designs and to determine the risk factors associated with stem subsidence after cementless total hip arthroplasty (THA) in Dorr type C femurs. [Methods] We retrospectively reviewed 48 hips using fit-and-fill stem and 43 hips using tapered wedge stem. Radiologically, the distance between the apex of the major trochanter and the stem shoulder were measured at three different time points (immediately [0 W], one week [1 W], and six weeks [6 W] after surgery) and the degrees of stem subsidence were assessed by comparing the distance between 0 W and 1 W, 1 W and 6 W, and 0 W and 6 W, respectively. [Results] The mean degrees of subsidence were significantly higher in the fit-and-fill stem group than in the tapered wedge stem group. In addition, the rates of >3 mm subsidence were 16.7% and 2.3%, respectively. There was also a significant difference between the two stems. Multivariate analysis demonstrated that higher age and fit-and-fill stem were risk factors for >3 mm subsidence after THA in Dorr type C femurs. [Conclusion] Our findings suggest that the tapered wedge stem is more suitable for Dorr type C femurs than the fit-and-fill stem to avoid early postoperative subsidence in cementless THA.

### W4-2

#### The Alteration in NGF concentration during total knee arthroplasty for the knee of rheumatoid arthritis and osteoarthritis

Tomohiro Onodera, Norimasa Iwasaki

Department of Orthopaedic Surgery, Hokkaido University Hospital

Conflict of interest: Yes

[Objective] The involvement of NGF in acute postoperative pain has not been sufficiently analyzed. The purpose of this study is to clarify the involvement of NGF in postoperative pain of total knee arthroplasty (TKA). [Methods] Twenty knees in 19 patients who underwent TKA for RA and OA were targeted (RA 9 knees, OA 11 knees). The NGF concentration was measured during and after the operation. Blood NGF was also measured before and after surgery. [Results] Plasma NGF levels in RA were significantly higher than those in OA during all periods. The intraoperative synovial fluid NGF concentration was significantly higher in the RA group than in the OA group (OA 6.0 pg/ml vs RA 45.1 pg/ml,  $p<0.05$ ). The concentration of NGF in the synovial fluid was significantly increased postoperatively in the OA group, while NGF concentration in the synovial fluid in RA group did not change significantly depending on the observation period. [Conclusions] In RA knee, there is no significant change in intra-articular NGF concentration was observed, possibly because the synovial resection possibly reduced the NGF concentration. In OA knee, an increase in NGF concentration in the knee joint was observed, suggesting that the increase of NGF concentration in the joint might contribute to postoperative pain.

### W4-3

#### Comparable short-term KOOS between open-wedge high tibial osteotomy and total knee arthroplasty in patients over age 60: A propensity score-matched cohort study

Yukio Akasaki<sup>1</sup>, Takenori Akiyama<sup>2</sup>, Tomohiro Horikawa<sup>3</sup>, Ken Okazaki<sup>4</sup>, Satoshi Ikemura<sup>1</sup>, Toshifumi Fujiwara<sup>1</sup>, Hidetoshi Tsushima<sup>1</sup>, Daisuke Hara<sup>1</sup>, Hisakata Yamada<sup>1</sup>, Yasuharu Nakashima<sup>1</sup>

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Conflict of interest: None

[Objective] The purpose of the present study was to evaluate improvement in KOOS after open-wedge HTO in comparison with TKA in cohorts over age 60 matched by pre-operative age, gender, BMI, HKAA, KOOS sub-scores, and osteoarthritis (OA) grade. [Methods] Propensity score matching was performed between 162 HTO patients and 134 TKA pa-

tients. When calculating the propensity score by multivariate logistic regression analysis, the following pre-operative confounders were included: age, gender, BMI, HKAA, KOOS sub-scores, and OA grade. Consequently, a total of 55 patients were included in each group. [Results] After propensity score matching, all matched pre-operative variables were identical, with no significant differences between the HTO and TKA group. None of the post-operative KOOS sub-scores at 1 year after surgery showed a significant difference between the HTO and TKA groups. Both groups demonstrated significant and comparable post-operative improvement in every KOOS sub-score. [Conclusion] In patients over age 60, short-term pain relief and improvements in activity and quality of life were comparable between HTO and TKA after propensity score matching including pre-operative age, KOOS sub-scores, and OA grade.

#### W4-4

##### **Examination of the incidence rates of metatarsal deviation at the osteotomy sites due to the difference in the start time of heel gait after hallux valgus surgery in patients with rheumatoid arthritis**

Haruki Tobimatsu, Katsunori Ikari, Koichiro Yano, Ken Okazaki

Department of Orthopedic Surgery, Tokyo Women's Medical University

Conflict of interest: None

**Object** Proximal rotational closing-wedge osteotomies of the first metatarsal have been performed for hallux valgus deformities in patients with rheumatoid arthritis (RA) at our institute. Patients were allowed to start heel gait a day after surgery, but some cases suffered from metatarsal deviations at the osteotomy site. To prevent this complication, we revised the start time of heel gait to 10 days after surgery. The aim of this study is to compare the incidence rates of metatarsal deviation between the difference of the heel gait start times. **Methods** We evaluated 86 RA patients (92 feet) who underwent this procedure between 2017 and 2021. The subjects were divided into two groups: started heel gait a day after surgery (46 feet) and started heel gait 10 days after surgery (46 feet). The incidence rates of metatarsal deviation in each group were evaluated. **Results** The incidence rate of metatarsal deviation in the group who started heel gait 10 days after surgery (0 feet, 0.0%) was significantly lower than those who started heel gait a day after surgery (21 feet, 45.7%) ( $P < 0.01$ ). **Conclusions** We found that the incidence rate of metatarsal deviation at the osteotomy sites 10 days after rheumatoid hallux valgus surgeries was significantly lower than that conducted a day after surgery.

#### W4-5

##### **Combination of modified Scarf osteotomy and metatarsal shortening offset osteotomy for rheumatoid forefoot deformity**

Yuki Etani<sup>1</sup>, Makoto Hirao<sup>1</sup>, Kosuke Ebina<sup>2</sup>, Takaaki Noguchi<sup>3</sup>, Gensuke Okamura<sup>5</sup>, Akira Miyama<sup>6</sup>, Hideki Tsuboi<sup>5</sup>, Akihide Nampo<sup>7</sup>, Shigeyoshi Tsuji<sup>3</sup>, Hajime Owaki<sup>8</sup>, Jun Hashimoto<sup>4</sup>, Seiji Okada<sup>1</sup>

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Conflict of interest: None

[Objective] For hallux valgus patients, we have been choosing the combined surgery: modified scarf osteotomy for the great toe and metatarsal shortening offset osteotomy for the lesser toes in RA cases. The purpose of this study was to investigate the factors that may predict the post-operative outcome of this combined surgery. [Methods] A retrospective observational study of 53 RA patients (mean follow-up period: 4.6 years) who underwent the surgery was completed. Radiographic evaluation and patient-standing scoring were evaluated before and after surgery. [Results] The clinical outcomes are all improved significantly with surgical treatment. Radiographic measurement showed significant improvement in

HVA, M1M2A, and M2M5A. Multivariate analysis showed that preoperative DAS28-CRP was negatively correlated with postoperative JSSF hallux score. In addition, preoperative M2M5A patency was a risk factor for redislocation of the lesser toe MTP joint. [Conclusions] The combined surgery improved radiographic measurements and patient-standing scoring. We should take care in cases of poor preoperative disease control or spread of M2-M5A, as these may be factors that worsen the postoperative outcome.

#### W4-6

##### **Clinical Outcome of combined surgery in modified Lapidus procedure for Rheumatoid Forefoot Deformity**

Tomohiro Onodera, Norimasa Iwasaki

Department of Orthopaedic Surgery, Hokkaido University Hospital

Conflict of interest: None

[Objective] Since modified Lapidus procedure has high valgus correction power, it is often used for severe RA forefoot deformity. We investigated the clinical outcomes after the modified Lapidus procedure focusing on the combined surgery for the lesser toes. [Methods] Of the 50 RA patients, 28 patients in 27 patients who were 12 months or more after surgery were included. Range of motion, HV angle, M1M2 angle, M1M5 angle, and JSSF RA scale was evaluated. [Results] Thirteen feet of shortening osteotomy of the metatarsal bone, 11 feet of resection arthroplasty, and 11 feet of interphalangeal joint fixation were performed. The HV angle was 48° to 19° on average before surgery, the M1M2 angle was 16° to 10°, and the M1M5 angle was 38° to 27° ( $P < 0.01$ ). The JSSF scale improved from 47 to 79 points ( $P < 0.01$ ). The preoperative HV angle showed a positive correlation with that of the final follow-up. Postoperative clinical outcomes for joint-preserved and resection arthroplasty were identical (76.1 vs 81.8,  $P > 0.31$ ). [Conclusions] It was clarified that the hallux valgus angle at the final follow-up was affected by the degree of preoperative deformation. The short-term clinical outcomes of 2-5 toe arthroplasty and resection arthroplasty combined with modified Lapidus were almost identical.

#### W5-1

##### **Treatments and incidence rate of vascular events in patients with Takayasu arteritis using Japanese health insurance database**

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Conflict of interest: Yes

[Objective] To investigate the treatment patterns and incidence rate (IR) of vascular events (VE) in patients with Takayasu arteritis (TAK). [Methods] Using claims data provided by Medical Data Vision Co., Ltd, we defined individuals as TAK cases if they had ICD10 code of TA, had at least one prescription of oral corticosteroids (CS) and medical aids for intractable diseases between January 2013 and September 2019, and were without ICD10 code of giant cell arteritis. VE events was defined by ICD10 codes and medical practice or medications. Patients were followed from the month of the first month in which cases met the above criteria until the month of loss of follow-up, or September 2020. We described treatment patterns and calculated IR (95% CI) of VE. [Results] In the study population ( $n=954$ ), the median age was 49 years, 83.4% were female, and median observation term was 51 months. The proportion of patients receiving CS was 36.2% for  $\leq 5$  mg/day, 48.1% for  $5 < \text{CS} \leq 30$  mg/day, and 15.7% for  $> 30$  mg/day. Twenty two percent of the patients had treatments with biological agents (18.3% for tocilizumab), and 4.4% had any surgery for TAK. IR/1,000 PY of VE was 13.0 [9.8-16.8]. [Conclusions] Recent treatment patterns and incidence rate of VE in patients with TAK in Japan were revealed.

## W5-2

### Efficacy of tocilizumab on the management of Takayasu's arteritis in clinical practice; a single-center experience

Azusa Kikuchi, Kazuhiro Kurasawa, Sara Komatsu, Yusuke Sakaue, Yui Yoshida, Yoriko Tasaka, Yuta Takamura, Tomoyuki Miyao, Ayae Tanaka, Satoko Arai, Reika Maezawa, Masafumi Arima  
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Conflict of interest: None

[Objective] A clinical trial has demonstrated that tocilizumab (TCZ) prevents relapse of Takayasu's arteritis and reduces the dose of glucocorticoids (GC). However, the efficacy of TCZ, particularly early administration, affects the management of TKA, is still unknown. [Methods] A retrospective observational study. The subjects were TKA patients who were treated initially in our hospital. Medical records were reviewed. [Results] Thirty-eight patients with TKA were included in the study, 8 males and 30 females, with a mean age of onset of 35.0 years. 15 patients received TCZ, 7 of whom received it after relapse of disease, and 8 patients received TCZ with GC as initial treatment. Relapse occurred in 13 of 30 patients (43%) who received initial treatment without TCZ. Seven of these patients were administered TCZ after relapse, and 23 received treatment without TCZ. In contrast, in the 8 patients who received initial treatment including TCZ, only 1 (12%) relapsed. None of the patients who received TCZ after relapse had a further relapse. Moreover, the dose of GC decreased to  $5.7 \pm 5.5$  mg of PSL, less than the  $12.7 \pm 3.3$  mg at relapse ( $p=0.04$ ). [Conclusions] TCZ reduces relapse and decreased GC dose, whether used for initial treatment or after relapse.

## W5-3

### Long-term efficacy and retention rate of biologics in Takayasu arteritis

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Department of Rheumatology, Tohoku University Hospital

Conflict of interest: None

[Objective] The relapse of Takayasu arteritis (TAK) is frequent, and biologics including tocilizumab (TCZ) are used. However, information about the long-term efficacy and retention rate is scarce. This study investigated the long-term effect of biologics in TAK. [Methods] 116 patients with TAK who visited our department during 2018 to 2021 were retrospectively evaluated for the long-term effects of biologics. [Results] 44 out of 116 patients (37.9%) received biologics. Seven patients required more than two biologics. The numbers of biologics used were as follows, TCZ, 34; TNF inhibitors, 12; JAK inhibitors, 2; abatacept, 1; rituximab, 1. The mean doses of prednisolone (PSL) before, upon initiation, and the most recent were  $10.1 \pm 3.9$ ,  $25.1 \pm 11.6$ , and  $5.6 \pm 3.7$  mg/day, respectively. The retention rate of TCZ was 82.4%, and TCZ was discontinued in following cases; infections, 2; exacerbation of other inflammatory conditions, 2; infusion reaction, 1; ineffectiveness, 1. Discontinuation of TNF inhibitors was not documented. Six patients with TCZ achieved steroid-free. [Conclusions] The retention rate of TCZ was about 80%, and TCZ was useful for maintain remission in relapsed cases. The retention rate of TNF inhibitors was also high, and useful for cases with other complications.

## W5-4

### A case of Takayasu's arteritis developing in a patient with ulcerative colitis while treated with infliximab

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Department of Nephrology and Rheumatology, Nakagami Hospital

Conflict of interest: None

(Case) A 24-year-old male was diagnosed with ulcerative colitis (UC) 8 years ago and treated with medications such as 5-aminosalicylic acid, glucocorticoids or azathioprine. As the disease was resistant to these treatments, infliximab was started 5 years ago. But a year and six months after the treatment with infliximab the disease flared and one month later severe back pain and high fever occurred. Because CT scan showed wall thickenings of aorta and three main branches of aortic arch, Takayasu's arteritis

(TA) was diagnosed, and treatment with methylprednisolone pulse therapy followed by oral prednisolone yielded rapid improvement of symptoms. Given that in the treatment with infliximab he had flares of UC and TA developed, infliximab was switched to tocilizumab. After that no recurrence of TA was observed, however he experienced some flares of UC with tocilizumab or other biologics. (Clinical significance) TA complicates about 10 percent of patients with inflammatory bowel disease (IBD). The efficacy of biologics for IBD is well appreciated and there is growing evidence that biologics are also effective for TA. Cases of TA which developed while treated with biologics for IBD have been rarely reported. We describe a patient of TA who developed while treated with infliximab for UC.

## W5-5

### A Case of Takayasu Aortitis with Cerebral Infarction due to Left Internal Carotid Artery Stenosis during Treatment of Latent Autoimmune Diabetes in Adults

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Conflict of interest: None

[Case] 51-year-old female [Chief complaint] Right hemiparesis [Present Illness] She developed type 1 diabetes at the age of 46 and observed general fatigue with tremor and transit hemiparesis on the right upper extremity at 50. A brain MRI revealed small old infarctions and left carotid stenosis. CT scan revealed diffusely thickened walls in the aorta. [Family history] Nothing significant [Clinical course] Reexamination revealed severe stenosis in the left internal carotid and subclavian artery with thrombocytosis, elevated CRP and ESR. As we ruled out other diseases including giant cell arteritis, we diagnosed her with Takayasu's aortitis (TA). High dose PSL was introduced with clopidogrel and argatroban. As inflammation was rapidly normalized, we introduced tocilizumab and tapered PSL which has been tapered to 5 mg every other day without recurrence. [Clinical significance] The coexistence of TA and latent autoimmune diabetes in adults (LADA) is very rare. MHC class associated with the risk for developing the disease is different between TA and LADA. Interestingly, our patient possessed both risk haplotypes in HLA-DRB\*52:01 for TA and HLA-DRB1\*04:01 for LADA. The coincident presence of these HLAs suggested that unknown second hits may have contributed to the acute progression of TA.

## W5-6

### Stenosis of the right subclavian artery due to a sports injury that required differentiation from Takayasu's arteritis

Machiko Mizushima, Seido Ooka, Kazuko Yamazaki, Momoko Kashiwado, Tatsuya Kawasaki, Kumiko Tonooka, Kimito Kawahata  
St. Marianna University School of Medicine

Conflict of interest: None

[Objective] Takayasu's arteritis is a disease that causes inflammation of the aorta and its major branches. We experienced a case that Takayasu's arteritis was suspected due to a young cerebral infarction and stenosis of the right carotid artery, but the patient was diagnosed with a sports injury due to baseball throwing form. [Case] Nineteen-years-old, Male. At the age of 19, Weakness and wobbling of the right lower limb appeared. Awareness of numbness and coldness in the right upper limb, MRI of the right upper limb showed occlusion of the right clavicle fossa artery and development of immediate accessory blood circulation. Since Takayasu's arteritis was suspected, he was referred to our department. The inflammatory response was negative, and PET-CT examination showed no findings suggestive of arteritis. Since the occlusion of the clavicle fossa artery was not at the origin but on the peripheral side, the patient was diagnosed with angiopathy due to a longer throwing motion than Takayasu's arteritis. After that, rehabilitation was performed under the guidance of an orthopedic



surgeon, and the symptoms were alleviated. [Conclusions] The involvement of abnormal blood circulation due to sports injuries also needs to be identified for Takayasu's aortitis.

## W6-1

### Proposal of a method for diagnosis as an optimization of Cranial type imaging diagnosis of giant cell arteritis: presentation of useful of vascular echo for early diagnosis and proposal of pitfall in diagnosis and method of simplification

Toshio Kawamoto<sup>1</sup>, Michihiro Ogasawara<sup>1</sup>, Yuko Matsuki<sup>1</sup>, Masakazu Matsushita<sup>1</sup>, Kenjiro Yamanaka<sup>2</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>

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Conflict of interest: None

[Objective] Giant cell arteritis (GCA) can quickly lead to blindness and stroke, and a rapid and appropriate diagnostic method is required, and we aim to optimize diagnostic imaging. [Methods] We evaluated the effect of optimizing diagnostic imaging and methods for patients with suspected GCA who visited our hospital during 2019. Vascular mapping was carried out using vascular ultrasonography for three-dimensional computed tomography angiography and other imaging methods as references. [Results] We diagnosed fifteen cases of GCA among the 40 patients; the positive predictive value of V-US was 80% (12 of 15 patients) and negative predictive value was 88% (22 of 25 patients). Some had positive findings in both biopsy and vascular ultrasonography. We present ultrasonography is the best imaging method to diagnose early GCA. No patients with GCA developed blindness or stroke during 2019-21. We are going to report new patients who are required for differential diagnosis in 2021-22 and show proposal of pitfall in diagnosis and method of simplification. [Conclusions] We propose that vascular ultrasonography should be performed as the first examination for the diagnosis of GCA by the creation of vascular mappings when GCA is suspected in order to prevent blindness and stroke.

## W6-2

### Disease-specific gene expression in biopsy specimen of temporal arteries in patients with giant cell arteritis

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Conflict of interest: None

[Objective] The pathogenesis of giant cell arteritis (GCA) remains unrevealed. This study aims to detect the disease-specific gene expression in patients with GCA, which explains the disease mechanism. [Methods] Temporal artery biopsy (TAB) specimens were collected from patients with pathologically proven GCA (GCA group). We included TAB samples of which patients' final diagnoses were other than GCA as the control (non-GCA group). We extracted messenger ribonucleic acid from the samples, performed a gene expression assay on the Agilent® Micro Array system, and compared the two groups' differences. [Results] We obtained four GCA (mean 70 years old) and four non-GCA TBA samples (78 years old, final diagnosis: two polymyalgia rheumatica, one microscopic polyangiitis, and one unclassified fever). Hierarchical cluster analysis and principal component analysis showed distinct differences in gene expression between the two groups. We found the higher expression of B-cell, T-cell, and dendritic cell activation-related genes in the GCA group. This result implies that various kinds of immune cells involve inflammation at the site of arteritis. [Conclusion] We observed diseases specific gene-expression patterns in TBA specimens in patients with GCA.

## W6-3

### Effectiveness of craniocervical blood vessel evaluation in giant cell arteritis using high-resolution CT angiography

Takako Hashimoto, Shusaku Fukaya, Jo Nishino, Daisuke Hirano, Megumi Kurumizawa, Konomi Akamatsu, Jun Fukui, Tatsuki Naganawa, Masashi Suzuki, Marika Sawada, Naoki Dosoden, Hidekata Yasuoka

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Conflict of interest: None

[Background] Reported herein are 3 cases we encountered where the thickened obstructed blood vessel and the constrained part of blood vessel, which could not be detected by temporal arterial echography, were detected by using high-resolution CT angiography (CTA) in order to evaluate initially pathological lesions in a cerebrovascular region of giant cell arteritis (GCA). [Representative case] 72-years-old women who consulted a doctor due to mild fever, back neck pain and jaw claudication. As high-resolution CTA indicated both constriction and wall thickening in the right temporal artery, the constriction site was precisely identified, and biopsy from the site was conducted. Pathological examination found endometrium thickening, infiltration of inflammatory cells to internal elastic membrane-media and multinucleated giant cells, based on which the woman was diagnosed as cranial GCA. [Discussion] Since high-resolution CTA exhibits higher sensitivity than temporal arterial echography, it enables precise identification of thickening of blood vessel wall and the part of constriction in the craniocervical region, which allows both for examination of relationship between the constrained part of blood vessel and clinical findings and for reliable identification of the biopsy site.

## W6-4

### The usefulness of Platelet-derived Microparticles in Differentiating Giant Cell Arteritis from Polymyalgia Rheumatica

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Division of Hematology and Rheumatology, Department of Internal Medicine, National Defense Medical College Hospital

Conflict of interest: None

[Objective] Approximately, 15% of polymyalgia rheumatica (PMR) is associated with giant cell arteritis (GCA). Imaging and temporal artery biopsy are required for GCA diagnosis. Thus, a simple method to predict the GCA association would be useful. Platelet-derived microparticles (PMPs) are 1 µm extracellular vesicles that are released from activated platelets. PMPs act as inflammatory mediators on peripheral tissues, including the vascular endothelial cells. In this study, we investigated the usefulness of PMPs in differentiating PMR and GCA. [Methods] Patients with PMR and GCA who visited our hospital from 2016 to 2021 were enrolled in this study. The PMR met the 2012 ACR/EULAR criteria, without aortitis on imaging results, as well as peripheral arthritis. The GCA met the 1990 ACR criteria, with arteritis confirmed by temporal artery biopsy. A commercial ELISA kit was used to measure PMPs. [Results] Five GCA and eight PMR cases were enrolled in this study. The CRP, ESR, hemoglobin, and platelet counts were the same between the two groups. PMPs were significantly higher in the GCA group (9.592 [9.26-18.328] U/mL) than that in the PMR group (7.395 [2.595-11.385] U/mL). [Conclusions] Peripheral blood PMPs are useful in differentiating PMR and GCA.

## W6-5

### A study of 31 cases of giant cell arteritis in our hospital

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Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine

Conflict of interest: Yes

[Objective] In this study, we investigated the risk of relapse in patients with GCA diagnosed at our hospital. [Methods] From March 2009 to August 2021, 31 cases of GCA (mean age 74.6±8.0 years, 71.0% female) diagnosed according to the classification criteria of the American College of

Rheumatology were included in this study. Clinical findings, laboratory results, comorbidities, and medications were analyzed retrospectively. [Results] Corticosteroid therapy was initiated in 30 patients, and the mean time from symptom onset to treatment was 5.5 ( $\pm 7.6$ ) months. The mean observation period was 2.6 years, and 10 patients required increased doses of steroids. When the patients who required increased doses of steroids were defined as the relapse group, there were no significant differences in age, CRP at the onset of disease, presence of vision loss, presence of PMR, comorbidities, concomitant use of immunosuppressive drugs, use of tocilizumab, or biopsy results in univariate analysis compared with the non-relapse group. [Conclusions] In this study, we were not able to identify predictive factors for refractory GCA, but early diagnosis and treatment are desirable because a delay in diagnosis can lead to blindness and irreversible organ damage.

## W6-6

### The evaluation of factors contribute to diagnostic findings of temporal artery biopsy in Giant Cell Arteritis

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Conflict of interest: None

[Object] We evaluated the factor contribute to positive of temporal artery biopsy in Giant Cell Arteritis (GCA) patients. [Methods] Fifteen GCA patients were included from June 2014 to June 2021. The patients were retrospectively analyzed disease duration, age, serum CRP, ESR and maximum intima media thickness (maxIMT) of temporal artery by ultrasound examination. [Results] Baseline patient characteristics (n=16) were as follows; ratio of male to female (M:10 F:6). Disease duration was 2.9 month. Age: 75.8 years. Serum CRP: 12.4 $\pm$ 7.4 mg/dl, ESR: 94.3 $\pm$ 12.4 mm/h. MaxIMT: 0.84 $\pm$ 0.35 mm. As for comparison analysis between positive and negative result of temporal artery biopsy, disease duration: 4.8 months vs 1.5 months ( $p=0.035$ ). Age: 75.7 years vs 75.8 years ( $p=n.s$ ). Serum CRP: 9.6 $\pm$ 4.6 mg/dl vs 14.0 $\pm$ 8.5 mg/dl ( $p=n.s$ ), ESR: 97.2 $\pm$ 4.0 mm/h vs 92.3 $\pm$ 15.7 mm/h ( $p=n.s$ ). MaxIMT: 1.12 $\pm$ 0.35 mm vs 0.67 $\pm$ 0.23 mm ( $p=0.007$ ). [Conclusions] Disease duration and ultrasonographic maxIMT of temporal artery were the factor contribute to positive of temporal artery biopsy in GCA patients with statistical significance.

## W7-1

### Clock controlled gene Tef regulates the proliferation of RA-FLS

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Conflict of interest: None

[Objective] We have reported that the expression of clock genes in peripheral blood leukocytes correlates with the disease activity of rheumatoid arthritis (RA). In this study, we examined effects of clock gene *Tef* on the proliferation of RA-fibroblast like synovial cells (FLS). [Methods] After transfected *Tef* siRNAs or *Tef* over expression vector, RA-FLS were stimulated with or without IL-6/sIL-6R (100 ng/ml) or TNF- $\alpha$  (10 ng/ml) for 72 hours to examine the cell viabilities by WST-8 assay. Expressions of *Tef* mRNA in leukocytes of RA patients and in splenic lymphocytes of arthritis model mice were compared with those of healthy subjects and control mice, respectively. [Results] *Tef* overexpression significantly decreased cellular viabilities under unstimulated, IL-6/sIL-6R, TNF- $\alpha$ , and co-stimulated conditions, while suppression of *Tef* expression significantly increased cellular viabilities under IL-6/sIL-6R and TNF- $\alpha$  stimulation.

Expressions of *Tef* mRNA in leukocytes of RA patients and splenic lymphocytes of model mice were significantly decreased compared to healthy subjects and control mice, respectively. [Conclusions] Result suggested that clock gene *Tef* is involved in the pathogenesis of RA by regulating the proliferation of RA-FLS.

## W7-2

### C646 suppresses cell migration and cytoskeleton formation by TNF $\alpha$ -dependent CCL2 expression via RORE

Miki Fukusumi<sup>1</sup>, Kanako Nakagawa<sup>1</sup>, Natsuko Morimoto<sup>1</sup>, Kenta Kaneshiro<sup>1</sup>, Kohsuke Yoshida<sup>1</sup>, Yoshiko Kawasaki<sup>2</sup>, Koji Tateishi<sup>3</sup>, Yasuhiro Terashima<sup>3</sup>, Nao Shibamura<sup>4</sup>, Yoshitada Sakai<sup>5</sup>, Akira Hashiramoto<sup>1</sup>

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Conflict of interest: None

[Objective] We have reported that RORE sequences are responsible for TNF $\alpha$ -induced regulation of clock genes, and CBP/p300 inhibitor C646 regulates the RORE-binding transcription factor ROR $\alpha$ /REV-ERB $\alpha$ . We investigate the relation between TNF $\alpha$ -induced CCL2 expression mechanism via RORE and migration ability of RA synovial cells. [Methods] RA synovial cells were pretreated with the ROR $\alpha$  antagonist SR1001, the REV-ERB $\alpha$  agonist GSK4112, and C646, or transfected with CBP and p300 siRNA before stimulation with TNF $\alpha$ . Then, CCL2 mRNA expression levels and culture supernatant CCL2 were quantified using qPCR and ELISA, respectively. We also performed a reporter assay by using mutated RORE in CCL2 gene. Wound healing assay and F-actin staining were performed using C646 pretreated culture supernatant under TNF $\alpha$  stimulation. [Results] TNF $\alpha$ -induced CCL2 expression was suppressed by the addition of SR1001/GSK4112 or C646, and repression of CBP/p300 expression. CCL2 transcriptional activity tended to be increased by mutation of RORE. C646 inhibited both TNF $\alpha$ -induced cell migration and reorganization of the F-actin. [Conclusions] The results suggest that C646 suppresses TNF $\alpha$ -induced CCL2 via RORE, resulting in suppression of cell migration and cytoskeleton formation in RA synovial cells.

## W7-3

### N-acetylgalactosaminyl transferase 12 (GalNAc-T12) contributes to the survival and proliferation of chondrocytes

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Conflict of interest: None

[Objective] We have previously reported that the single nucleotide polymorphism (SNP) rs2295926 belonging to *GALNT12* gene (N-acetylgalactosaminyl transferase 12; GalNAc-T12) was strongly associated with rapid joint destruction in the patients with rheumatoid arthritis (RA) (TSS/years of RA  $\geq 50$ ). Here we examined the effects of GalNAc-T12 on chondrocytes. [Methods] Normal human knee chondrocytes (NHAC-Kn) were cultured with GalNAc-T12. The viability and proliferation of chondrocytes were studied by using WST-8 assay. Further, chondrocytes were induced apoptosis by the culture with actinomycin D, and we examined the effect of GalNAc-T12 on apoptosis in chondrocytes. [Results] When the chondrocytes were cultured in the medium supplemented with 10% fetal bovine albumin (FBS), GalNAc-T12 induced significant proliferation of cells. Whereas, chondrocytes were decreased by 80% when the cells were cultured in serum-free medium. However, this reduction of chondrocytes was significantly improved by the addition of GalNAc-T12. Further, GalNAc-T12 also significantly ameliorated the reduction of chondrocytes by apoptosis *via* actinomycin D. [Conclusions] GalNAc-T12 may involve the

rapid joint destruction in RA by contributing to the survival and proliferation of chondrocytes.

## W7-4

### **TNFR2 is essential for the inflammatory response in RA-FLS**

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Gunma University Graduate School of Medicine

Conflict of interest: None

[Objective] TNF-mediated fibroblast-like synoviocyte (FLS) activation is important for inflammation and joint destruction in rheumatoid arthritis (RA). The role of TNF-receptor 1 (TNFR1) in FLS has thoroughly been characterized. The functions of TNFR2 are, however, largely unknown. The aim of this study is to investigate the contribution of TNFR2 to the TNF-mediated activation of FLS. [Methods] RA-FLSs were transfected with TNFR2-targeting siRNA pools and transcriptional changes were determined by RNA-seq. QPCR, ELISA and immunoblotting were used to confirm the RNA-seq results and to gain insights into the pathways that regulate TNFR2 mediated changes in FLS. [Results] TNF stimulation resulted in a strong upregulation of proinflammatory cytokines, chemokines, tissue-degrading enzymes and other genes that are associated with synovial inflammation in RA. Silencing of TNFR2 markedly diminished the master regulators of joint inflammation, such as the CXCR3 chemokines CXCL9, 10 and 11. Consistently, immunoblots showed that TNFR2 was required for the TNF-induced phosphorylation of the transcription factor STAT1. [Conclusions] TNFR2 regulates proinflammatory gene expression in RA-FLS via STAT1 and thereby contributes to the detrimental effects of TNF in synovial joint inflammation.

## W7-5

### **Toll-like receptor 4 signaling pathways are involved in enhanced expression of BAFF receptor in peripheral monocytes of patients with primary Sjögren's syndrome**

Yumi Ikeda, Keiko Yoshimoto, Katsuya Suzuki, Hiroyuki Fukui, Masaru Takeshita, Kotaro Matsumoto, Tsutomu Takeuchi, Yuko Kaneko  
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: None

[Objective] We found that expression levels of BR3 and CD16 were elevated in LPS-stimulated THP-1, and that TLR4 expression was upregulated in peripheral CD14<sup>+</sup>CD16<sup>+</sup> monocytes in patients with primary Sjögren's syndrome (pSS). In this study, we investigated contribution of TLR4 signaling pathways to elevated expression of BAFF receptor (BR3) in pSS monocytes. [Methods] The expression levels of TLR4 and BR3 in peripheral monocytes of pSS patients (n=26), active SLE patients (n=15) and healthy controls (HC, n=14) by FACS. The expression of phosphorylated TLR4 signaling molecules in peripheral monocytes were analyzed by Western blotting. [Results] The expression levels of TLR4 and BR3 in peripheral CD14<sup>+</sup>CD16<sup>+</sup> monocytes were significantly enhanced in pSS patients as compared with active SLE (TLR4; p=0.0015, BR3; p<0.001) and HC (TLR4; p<0.001, BR3; p<0.001). Notably, the expression of TLR4 in CD14<sup>+</sup>CD16<sup>+</sup> monocytes was positively and significantly correlated with that of BR3 in pSS patients (p<0.001). In addition, phosphorylation of IRAK4, IKK $\alpha$ / $\beta$  and NF- $\kappa$ B were upregulated in pSS monocytes as compared to control. [Conclusions] Our results suggest that activation of TLR4 signaling pathways including IRAK4, IKK $\alpha$ / $\beta$  and NF- $\kappa$ B contribute to the elevated expression of BR3 in pSS monocytes.

## W7-6

### **Monocyte cytokine signature induced by serum from patients with connective tissue diseases**

Shohei Nakamura, Yuko Okamoto, Yasuhiro Katsumata, Masayoshi Harigai  
Division of Rheumatology, Department of Internal Medicine, Tokyo Women's Medical University School of Medicine

Conflict of interest: Yes

[Objective] We investigated cytokine-induction ability of serum from systemic lupus erythematosus (SLE), anti-ARS antibody positive polymyositis/dermatomyositis (PM/classic DM), and anti-MDA5 antibody positive clinically amyopathic DM (CADM) patients. [Methods] Serum was collected from newly diagnosed, untreated, and clinically active adult SLE, PM/classic DM, CADM patients and healthy controls. Heparinized whole blood from healthy donor was incubated with control serum, patient serum, or IFNs (IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\gamma$ ) with protein transport inhibitor cocktail for six hours and fixed. Production of 11 cytokines from CD14<sup>+</sup> monocytes were analyzed by flow cytometry. [Result] Serum from SLE and CADM patients induced significantly higher MCP1 (p<0.01) and IL-1RA (p<0.01) production in CD14<sup>+</sup> monocytes, which most closely resemble INF- $\beta$  stimulation. Serum from PM/classic DM patients did not induce any significant cytokine production in CD14<sup>+</sup> monocytes. [Conclusions] Serum from SLE and CADM patients induced unique monocyte cytokine signature mostly resembling IFN- $\beta$  stimulation, which is MCP1 and IL-1RA production in CD14<sup>+</sup> monocytes. This finding suggests serum from SLE and CADM patients can activate type I IFN pathway in CD14<sup>+</sup> monocytes.

## W8-1

### **The transcription factor Sox4 controls thymic tuft cell development**

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Conflict of interest: None

[Objective] Breakdown of immune tolerance is the origin of autoimmune diseases. In the thymus, medullary thymic epithelial cells (mTECs) express a large variety of tissue-restricted antigens (TRAs) to establish self-tolerance of T cells. One of the mechanisms underlying such diverse self-antigen expression is the heterogeneity of mTECs. Recently, thymic tuft cells were discovered as a new mTEC subset, but their developmental mechanisms have not been fully elucidated. [Methods] We analyzed single-cell RNAseq datasets and identified a transcription factor Sox4 as being highly expressed in mTECs. Phenotype of Sox4-conditional KO mice was examined. [Results] Mice lacking Sox4 specifically in TECs exhibited a significant reduction of thymic tuft cells without marked influence on other mTEC subsets. Furthermore, the expression of Sox4 was diminished in lymphotoxin  $\beta$  receptor (LT $\beta$ R)-deficient mTECs, suggesting that the LT $\beta$ R-Sox4 axis contributes to the development of thymic tuft cells. [Conclusions] We found that Sox4 is involved in the development of thymic tuft cells. Given that Sox4 promotes the differentiation of intestinal tuft cells, our results suggest that mTECs employ a common transcriptional program with peripheral epithelial cells for immunological tolerance.

## W8-2

### **Chondroprotective effects of CDK4/6 inhibition via ubiquitin-proteasome dependent degradation of JUN**

Tadashi Hosoya, Tetsuya Saito, Hiroyuki Baba, Nao Tanaka, Seiji Noda, Yoji Komiya, Yasuhiro Tagawa, Akio Yamamoto, Shinsuke Yasuda  
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Conflict of interest: None

[Objective] Targeting synovial fibroblast (SFs) using cyclin-dependent kinase (CDK) 4/6 inhibitor (CDKI) would be a potent therapy for rheumatoid arthritis (RA). This study was designed to discern the mechanism of chondroprotective effects by CDKI. [Methods] Chondroprotective effects were evaluated in collagen induced arthritis (CIA). RNA-Seq was performed to identify gene sets affected by CDKI treatment. Gene and protein expression were evaluated with quantitative PCR, ELISA, WB and EMSA. CDK4/6 activity was inhibited or enhanced using a CDKI or adenoviral gene transduction. [Results] CDKI attenuated cartilage destruction in CIA. In SFs, RNA-Seq analysis identified CDKI-sensitive inflammatory genes, which were associated with the pathway of RA-associated genes. CDKI inhibited the production of MMP-1 and MMP-3, and impaired the binding of AP-1 components to DNA. CDK4/6 protected JUN from proteasome-dependent degradation by inhibiting ubiquitination. Notably, the



AP-1 motif was enriched in these genes. [Conclusions] CDK4/6 inhibition demonstrated chondroprotective effects with the attenuated AP-1 transcriptional activity via the impaired stability of JUN. Inhibition of CDK4/6 could be beneficial in patients with RA due to its chondroprotective and anti-inflammatory effects.

### W8-3

#### **Oral administration of a low molecular weight compound that inhibits BAFF signaling ameliorates B cell activation in autoimmune model mice**

Keiko Yoshimoto, Katsuya Suzuki, Yumi Ikeda, Shuntaro Saito, Jun Kikuchi, Tsutomu Takeuchi, Yuko Kaneko  
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: None

[Objective] We discovered a low molecular weight compound, BIK-387, which inhibits BAFF signaling. In this study, we investigated effects of BIK-387 on B cell activation in autoimmune model mice. [Methods] BIK-387 was orally administrated to MRL/lpr mice at a dose of 0.03, 0.1, 0.3 and 1 mg/kg for 20 weeks. The titer of an anti-dsDNA antibody was measured by ELISA. The proportion of B cells and plasma cells in whole blood and splenocytes were analyzed by FACS. IgG production by splenic B cells stimulated with a mixture of an anti-IgM antibody, ODN1826, BAFF and IL-4 *in vitro* was measured by ELISA. [Results] Serum level of an anti-dsDNA antibody in MRL/lpr mice received BIK-387 was significantly suppressed in a dose dependent manner between 8-16 weeks (1 mg/kg vs saline,  $p=0.012$ , 1 mg/kg vs 0.03 mg/kg,  $p=0.02$ ). The proportion of B cells both in whole blood and splenocytes were declined and the proportion of plasma cells was declined in splenocytes in BIK-387 treated mice as compared to the control. IgG production by splenic B cells from BIK-387 treated mice was suppressed compared to the control upon stimulation *in vitro*. [Conclusions] Our data suggest that oral administration of BIK-387 ameliorates B cell activation *in vivo* and shows the therapeutic possibility to treat autoimmune diseases.

### W8-4

#### **Creation of a mouse model of severe psoriasis-like dermatitis using interleukin (IL)-18 receptor (R)-deficient mice**

Hiroki Akazawa, Hirotaka Yamazawa, Kaori Ishimura, Chisato Ashida, Akinori Okada, Daisuke Tomita, Tetsu Itami, Kenji Sakai, Toshihiko Shiga, Kazuya Kishimoto, Yuji Nozaki, Koji Kinoshita, Masanori Funauuchi, Itaru Matsumura

Department of Hematology and Rheumatology, Kinki University Faculty of Medicine

Conflict of interest: None

[Objective] Psoriasis is a chronic inflammatory skin disease characterized by excessive keratinization of the skin. This inflammatory skin disease is known to develop arthritis during the course of the disease. In this study, we induced dermatitis in mice lacking IL-18R, a proinflammatory cytokine, and investigated the cytokines in serum and skin involved in psoriasis. [Methods] The back skin of IL-18R-deficient mice and wild type (WT) was shaved, and psoriasis-like dermatitis was induced by applying imiquimod (IMQ) for 5 consecutive days. The severity of the dermatitis was scored by observing the skin condition over time in terms of erythema, scaling, and thickening. Cytokines in serum were examined by ELISA, and cytokines expressed in skin tissue were examined by RT-PCR. [Results] The dermatitis scores of IL-18R-deficient mice were significantly higher than those of WT mice in erythema, scaling, and thickening. Histology also showed more intense skin cell keratinization and inflammatory cell infiltration, and the expression of IL-6 and IL-17 in skin tissue was also significantly higher. [Conclusions] Suppression of the IL-18 signaling pathway via IL18R exacerbates psoriasis pathogenesis. This pathway may also exacerbate the pathogenesis of psoriatic arthritis.

### W8-5

#### **Baricitinib inhibit microglial activation in the area postrema during collagen-induced arthritis**

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Conflict of interest: Yes

[Objective] Baricitinib drastically attenuates patients-reported outcomes associated with subjective symptoms, such as pain and fatigue, in patients with RA, which suggests that this agent can affect the brain. However, it remains unclear what influence baricitinib have on the brain. We previously reported microglial activation in the area postrema (AP), a brain region without a blood brain barrier, during collagen-induced arthritis (CIA). Here, to examine influence of baricitinib on the AP, we analyzed the brain of CIA mice. [Methods] First, we performed immunostainings for phospho-STAT3 using brain sections, and quantitatively analyzed immunoreactivity in the AP of CIA and control mice. Next, microglial morphology in the AP of CIA mice with baricitinib or vehicle treatment were quantitatively analyzed by immunostaining for Iba-1. To classify cells according to morphologies, principal component analysis was used. [Results] phospho-STAT3 expression in the AP significantly increased in CIA mice. In comparison with vehicle-treatment mice, CIA mice with baricitinib showed significant decrease in the number of activated-form microglia in the AP. [Conclusions] Baricitinib inhibited microglial activation in the AP during CIA. This agent might act on the brain during autoimmune arthritis.

### W8-6

#### **Single-cell RNA-sequencing of antigen receptors in the synovial B cells in gp130F759, a murine rheumatoid arthritis model, at the transitional phase from innate to acquired immunity**

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Conflict of interest: None

[Objective] Effective therapies with biologics urged us to develop therapies preventing bone erosion in rheumatoid arthritis (RA). To clarify pathophysiology of arthritis in a preclinical phase, we have studied a knock-in mouse gp130F759 having a gp130Y759F mutation, and reported that expression of *Padi4* is induced in neutrophils by IL-6 produced by synovial fibroblasts in this phase (IL-6-PAD4 axis). To explore the initial events in acquired immunity, we performed single-cell RNA-sequencing of antigen receptors in synovial lymphocytes. [Methods] Viable synovial cells from knee joints of WT and gp130F759 at 5 M.O. were purified and single-cell cDNA library was prepared with Chromium Controller. [Results] NGS revealed sequences of 6514 and 5734 cells from gp130F759 and WT, respectively. T cell numbers were 24 and 16, whereas B cell numbers were 170 and 52, respectively, indicating that synovial B cells expanded in gp130F759. Almost all Igh isotypes were  $\mu$  but not  $\gamma$  and usages of  $\kappa$  and  $\lambda$  were not different in both strains. Although average lengths of CDR3 in Igh were similar, a certain length of CDR3 dominated in the B cell repertoire of gp130F759. [Conclusions] At the transition from innate to acquired immunity in preclinical arthritis of gp130F759, synovial B cell repertoire has changed.

### W9-1

#### **Early Intervention with Immunomodulators Leads to Better Outcomes in Patients with Systemic Sclerosis**

Keina Yomono, Masataka Kuwana

Department of Allergy and Rheumatology, Nippon Medical School Graduate School

Conflict of interest: None

[Objective] To examine whether early therapeutic intervention is beneficial for patients with early systemic sclerosis (SSc). [Methods] We enrolled patients who received cyclophosphamide, mycophenolate mofetil,

or tocilizumab for diffuse cutaneous SSc (dcSSc) or interstitial lung disease (ILD) within 6 years after disease onset. The patients were divided into early and delayed intervention groups based on the disease duration of  $\leq 18$  and  $>18$  months at treatment introduction. Clinical worsening was defined as the development of any original or revised ACR Composite Response Index in Systemic Sclerosis (CRISS) step1 event or progressive fibrosing ILD (PF-ILD). [Results] 24 and 20 patients were classified into the early and delayed intervention groups. When the changes in skin thickening and pulmonary function over one year were categorized into worsened, stable, and improved, skin thickening and pulmonary function remained stable in the majority of the delayed intervention group. Cumulative rates free from clinical worsening events defined by the revised ACR-CRISS and PF-ILD were significantly higher in the early versus delayed intervention groups ( $p=0.02$  and  $0.001$ , respectively). [Conclusions] Therapeutic “window of opportunity” might exist in SSc patients.

## W9-2

### Therapeutic Effects of Rituximab on Systemic Sclerosis

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Division of Diabetes, Endocrinology and Clinical Immunology, Department of Internal Medicine, Hyogo College of Medicine

Conflict of interest: None

[Objective] Systemic sclerosis (SSc) is a refractory autoimmune disease that causes skin sclerosis, blood flow disorders in various organs. There is also a report that correlates the degree of skin hardening with the prognosis of SSc. The prognosis of SSc is poor in cases where skin sclerosis progresses rapidly, and organ complications are observed from the early stage of disease. Therefore, rituximab was administered to improve patients' prognoses. In this study, the course of disease was retrospectively examined. [Methods] Eight SSc patients who visited our department were diagnosed according to the 2013 ACR/EULAR classification criteria. The disease type was diffuse cutaneous SSc in all cases. The mean age of SSc patients was  $41.4 \pm 23.8$  years, the duration of illness was  $9.3 \pm 11.9$  years, and the total skin thickness score (TSS) was  $21.6 \pm 7.2$ . [Results] One month after the administration of rituximab, the TSS was  $14.6 \pm 7.2$ ; three months after the administration of rituximab, the TSS improved to  $12.8 \pm 6.3$ . Five patients had been on rituximab for one year. Five had a TSS of  $21.8 \pm 8.4$  before treatment with rituximab, TSS of  $9.4 \pm 5.9$  after 6 months, and TSS of  $9.4 \pm 4.0$  after one year. [Conclusions] The effects of rituximab may be useful in treating SSc.

## W9-3

### The effects of nintedanib on immunophenotypes in patients with systemic sclerosis associated interstitial lung disease

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Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

Conflict of interest: Yes

[Objective] Nintedanib, a multiple tyrosine kinase inhibitor, has been shown to slow progression of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). It has been recognized that the mechanism in suppressing fibrosis is mediated through fibroblasts and their precursors, but nintedanib is also capable of inhibiting tyrosine kinases on immune cells. This study aimed to examine serial changes of immunophenotypes in peripheral blood from SSc-ILD patients in nintedanib treatment. [Methods] 32 SSc patients and 14 healthy controls were enrolled. Peripheral blood mononuclear cells were isolated, and were subjected to comprehensive immunophenotyping by multi-color flow cytometry. In 13 patients with SSc-ILD who newly started nintedanib, immunophenotype was serially evaluated at baseline, 3, 6, and 12 months after introduction of nintedanib. [Results] There were no significant changes in T cell subsets. Memory B, IgA<sup>+</sup> memory B, and IgG<sup>+</sup> memory B cells were increased after nintedanib treatment. There were no significant changes in M1 or M2 monocyte, but rare monocyte subsets, M1+M4 and M2+M4, were decreased after nintedanib treatment. [Conclusions] Nintedanib may exert anti-fibrotic effects through modulation of phenotypes of B cells and monocytes in patients with SSc-ILD.

## W9-4

### Anti-fibrotic therapy does not exacerbate pulmonary hypertension associated with systemic sclerosis-interstitial pneumonitis. - analysis of five cases

Takahiro Seno, Makoto Wada, Masataka Kohno, Risa Sagawa, Tomoya Sagawa, Takuya Inoue, Wataru Fujii, Yutaka Kawahito  
Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Background] Nintedanib is approved for progressive fibrosing interstitial lung diseases (PF-ILD) in addition to scleroderma ILD. Nintedanib has been used for many collagen vascular disease (CVD)-induced ILDs. Some reports have suggested that Nintedanib exacerbates pulmonary arterial hypertension (PAH). But the impact of antifibrotic therapies on CVD-associated pulmonary hypertension is not clear. [Methods] Patients with antifibrotic therapy and PAH treatment were extracted. And the disease activity, pulmonary function tests, imaging, and echocardiography were analyzed retrospectively. [Results] Five patients were extracted from October 2019 to September 2021. All patients with scleroderma (two of them with Sjogren's syndrome) received pirfenidone in one case and nintedanib in four cases. All patients showed improvement in the progression of ILD on imaging; two patients had improvement in pulmonary hypertension; three patients showed no worsening, and one of these patients subsequently had improvement in pulmonary hypertension with multiple PAH treatments. Skin stiffness did not change significantly. [Conclusions] Antifibrotic therapy is effective in scleroderma ILD and does not adversely affect the outcome of pulmonary hypertension. It may improve group 3 pulmonary hypertension.

## W9-5

### Therapeutic effects of adipose-derived mesenchymal stem/stromal cells with enhanced migration ability and hepatocyte growth factor secretion due to low-molecular-weight heparin on bleomycin-induced mouse models of systemic sclerosis

Takayasu Suzuka, Takuya Kotani, Shogo Matsuda, Tohru Takeuchi  
Division of Rheumatology, Department of Internal Medicine, Osaka Medical and Pharmaceutical University

Conflict of interest: None

[Objective] This study investigated the effects of Low-molecular-weight heparin (LMWH) on the functions of mouse adipose-derived mesenchymal stem cells (mASCs) and the therapeutic effects of mASCs activated with LMWH (hep-mASCs) in mouse models of SSc. [Methods] The cellular functions of mASCs cultured with different concentrations of LMWH were determined. Mice were divided into four groups: bleomycin (BLM)-induced SSc (BLM-alone), BLM-induced SSc administered with mASCs (BLM-mASC), and BLM-induced SSc administered with mASCs activated with 10 or 100  $\mu\text{g/mL}$  LMWH (BLM-hep-mASC) groups. [Results] In vitro assays showed that migration ability and HGF production were significantly higher in hep-mASCs than in mASCs alone. The hep-mASCs accumulated in the skin tissues more than mASCs alone. The thickness of skin and hydroxyproline contents in BLM-hep-mASC groups were significantly decreased, and the skin mRNA expression levels of genes related to tissue inflammation and fibrosis were significantly down-regulated compared to those in the BLM-alone group. [Conclusions] hep-mASCs showed higher anti-inflammatory and anti-fibrotic effects than mASCs alone and may be a promising candidate for SSc treatment.

## W9-6

### Survey of doctors/patients' awareness of disease understanding and communication in care of systemic sclerosis associated with interstitial lung disease

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<sup>1</sup>Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, <sup>2</sup>Nippon Boehringer Ingelheim Co., Ltd.

Conflict of interest: Yes

[Objective] To clarify the agreements and disagreements in under-

standing and communication in care of systemic sclerosis associated with interstitial lung disease (SSc-ILD) between doctors and patients through an awareness survey. [Methods] An online questionnaire was completed by rheumatologists at university hospitals, national public hospitals, general hospitals or clinics who manage one or more SSc-ILD patients at the time of the survey. An independent survey was conducted on SSc-ILD patients referred by the participated physicians. [Results] A total of 121 rheumatologists answered the questionnaires. About 80% of doctors answered necessity of ILD screening at diagnosis of SSc. Satisfaction of the drug selection, efficacy and safety of current treatment options was less than 10%, indicating high unmet needs. In communication with patients, the rate of consultation on prognosis was as high as 80%, and about 70% of them thought it was difficult to explain the prognosis. [Conclusions] In doctors survey, while knowledge on screening, diagnosis, monitoring and treatment of SSc-ILD was adequately shared, the satisfaction of treatment environment was still low. In communication with patients, the explanation of prognosis was extracted as an issue.

## W10-1

### Pathogenetic role of Th10 like cells in lupus model mice induced by Toll-like receptor 7 agonist imiquimod

Reona Tanimura, Yuya Kondo, Kotona Furuyama, Masaru Shimizu, Hiroyuki Takahashi, Hiroto Tsuboi, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Japan

Conflict of interest: Yes

[Objective] To evaluate the involvement of CD4<sup>+</sup> T cell subset in IMQ induced SLE model mice. [Methods] 1) After administration of IMQ for 2, 4, or 8 weeks, expression of superficial antigens on CD4<sup>+</sup> T cells were evaluated by flowcytometry (FCM). 2) CD4<sup>+</sup> T cells of 1) were isolated and stimulated in vitro, and cytokine production from them was evaluated by FCM. 3) After the administration of IMQ for 8 weeks in IFN $\gamma$  knockout (KO) mice, lupus phenotype was evaluated by measuring serum anti-dsDNA IgG and urinary protein, and immunofluorescent staining of C3 and IgG in kidney. [Results] 1) PD-1 and CXCR3 co-expressing CD4<sup>+</sup> Th10 like cells were up-regulated in a time dependent manner. 2) IFN $\gamma$ , IL-10, or IL-17-producing CD4<sup>+</sup> T cells were significantly increased after administration of IMQ for 2 weeks compared with control mice. IFN $\gamma$  and IL-10-co-producing CD4<sup>+</sup> T cells were also increased in IMQ-administrated mice. 3) Although anti-dsDNA IgG was significantly decreased in KO mice, there were no difference in urinary protein and C3 and IgG deposition in kidney between KO mice and WT mice. [Conclusion] Our results suggested the possibility that Th10 like cells were differentiated and activated by IMQ, and might be produced IFN $\gamma$  that involved in the induction of SLE through autoantibody formation.

## W10-2

### Role of programmed cell death-1in lupus model mice induced by Toll-like receptor agonist imiquimod

Yuya Kondo, Reona Tanimura, Kotona Furuyama, Masaru Shimizu, Hiroyuki Takahashi, Hiroto Tsuboi, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: Yes

[Objective] To analyze the functional role of programmed cell death-1 (PD-1) in mouse model of systemic lupus erythematosus induced by Toll-like receptor agonist imiquimod (IMQ). [Methods] 1) After topical IMQ treatments for 8 weeks to C57BL/6 (WT) mice or PD-1 knock out (KO) mice, anti-double strand (ds) DNA IgG in sera were measured by ELISA. 2) Expression of transcription factors in splenic CD4<sup>+</sup> T cells were analyzed by flowcytometry (FCM). Cytokines production from in vitro-stimulated CD4<sup>+</sup> T cells was also evaluated by FCM. 3) PD-1 expression in B cell subpopulations was analyzed before and after the treatment of IMQ in WT mice. [Results] 1) In KO mice, anti-dsDNA IgG tended to be higher compared to WT mice, and also significantly elevated compared to naïve KO mice. 2) T-bet in splenic CD4<sup>+</sup> T cells was elevated in KO mice compared to WT mice. There was no significant difference in cytokines such as IFN $\gamma$ , IL-10, IL-17, and IL-21 in CD4<sup>+</sup> T cells between WT and KO mice.

3) Expression of PD-1 was elevated in plasmablasts compared to the other B cell subpopulations, and up-regulated after the treatment of IMQ. [Conclusions] PD-1 expressed in CD4<sup>+</sup> T cells and B cells might play a role in the generation of lupus phenotype induced by IMQ.

## W10-3

### Lysophosphatidic Acid (LPA) treatment improves depressive-like behavioral abnormalities in a mouse model of SLE

Wataru Nagata, Toshiaki Ishizuka  
Department of Pharmacology, National Defense Medical College, Tokorozawa, Japan

Conflict of interest: None

[Objective] Recent studies reported that lysophosphatidic acid (LPA) reduces neuroinflammation. MRL/lpr mouse has been used as an animal model of neuropsychiatric SLE because of behavioral abnormalities. In this study, we examined the effects of LPA on neuroinflammation, abnormal behaviors, and systemic immunity in MRL/lpr mice. [Methods] 15-week-old MRL/lpr mice were treated with or without LPA for 2 weeks. After the treatment, behavioral tests were performed as indices of depression. Histological examinations were performed in the harvested brain tissues. In addition, after the treatment, the spleen-derived immune cells of MRL/lpr mice were analyzed by flow cytometer (FACS). [Conclusions] MRL/lpr mice showed more depressive behaviors compared to control mice. The treatment with LPA significantly suppressed depressive behaviors. The expressions of Iba1 and CD68 were increased in the hippocampus and prefrontal cortex of MRL/lpr mice compared to control mice and LPA treatment inhibited the expressions. In addition, FACS analysis showed that LPA treatment decreased CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup> T cells and increased CD8<sup>+</sup> T cells, CD4<sup>+</sup>CD25<sup>+</sup> T cells, and CD11b<sup>+</sup>ly6G<sup>+</sup> cells. These findings suggest that LPA treatment may suppress increased microglial expression, depressive behaviors, and systemic immunity.

## W10-4

### STING activation induce senescence phenotype and enhanced IFN- $\alpha$ production via GATA4 in monocytes of SLE

Taiga Kuga<sup>1,2</sup>, Asako Chiba<sup>2</sup>, Go Murayama<sup>1</sup>, Makio Kusaoi<sup>1</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Sachiko Miyake<sup>2</sup>

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Conflict of interest: None

[Objective] Interferon  $\alpha$  (IFN $\alpha$ ) is associated with the pathogenesis of systemic lupus erythematosus (SLE). We previously reported that IFN $\alpha$  production by monocytes activated with stimulator of IFN genes (STING) pathway is enhanced in patients with SLE. We aimed to elucidate the mechanism of enhanced IFN $\alpha$  production in SLE monocytes. [Methods] Monocytes enriched from peripheral blood of SLE patients and healthy control (HC) were stimulated with 2'3'-cGAMP, a ligand of STING pathway. IFN $\alpha$  positive/negative cells were FACS-sorted and processed for RNA-sequence (RNA-seq) analysis. HEK293T cells were transfected with GATA4 siRNA or negative control siRNA (NC) and then stimulated with 2'3'-cGAMP. [Results] Differentially expressed gene (DEG) analysis of IFN $\alpha$  positive monocytes between SLE and HC revealed senescence-related genes including CDKN2A were overexpressed in SLE monocytes. DEG analysis revealed that IFN $\alpha$  positive SLE monocytes overexpressed GATA4, a novel gene related to the enhanced cytokine production in senescent cells. IFN $\alpha$  production by HEK293T cells was reduced by GATA4 deletion using siRNA. [Conclusions] The overexpression of GATA4 and senescence phenotype may contribute to enhanced production of IFN $\alpha$  in SLE monocytes.

## W10-5

### Effects of steroid pulse for systemic lupus erythematosus on neutrophil extracellular trap formation

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Conflict of interest: None

[Objective] Steroid pulse is an essential therapy for severe systemic lupus erythematosus (SLE), but it also affects the coagulation-fibrinolysis system. Neutrophil extracellular traps (NETs) are associated with micro-circulatory disturbance. We aimed to determine the effects of steroid pulse for SLE on NET formation. [Methods] Imiquimod (IMQ)-induced SLE model mice were employed. Six of them were given methylprednisolone (mPSL) intraperitoneally on Days 39, 40, and 41. Five were given PBS instead. Six normal mice were given mPSL and another six normal mice were given PBS similarly. Histological evaluation was performed on Day 56, and circulating NETs were detected with flow cytometry (FCM). [Results] In the IMQ-induced SLE mice, lupus nephritis was developed and the number megakaryocytes was increased in the bone marrow. In the IMQ-induced SLE mice given steroid pulse, although the glomerulonephritis did not improve obviously, the bone marrow megakaryocyte counts recovered to the normal level, and circulating NETs were significantly increased with clear leukocyte differentiation in FCM. [Conclusions] Steroid pulse for SLE might induce differentiation of leukocytes and platelets and recruit them from the bone marrow, and putative factors could induce an increase in circulating NETs.

## W10-6

### DOCK8-expressing Tfh cells cause SLE

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Conflict of interest: None

[Objective] SLE was induced in mice normally not prone to autoimmunity by stimulating TCR with an antigen repeatedly to levels that surpass host's steady-state response, self-organized criticality, wherein T follicular helper (Tfh) cells expressing guanine nucleotide exchange factor DOCK8 on the cell surface were newly generated. In the present study, we quantified the DOCK8<sup>+</sup>Tfh in the peripheral blood and spleen of patients diagnosed with SLE to confirm that DOCK8<sup>+</sup>Tfh cause SLE. [Methods] Dock8<sup>+</sup>Tfh cells were stained with biotinylated anti-DOCK8 mAb, alkaline phosphatase avidin D and anti-rabbit Novolink. CD4<sup>+</sup>T cells were stained with anti-IFN  $\gamma$  Ab. Peripheral blood were dyed with anti-DOCK8 mAb and anti-rabbit IgG Ab. [Results] DOCK8<sup>+</sup>Tfh cells passed through TCR re-revision and induced varieties of autoantibody and lupus lesions. They existed in splenic red pulp and peripheral blood of active lupus patients, which subsequently declined after therapy. Autoantibodies and disease were healed by anti-DOCK8 antibody in SLE-model (NZBx-NZW) F1 mice. [Conclusions] DOCK8<sup>+</sup>Tfh cells, generated after repeated TCR stimulation by immunogenic form of pathogen, either exogenous or endogenous, in combination with HLA to levels that surpass system's self-organized criticality, cause SLE.

## W11-1

### Filgotinib Demonstrates Clinical Efficacy in Rheumatoid arthritis Independent of Smoking Status: A Post-Hoc Subgroup Analysis of Three Phase 3 Clinical Trials

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Conflict of interest: Yes

**Objective** We present the impact of smoking on the efficacy of filgotinib (FIL), a preferential Janus kinase 1 inhibitor, in patients (pts) with moderate-to-severe RA who were treated in the phase 3 FINCH1 (NCT02889796), FINCH2 (NCT02873936) and FINCH3 studies (NCT02886728). **Methods** Endpoint data (ACR20/50/70, CDAI  $\leq$  10, DAS28 (CRP)  $\leq$  3.2 or  $<$  2.6 at weeks 12/24) from 3452 pts were assessed by logistic regression. P values are nominal. **Results** In methotrexate inadequate responders (MTX-IR), current (12% of pts) and former (13%) smokers treated with ADA+MTX had lower Week (W) 12 ACR50 response rates vs non-smokers (25% [p=0.095] and 28% [p=0.21] vs 39%). ACR50 responses at W12 in FIL+MTX pts showed no association with smoking status. Former smokers (MTX-IR and naïve) had higher response rates than non-smokers. There was no difference in ACR50 between the non-smoking MTX-IR FIL200 mg+MTX and ADA+MTX-arms (46% vs 39%; p=0.08). Better W12 ACR50 rates with FIL200+MTX vs ADA+MTX were seen for former (62% vs 28%; p=0.0017) and current smokers (50% vs. 25%; p=0.016). Other endpoints (W12/24) followed this trend. **Conclusion** FIL+MTX was efficacious independent of smoking status in MTX-IR and naïve pts. Current or former smokers were more likely to respond to FIL200+MTX vs ADA+MTX across endpoints.

## W11-2

### Integrated Safety Analysis Update for Filgotinib in Patients With Moderately to Severely Active Rheumatoid Arthritis Receiving Treatment Over a Median of 2.2 Years

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Conflict of interest: Yes

**Objective** To update the as-treated integrated safety analysis from the RA development programme of filgotinib (FIL) - a preferential Janus kinase 1 inhibitor approved for moderately to severely active RA treatment in Europe and Japan. **Methods** Data from 2 Phase 2 (NCT01668641, NCT01894516), 3 Phase 3 (NCT02889796, NCT02873936, NCT02886728), and 2 long-term extension (NCT02065700, NCT03025308) studies are included. Patients (pts) received  $\geq$  1 dose of FIL200 mg or FIL100 mg. **Results** 3691 pts received FIL200 or FIL100 for 8085.1 pt-years of exposure (PYE: median 2.2 yrs; max 6.8 yrs). Exposure-adjusted incidence rates (EAIR)/100 PYE were higher with FIL100 (N=1647; PYE=2782.6) vs FIL200 (N=2267; PYE=5302.5) for treatment emergent AEs (54.4 v 32.9). Death EAIRs were 0.5 (FIL100) and 0.3 (FIL200). Infection/serious infection EAIRs were numerically greater with FIL100 (30.2/2.7) vs FIL200 (21.1/1.5). AEs of specific interest EAIRs were generally low, comparable between doses and tended to decrease since the 2020 update, except for VTE (total FIL 0.1 to 0.2) and non-NMSC malignancies (total FIL 0.5 to 0.6). **Conclusion** Since the 2020 report FIL continued to be well tolerated with no new safety signals. In the context of demonstrated efficacy, both FIL doses had an acceptable risk/benefit profile.

## W11-3

### Long-term safety of baricitinib in patients with moderate to severe active rheumatoid arthritis (including Japanese patients) up to 9.3 years: results of an integrated safety analysis

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Conflict of interest: Yes

[Objective] Baricitinib (bari) is a selective JAK1/JAK2 inhibitor approved for treating rheumatoid arthritis (RA) in patients (pts) that showed inadequate response to existing therapies. The long-term safety of bari was evaluated using the integrated data of pts with moderate to severe active RA, including Japanese pts. [Methods] The data of nine phase 1-3 and one long-term extension studies were assessed. Incidence rates (IRs) per 100 patient-years were calculated. [Results] A total of 3770 pts (including 514 Japanese) received bari for 14,744.4 patient-years of exposure (Japanese: 1810.0 patient-years), with a median and maximum exposure of 4.6 and 9.3 years, respectively. IRs in the total population were 2.58 for serious infections, 0.49 for DVT/PE, 0.51 for MACE, and 0.92 for malignancy and remained stable over time. The IRs of malignancy and death (IR: 0.56) were similar to the general US population. *Herpes zoster* infections occurred more frequently in Japanese pts than in the overall population (6.27 vs 2.98), but the IR did not change with longer exposure. [Conclusions] In the overall and Japanese populations with active RA, bari maintained a safety profile similar to that previously reported with no increase of IRs across safety events through exposures up to 9.3 years.

## W11-4

### Safety and effectiveness of baricitinib in patients with rheumatoid arthritis: 24-week data of all-case postmarketing surveillance in clinical use in Japan

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Conflict of interest: Yes

[Objective] We assessed safety and effectiveness of baricitinib (Bari) in patients (pts) with RA under real-world conditions. [Methods] In Bari's all-case postmarketing surveillance from Sep 2017, demographics, adverse events (AEs), and disease activity were collected for pts with 24 weeks' observation (including after discontinuation, where applicable). (Database lock: 25 Feb 2021) [Results] Of 4758 pts, 4731 were included in the safety analysis set. Mean age was 64 years, 80% were female, mean RA duration was 12 years, and 54% of pts received MTX. The persistence rate of 24-week Bari treatment was 75%. Serious AEs occurred in 203 (4.3%) pts; 18 deaths (0.4%) were reported. Common AEs of special interest were herpes zoster (3.1%) and hepatic function disorder (2.8%). Incidence proportions of malignancies, major adverse cardiovascular events, and venous thromboembolic events were 0.4%, 0.1%, and 0.1%. In the effectiveness analysis set (n=4724) assessed at Week 24, the numbers of pts who achieved remission were 588 of 1706 (34.5%) for DAS28-ESR, 1411 of 2300 (61.3%) for DAS28-CRP, 729 of 2212 (33.0%) for SDAI, and 739 of 2349 (31.5%) for CDAI. [Conclusions] The safety profile of Bari was consistent with previous reports and disease activity was im-

proved in pts assessed at Week 24.

## W11-5

### Long-Term Safety and Efficacy of Upadacitinib or Adalimumab in Patients with Rheumatoid Arthritis: Results at 3 years from the SELECT-COMPARE Study

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Conflict of interest: Yes

**Objective:** To assess safety and efficacy of UPA vs ADA over 3 years (yrs) in the ongoing long-term extension (LTE). **Methods:** Patients (pts) with MTX were randomized to UPA 15 mg QD, PBO or ADA 40 mg EOW. Between 14-26 W, rescue was mandated for either lack of response or failure to achieve CDAI LDA at 26 W. Pts completed 48 W could enter an LTE for up to 10 yrs. Pts who were rescued or prematurely discontinued were categorized as non-responders. **Results:** At BL, 651, 651 and 327 pts were randomized with UPA, PBO, and ADA. Between 14-26 W, 252 or 159 pts were rescued from UPA to ADA or ADA to UPA, and all PBO were switched to UPA by 26 W. A higher proportion of UPA completed 3 yrs without rescue vs ADA (47% vs 36%). UPA was generally well-tolerated including serious AEs, AEs leading to discontinuation and AESIs. The event rates of AESIs were generally comparable between UPA and ADA, while higher rates in HZ, lymphopenia, hepatic disorder and CPK elevation with UPA. Greater proportions of UPA achieved CDAI LDA and remission at 3 yrs, as well as DAS28 (CRP)  $\leq 3.2$  or  $< 2.6$ , compared with ADA. **Conclusion:** The safety profile of UPA was consistent with the results reported previously and with the integrated Phase 3 safety analysis. Higher clinical response continued to be observed with UPA vs ADA.

## W11-6

### Long-term efficacy and safety of upadacitinib in Japanese patients with rheumatoid arthritis who had an inadequate response to conventional synthetic DMARDs: 4-year data from the SELECT-SUNRISE study

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Conflict of interest: Yes

**Objectives:** To evaluate the long-term (4-year) efficacy and safety of upadacitinib (UPA) in Japanese patients (pts) with RA who had an inadequate response to csDMARDs. **Methods:** Pts who completed the 12-week (wk) double-blind period proceeded to a blinded extension study to continue to receive UPA 7.5 mg, 15 mg or 30 mg QD while pts randomized to placebo was switched to UPA 7.5 mg, 15 mg or 30 mg QD. Pts receiving 30 mg QD were switched to 15 mg QD prior to marketing approval. **Results:** Among randomized 197 pts, 126 pts completed wk 204. At wk 204, DAS28 (CRP)  $< 2.6$  was achieved in 91.7%, 87.9% and 88.9% of UPA 7.5 mg, 15 mg and 30 mg groups, respectively (As Observed). Efficacies were similar in the placebo to UPA switch groups. The incidences of serious

adverse events (AEs) (events/100 PYs) in UPA 7.5 mg, 15 mg and 30 mg were 12.7, 22.1 and 20.4, respectively. The incidences of AEs of special interest in UPA 7.5 mg, 15 mg and 30 mg were 108.7, 121.8 and 150.2 for infections; 4.5, 5.6 and 10.4 for serious infections; 6.5, 11.3 and 14.4 for herpes zoster; 0.4, 0.9 and 0.5 for MACE; 0, 0 and 0.5 for VTE; 0, 1.3 and 0.5 for malignancy, respectively. **Conclusion:** Efficacy of UPA was maintained through 4 years. No new safety signals for UPA were identified.

## W12-1

### Long-Term Safety Profile of Upadacitinib in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, or Ankylosing Spondylitis

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Conflict of interest: Yes

**Objectives:** To describe the long-term safety profile of upadacitinib (UPA) across RA, PsA, and AS from the SELECT clinical program. **Methods:** Safety data were compiled for RA (6 trials, pooled UPA 15 mg QD, adalimumab [ADA] 40 mg EOW, and MTX), PsA (2 trials, pooled UPA 15 mg QD and ADA 40 mg EOW), and AS (1 trial, UPA 15 mg QD). **Results:** In total, 4298 patients (RA, 3209; PsA, 907; AS, 182) received  $\geq 1$  dose of UPA 15 mg (8562 patient-years). AEs leading to discontinuation and rates of serious infection (SI) and opportunistic infection were generally similar across all treatment groups (TGs; UPA, ADA and MTX) and patient populations (PPs; RA, PsA, and AS). Herpes zoster (HZ) and increased CPK were reported more often with UPA vs ADA or MTX, with UPA showing similar rates of HZ across PPs. Malignancies excluding NMSC were reported at similar rates across all TGs and PPs. NMSC was not common, with numerically higher rates with UPA vs MTX and/or ADA in RA and PsA. Similar rates of adjudicated MACEs and adjudicated VTEs were observed across all TGs (no events in AS). Rates of death were not higher than expected in the general populations. **Conclusions:** With the exception of HZ, exposure-adjusted AE rates were generally similar across UPA, ADA, and MTX in RA, as well as UPA and ADA in PsA.

## W12-2

### Possible Discontinuation of Methotrexate by Combination with Tofacitinib and Sustained Drug Survival of Tofacitinib Monotherapy in Rheumatoid Arthritis

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Conflict of interest: None

[Objective] This retrospective study was undertaken to find out the problems in long-term combination with MTX from the drug survival data of tofacitinib (TOF) therapy in the real-world. [Methods] The medical charts of the patients with RA treated with TOF were reviewed to collect duration of the disease, the combination drugs including MTX, rheumatoid factors (RF) and anti-CCP antibodies (ACPA), and the duration of TOF use. The study protocol was approved by the ethical committee of our hospital (H30-057-467). [Results] A total of 107 (86 females and 21 males) patients with RA treated with TOF were eligible for this retrospective study. TOF was initiated in combination with MTX in 22 (20.6%) patients and not in 85 (79.4%) patients. MTX was not used in combination with TOF due to adverse events, including pulmonary symptoms and liver dysfunction. The dose of MTX was reduced in one and discontinued in five. During the observation period, 80 (74.8%) patients continued using

TOF, including 65 patients (61.3%) with TOF monotherapy. Continuity of TOF therapy was independent of combination with MTX and the values of RF and ACPA. [Conclusions] Long drug survival was observed in more than half of patients with TOF monotherapy. One in five patients with TOF plus MTX discontinued MTX.

## W12-3

### Safety profiles in Rheumatoid Arthritis patients treated with JAK inhibitors, including subgroup analysis with moderate to severe RA aged 50 or more with 1 or more additional CV risk factor

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Conflict of interest: None

[Objective] ORAL surveillance [Methods] Cases were recruited to SHIN-yokohama Arthritis REgister (SHARE) between 2015 and 2021 (n=3,869). 286 patients were diagnosed according to ACR/EULAR 2010 classification criteria and treated with JAK inhibitors. [Results] All patients were treated with JAK inhibitors, 31 tofacitinib, 187 baricitinib, 67 upadacitinib and 1 filgotinib. There were 3 MACE, none of non-fatal MI, 1 dissecting aortic aneurysm and 2 strokes and incident rate was 1.2/100 PY. Malinancies were shown 5 cases and 2.0/100 PY. Severe infectious events was 1 case, 0.4/100 PY. Herpes zoster were 16 cases, 6.3/100 PY. There were no VTE cases. 179 patients who fulfilled moderate to severe RA aged 50 or more with 1 or more additional CV risk factor same as ORAL surveillance. In our subgroup cases, MACE were 1.9/100 pY (ORAL surveillance 0.91/100 PY). Malignancies were 1.29/100 pY (ORAL surveillance 1.13/100 PY). SIEs were 0.64/100 pY (ORAL surveillance 0.91/100 PY). [Conclusions] It was revealed that safety is most important consideration when prescribing JAK inhibitors who were elderly and had 1 or more CV risks.

## W12-4

### Persistence of tofacitinib for patients with rheumatoid arthritis -multicenter analysis using FIT-RA registry-

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Conflict of interest: None

[Objective] To analyze the long-term retention rate of tofacitinib for patients with rheumatoid arthritis (RA). [Methods] We enrolled 118 patients with RA who were treated by tofacitinib and extracted from FIT (Fukui, Ishikawa, Toyama)-RA database. Kaplan-Meier estimates for tofacitinib drug survival and reasons for discontinuation were evaluated. We compared differences of the retention rate in ages of patients, with or without concomitant MTX and in biological DMARDs used immediately before tofacitinib. [Results] The mean age was 63.6 years old and the mean disease duration of RA was 14.8 years. Sixty-three patients (53.4%) received concomitant MTX. Median (maximum) treatment duration by tofacitinib was 3.0 (7.4) years. Sixty-five patients withdrew from tofacitinib treatment during follow-up periods. Thirty patients discontinued due to insufficient efficacy and 23 patients discontinued due to adverse events. The retention rate of tofacitinib was 71.0% at 1 year, 55.8% at 3 years, 46.5% at 5 years and 32.6% at 7 years, respectively. The retention rate of tofacitinib was no significant differences between each group. [Conclusion] Long term retention rate of tofacitinib for patients with rheumatoid arthritis was similar between treatment with and without concomitant MTX.



## W12-5

### Do JAK inhibitors elevate the creatine kinase in patients with rheumatoid arthritis?

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Conflict of interest: None

[Object] Some cases of elevated creatine Kinase (CK) by JAK inhibitors (JAKi) for RA at trial were reported. However, the frequency and background at practice are not known. Correlation of JAKi for RA and the change of CK at practice were investigated. [Methods] We use the multi-center database of JAKi. 103 from 265 RA were followed-up at 24 weeks (W) and evaluated CK. The outlier rate was calculated. The relative factors of elevated CK at 24 W were investigated from background at stating JAKi by univariate analysis. [Results] Female rate was 85.4%, mean age was 68 years, disease duration was 15 years, and DAS28ESR was 5.00. CK of both men and women significantly elevated at 4 W and maintained until 24 W (men, women; 63, 62 (0 W), 101, 95 (4 W), 119, 96 (12 W), 155, 99 (24 W), U/L, P<0.001). The outlier rate also was significantly increased at 4 W and maintained until 24 W (0 W: 5.8%, 4 W: 20.7%, 12 W: 26.3%, 24 W: 24.3%, P=0.002). The relative factors of elevated CK at 24 W significantly correlated with men, CK, Cr, and LDH, positively, and stage, class, mHAQ, eGFR, and PSL dosage, negatively. [Conclusions] CK significantly elevated at 4 W and maintained until 24 W. However, there were no patients felt muscle pain and stopped JAKi. We should pay attention to elevated CK from 4 W in clinical practice.

## W12-6

### Drug retention and discontinuation reasons of 6666 treatment courses of biologics and JAK inhibitors in patients with rheumatoid arthritis -Kansai consortium for well-being of rheumatic disease patients (AN-SWER cohort)-

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Conflict of interest: Yes

[Objective] To evaluate the real-world drug retention and discontinuation reasons of biologics (Bio) and JAK inhibitors (JAKi) in RA patients. [Methods] 6666 treatment courses [TNF inhibitors (TNFi) =3577, anti-IL-6 receptor antibody (aIL-6R) =1497, CTLA4-Ig=1139, JAKi=453; Bio/JAK naive cases 55.4%, age 58.8 y, female 82.6%, disease duration 9.7 y, DAS28-ESR 4.3, combined MTX dose 8.3 mg/week, and combined PSL dose 5.7 mg/day] were included in this multi-center, retrospective study. Reasons of discontinuation was classified into 4 major categories

(lack of effectiveness, toxic adverse events, non-toxic reasons, and remission). Data was adjusted by potent confounders (age, sex, concomitant MTX and PSL, and prior Bio/JAK use and switched number) with a Cox proportional hazards model and evaluated at 36 months. [Results] Discontinuation rate due to lack of effectiveness was aIL-6R=19.1%, JAKi=24.9%, CTLA4-Ig=26.5%, and TNFi=33.8% (Cox P<0.001 between 4 groups), due to toxic adverse events was CTLA4-Ig=12.1%, JAKi=13.3%, aIL-6R=15.9%, and TNFi=16.3% (Cox P=0.026). Overall retention rates (%) excluding non-toxic reasons and remission was aIL-6R=67.9%, JAKi=64.8%, CTLA4-Ig=64.3%, and TNFi=55.1% (Cox P<0.001). [Conclusions] Remarkable difference was observed in the drug retention between 4 groups.

## W13-1

### Long-term outcomes of metacarpophalangeal joint arthroplasty with silicone implant for rheumatoid thumb

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Conflict of interest: None

[Objective] The aim of this study is to evaluate clinical outcome of silicone arthroplasty of thumb metacarpophalangeal (MCP) joint retrospectively. [Methods] 45 RA thumbs underwent silicone arthroplasty of thumb MCP joint between 2009 and 2019, with a minimum follow-up of 2 years. There were 42 females and 3 males. The mean age was 63.5 years and the average disease duration was 25.7 years at the surgery. The mean follow-up was 6.0 years. The clinical outcome of the surgery was assessed by range of motion of the MCP joint, grip strength, pinch ability, Disability of Arm Shoulder and Hand (DASH), Hand 20 before surgery and after surgery at final follow-up, and implant failure by radiography. [Results] The mean of MCP joint range of motion significantly improved after the surgery. There was no difference at other terms before and after surgery. 6 thumbs had implant failure, and 2 thumbs required revision surgery. Hand20 after surgery in implant failure group was significantly higher than non-implant failure group. The survivorship was 85.8% using an endpoint of implant failure, and 93.1% using an endpoint of revision surgery at 5 years. [Conclusions] The clinical outcomes of silicone arthroplasty of thumb MCP joint for RA patients is satisfactory at the mean follow-up of 5 years.

## W13-2

### Correction of the boutonniere deformity of the rheumatoid fingers by Ohshio method

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Conflict of interest: None

[Objective] To investigate the results of Ohshio method for correction of the boutonniere deformity in patients with RA, and to find its adequate indication. [Patients and Methods] Thirty fingers in 22 patients were surgically corrected by Ohshio method. The average age at surgery was 56.1 years, the average duration of RA was 16.4 years and the average follow-up period was 3.6 years. The severity of deformity using Nalebuff stage was I in 6 fingers, II in 3, III in 21. And Larsen grade was I in 10 fingers, II in 13, III in 7. After synovectomy and flexion contracture release, the lateral bands on both sides were lifted dorsally with the transverse retinacular ligaments and sutured together at on the dorsum of the PIP joint combining shortening the central band. [Results] After the operation, all fingers were pain-free, and the average range of motion (active extension/flexion) at the PIP joint changed from -48°/98° to -23°/85°. The

postoperative extension loss was minimal at  $-5^{\circ}$  in stage I & II, but it was insufficient at  $-32^{\circ}$  in stage III, and notably  $-44^{\circ}$  in Larsen grade III ( $n=6$ ). [Conclusions] This method is adequately applied for the PIP joints with Nalebuff stage II or less (extension loss:  $40^{\circ}$  or less and passive correction: possible) and none- or mild joint deterioration.

### W13-3

#### Postoperative range of motion of MCP joint replacement surgery- A comparative study of INTEGRA versus SBi silicone (AVANTA) finger implant

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Conflict of interest: None

[Objective] To investigate the postoperative range of motion (ROM) between the two deferent implants, AVANTA and INTEGRA silicone, used for the MCP joint deformity in patients with rheumatoid arthritis. [Methods] Consecutive 20 cases were included in the current study. Cases with AVANTA prosthesis (group A, until April 2020) and with INTEGRA (group I, after April 2020) were 38 fingers of 11 patients and 29 fingers of 9 patients, respectively. ROM of the MCP joint, grip strength and pinch strength before and six months after surgery were compared between these two groups. [Results] The mean preoperative extension and flexion angle ( $^{\circ}$ ) of each group (group A/I) were  $-60.4/-31.3$  and  $83.6/78.8$ , respectively. Although the flexion angle decreased to  $61.1/69.4$ , the extension angle significantly improved to  $-10.4/-8.5$  in the first six months after surgery. The pre- and postoperative grip strength (mmHg) were  $84.7/110$  and  $75.0/60.5$ , respectively. The pre- and postoperative pinch strength (kg) were  $1.47/1.68$  and  $1.78/1.55$ , respectively. No significant difference in postoperative ROM, grip or pinch strength between the two groups was observed. [Conclusions] Although the INTEGRA silicone implant has a pre-flexed design, significant difference was not observed in postoperative ROM between the two implants.

### W13-4

#### Radiocarpal arthrodesis in the rheumatoid wrist: a retrospective clinical and radiological long-term follow up

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Conflict of interest: None

[Objective] This study was performed to evaluate the outcomes of radiolunate arthrodesis for rheumatoid arthritis (RA) with long-term follow-up as well as the predictive factors of secondary osteoarthritis (OA) or ankylosis of the midcarpal joint. [Methods] We retrospectively reviewed 16 wrists of 14 patients with RA. The mean follow-up period was 14 years. Ten wrists had Larsen classification grade III and 6 wrists had grade IV. The range of motion (ROM), the Mayo wrist score and Stanley classification were assessed. The carpal height index (CHI), ulnar translation index (UTI), and changes in the midcarpal joint contour were determined from radiographs. [Results] At the final follow-up, the clinical scores were improved but the ROM of extension/flexion was significantly reduced. The CHI and UTI improved and remained stable until the final follow-up. The changes in the midcarpal joint were categorized as unchanged in 6 wrists, OA in 6 wrists, and ankylosis in 4 wrists. The preoperative UTI was significantly higher in the OA and ankylosis groups than in the unchanged group. [Conclusions] Although radiolunate arthrodesis for RA maintained good outcomes throughout long-term follow-up, severe ulnar translation of the carpal bone might cause OA and ankylosis of the midcarpal joint.

### W13-5

#### Radiographic Analysis of Total Wrist Arthroplasty

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Conflict of interest: None

[Objective] Although total wrist arthroplasty using the prosthesis we have developed (DARTS Total Wrist System) leads to favorable clinical results, loosening of the carpal component is observed in some patients. Therefore, the purpose of this study was to investigate the causes of carpal loosening radiologically. [Methods] Seventeen patients with rheumatoid arthritis (17 wrists) who underwent total wrist arthroplasty at our institution were included in our study. The preoperative Larsen classification was grade IV in 13 wrists and grade V in 4 wrists. The mean postoperative follow-up period was 4.5 years. [Results] Three patients who showed preoperative evidence of residual joint space in the carpometacarpal (CMC) joints of the middle to little fingers exhibited loosening of the carpal components. In contrast, none of the eight patients with preoperative CMC joint ankylosis exhibited carpal loosening. [Conclusions] The radiological results were favorable in patients with preoperative ankylosis of the CMC joints. However, in patients with residual joint space in the CMC joints, loosening of the carpal component might occur. Therefore, it is important to enhance the initial fixation with appropriate cementing techniques and bone grafting.

### W13-6

#### Patient reported outcome for patients with rheumatoid arthritis who underwent the finger or wrist surgery using Japanese version of the Decision Regret Scale

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Conflict of interest: None

[Objective] In patients with rheumatoid arthritis (RA) who underwent small joint surgery such as finger and wrist joints, we sometimes recognize cases with dissatisfaction even if their clinical outcomes are good. This study evaluated patient reported outcome of the finger and wrist surgery for RA patients using Japanese version of the decision regret scale (DRS) which is used to measure patient's regret for the health care decisions. [Methods] Thirty-two surgeries were involved in this study. The DRS and patient's satisfaction using visual analogue scale were investigated and analyzed the relationship between DRS and patient's satisfaction. [Results] In approximately 60% of the surgeries, patients expressed complete satisfaction, on the other hand, there were 3 cases who were judged as regret for the surgery by DRS. In cases with MCP finger joint arthroplasty, significant negative correlation was observed between DRS and general satisfaction, function, and appearance, however, no correlation was observed with appearance in the other cases. [Conclusions] From the results of this study, many of the patients who underwent MCP finger joint arthroplasty regard both function and appearance as important, on the other hand, patients with other surgery value the function above the appearance.

### W14-1

#### Differentiation of ultrasound (US) finding in musculotendinous inflammation of supraspinatus tendon (SSP) between patients with polymyalgia rheumatica (PMR) and rheumatoid arthritis (RA)

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Conflict of interest: None

[Object] To assess US finding of musculotendinous lesion of SSP in patients with PMR, compared with RA. [Methods] We recruited patients with PMR ( $n=11$ ) and RA ( $n=8$ ) complaining shoulder pain in our hospital. We evaluated tendinitis of SSP, bursitis of subacromial-subdeltoid bursa (SASDB), tenosynovitis of long head of biceps tendon sheath (LHB) and

synovitis of glenohumeral joint (GHJ), before treatment. We divided tendinitis into 3 subtypes based on the cite of power doppler; Tendinitis-A was the cite within 2 mm from peri-bursal fat plane of SASDB without bursitis, Tendinitis-B was the cite within 2 mm from facet of greater tubercle of humerus, and Tendinitis-C was the other cite of SSP. Bursitis was defined if the thickness of hypoechoic fluid-filled bursa was  $\geq 2$  mm. [Results] The proportion of patients with PMR group with synovitis, bursitis, tendinitis-A, -B, -C, tenosynovitis (bilateral/unilateral, %) was as followed; 0/9, 9/0, 73/0, 18/27, 0/18, 45/36. Tendinitis-A, -B and tenosynovitis were more common in PMR group than RA group (73% vs 0%,  $p=0.002$ ; 45% vs 0%,  $p=0.03$ ; 81% vs 38%,  $p=0.009$ ). Multivariate analysis revealed that Tendinitis-A was associated with PMR group ( $p=0.03$ ). [Conclusions] US findings of tendinitis-A, representing musculotendinitis, is useful to diagnose PMR.

## W14-2

### Comparison of 18F-FDG Positron Emission Tomography (PET) and contrast-enhanced MRI in polymyalgia rheumatica

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Conflict of interest: None

[Objective] We investigated whether 18F-FDG Positron Emission Tomography/Computerized Tomography (PET/CT) accumulation in PMR can be detected by contrast-enhanced MRI (cMRI). [Methods] We studied 26 patients with new-onset PMR diagnosed between June 2017 and August 2021, who underwent PET/CT and cMRI at the same time. We investigated spinous process of lumbar vertebra, pubis, ischial tuberosity, great trochanter, and femoral to determine whether the presence of PET/CT accumulation was consistent with the presence of cMRI high signal. [Results] The age was 77.0 (73.0-80.0) years and included 12 females. The level of CRP was 5.49 (2.85-9.36) mg/dL. None of the patients administered either glucocorticoids or immunosuppressant. There was significantly correlation between PET/CT accumulation and high intensity by cMRI in the pubis, sciatic tuberosity, and greater trochanter ( $P=0.00341$ ,  $P=0.00175$ , and  $P=0.00000174$ , respectively). There was no significant association between PET/CT accumulation and high intensity by cMRI in the inferior lumbar spinous process and femoral. ( $P=0.27$  and  $P=0.48$ , respectively). [Conclusions] PET/CT accumulation in PMR can be detected by using cMRI in the pubis, ischial tuberosity and great trochanter.

## W14-3

### Evaluation of rheumatoid arthritis and polymyalgia rheumatica with ultrasound using the shoulder gray scale

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Conflict of interest: None

[Objective] We have evaluated imaging in RA and PMR using power Doppler and pulse Doppler of the shoulder. The purpose of this study was to investigate the differences between RA and PMR using the gray scale (GS). [Methods] The subjects were 25 patients in the RA group, mean age 66.1 years, and 16 patients in the PMR group, mean age 68.4 years. Controls were 23 patients in the frozen shoulder (FS) group, mean age 54.0 years. US evaluation was performed at the bicipital groove (BG), rotator interval (RI), subacromial bursa (SAB), and posterior glenohumeral joint (post GH). These sites were classified using the GS method (grade 0-3) and examined using the chi-square test. [Results] BG (RA: grade 0:0/grade 1:8/grade 2:9/grade 3:8, PMR group: 4/10/2/0, FS group: 11/8/4/0), RI (RA group: 0/5/9/11, PMR group: 11/5/0/0, FS group: 7/12/4/0), SAB (RA group: 9/4/8/4, PMR group: 11/5/0/0, FS group: 7/12/4/0), SAB (RA group: 9/4/8/4, PMR group: 11/5/0/0, FS group: 7/12/4/0), SAB (RA group: 9/4/8/4, PMR group: 11/5/0/0, FS group: 7/12/4/0), SAB (RA group: 9/4/8/4, PMR group: 11/5/0/0, FS group: 7/12/4/0). The RA group had significantly higher grades in BG, SAB, RI, and post GH ( $p<0.05$ ). [Conclusions] The grade was significantly higher in the RA group than in the PMR and FS groups, which could be diagnostic of RA and PMR.

## W14-4

### Increasing trend of radiographic features of knee osteoarthritis in rheumatoid arthritis patients before total knee arthroplasty

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Conflict of interest: None

[Objective] To investigate the trend and factors related to the occurrence of osteoarthritis (OA)-like features on knee radiographs of rheumatoid arthritis (RA) patients who underwent total knee arthroplasty (TKA). [Methods] To classify knee radiographs into the RA and OA-like RA groups, a deep learning model with an accuracy of 98.3% was developed using knee radiographs of end-stage arthropathy in RA patients ( $n = 104$ ) obtained during 2002-2005 and in primary OA patients ( $n = 96$ ) obtained during 2007-2009. With this model, 796 knee radiographs was categorized, which were recorded in RA patients before TKA during 2006-2020, into the OA-like RA and RA groups. The annual trend of the percentage of OA-like RA was investigated. Moreover, univariate and multivariate analyses were performed to identify the factors associated with OA-like RA using clinical data from 240 patients. [Results] An increasing trend of OA-like RA was observed. The OA-like RA group had significantly higher BMI, more frequent usage of biologics, and lower level of CRP. Multivariate analysis identified all these three items as independent factors. [Conclusions] An increasing trend of knee radiographs before TKA with OA-like features was observed. Advances in pharmacotherapy might affect knee joint-destruction pattern.

## W14-5

### Pathological findings of ultrasound examination of in SAPHO syndrome including pustulotic arthro-osteitis

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Conflict of interest: None

[Objective] We investigated the pathophysiology from the ultrasound findings in SAPHO syndrome patients including pustulotic arthro-osteitis (PAO). [Methods] We analyzed 31 patients with SAPHO syndrome who underwent ultrasound examination from February 2017 to September 2021 in our hospital. All 31 patients had clinically sternoclavicular joints or costovertebral joints symptoms. Ultrasound examinations was performed including fingers, wrist, tendon enthesis (lateral epicondyle of humerus, triceps tendon, quadriceps tendon, proximal and distal patellar tendon, Achilles tendon, plantar fascia) and sternoclavicular joints or costovertebral joints. [Results] Of the 31 patients, 27 (87%) were PAO patients with palmoplantar pustulosis (PAO group), and 4 (13%) were SAPHO syndrome patients (SAPHO group) without palmoplantar pustulosis. 16 patients (59.3%) in the PAO group and 0 patients (0%) in the SAPHO group had peripheral joints arthritis findings. 21 cases (77.7%) in the PAO group and 0 cases (0%) in the SAPHO group had power Doppler positive findings at least one enthesis. [Conclusions] Peripheral arthritis and enthesitis were highly observed in PAO patients. Enthesitis may be the cause of joint symptoms of PAO.

## W14-6

### Quantitative evaluation of ulnar deviation of finger MP joints by plain radiography

Daisuke Kawamura, Yuichiro Matsui, Norimasa Iwasaki



Conflict of interest: None

[Objective] To quantify ulnar deviation of finger MP joints by plain radiography. [Methods] posterior-anterior and anterior-posterior radiography of hands were acquired from 74 fingers in 13 rheumatoid arthritis patients. [Results] Ulnar deviation angle obtained by posterior-anterior radiography was 21.4°, by anterior-posterior radiography was 50.8°. [Conclusions] Anterior-posterior radiography was useful to quantify the ulnar deviation of MP joints.

## W15-1

### The prevalence of chronic kidney disease in NinJa2020 RA patients

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Conflict of interest: None

[Objective] To clarify the prevalence of chronic kidney disease (CKD) in NinJa2020 RA patients and to compare it with that in NinJa2012. [Methods] Cross-sectional study. Data of 11781 patients registered to NinJa2020 with serum creatinine level were used, and patient number and percent of each CKD stage (G1-G5) in total were generated. Age-specific subgroup analysis was done (younger than 50, 50-60, 60-70, 70-80, older than 80). Kruskal-Wallis test, Dunn's multiple comparison test were employed for statistical analysis. [Results] Age 67.2±12.9 years old, disease duration 14.5±11.5 years, ESR 25.3±21.4 mm/hr, CRP 0.1 (0.10-0.40) mg/dL. G1 (≥90) 1461, 12.5%, G2 (60≤eGFR<90) 6791, 57.6%, G3 (30≤eGFR<60) 3304, 28.0%, G4 (15≤eGFR<30) 162, 1.4%, G5 (eGFR<15) 43, 0.4%. The older patients were, the less eGFR was. In NinJa2012, age 63.3±13.0 years old, disease duration 11.8±10.6 years, ESR 29.3±24.2 mm/hr, CRP 0.19 (0.10-0.56) mg/dL. G1: 1815, 25.4%, G2: 3991, 55.9%, G3: 1252, 17.5%, G4: 59, 0.8%, G5: 18, 0.2%. Patient number with eGFR<60 in NinJa2020 was more than that in NinJa2012 in all age subgroups. [Conclusions] Patients in NinJa2020 were less inflammatory and older than those in NinJa2012. Percent of patients with eGFR<60 in NinJa2020 increased to 29.8% from that in NinJa2012 18.5%.

## W15-2

### Characteristics of elderly-onset rheumatoid arthritis patients in SDAI remission by analysis of NinJa data

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Conflict of interest: Yes

[Objective] To examine the characteristics of elderly-onset rheumatoid arthritis (RA) patients in SDAI remission. [Methods] Using the data of RA database "NinJa" in 2019 (n=15,943) patients were divided into 4 groups by the age of onset; G1: <65 (G1a<65 and G1b≥65 depending on the present age), G2: 65-74 and G3: ≥75. The characteristics of elderly-onset RA patients (G2: 964 cases and G3: 367 cases) in SDAI remission were compared with those of younger-onset ones. [Results] SDAI remission rates were G1: 44.6%, G1b: 35.2%, G2: 42.2%, and G3: 39.3%, respectively. Compared to patients in non-remission, those in remission showed lower RF positive rate and ACPA positive rate in all four groups. Compared to patients of G1, those of G2 and G3 in remission showed lower rates of MTX usage (G1a: 71.2%, G1b: 62.9%, G2: 61.7%, G3: 40.9%). The usage rate of bDMARDs / JAK inhibitors in remission (33.8%, 32.5%, 23.6%, 15.3%) decreased in the order of G1 → G2 → G3. The corticosteroid usage rate was higher in G3 (30.2%) than in G1a (15.4%), G1b (20.3%), and G2 (20.6%). [Conclusions] The remission rate of elderly-onset patients was about the same as that of younger-onset patients. Compared these two groups in remission, their backgrounds were similar, but the treatment contents were apparently different.

## W15-3

### Analysis of medical cost for care of rheumatoid arthritis patients: result from the IORRA cohort

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Conflict of interest: None

[Objective] To examine the annual medical costs for care of rheumatoid arthritis (RA) using the IORRA cohort. [Methods] Annual medical costs [out of pocket to hospitals and pharmacies and for complementary and alternative medicine (CAM)] were cross-sectionally calculated for RA patients who were participants in the IORRA conducted in 2020. Correlations between these costs and RA disease activity, disability level, and quality of life (QOL) were assessed. The costs in RA patients with and without bDMARDs or JAK inhibitors users was also evaluated. [Results] Of the 2,793 RA patients, data from 2,544 (91.1%) were analyzed. The average annual medical cost was JPY257,000, which consisted of JPY164,000 (out of pocket to hospitals), JPY92,000 (out of pocket to pharmacies), and JPY191,000 (CAM; proportion of user 11.2%). These costs tended to be increased with increasing RA disease activity and disability level or worsening QOL. In addition, the costs in RA patients with and without bDMARDs or JAK inhibitors users were JPY450,000 and JPY149,000, respectively. [Conclusions] Patients with RA bear heavy economic burden that increased as the disease was exacerbated. Especially in bDMARDs or JAK inhibitors users, it was shown that economic burden was large.

## W15-4

### To evaluate an association of the modified Japanese Diet Index (mJDI) with the achievement of remission in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objective] To evaluate an association of the modified Japanese Diet Index (mJDI) with the DAS28 remission in patients with rheumatoid arthritis (RA). [Methods] A dietary survey form using BDHQ was conducted to the RA patients in the IORRA study in 2021. mJDI was calculated (0-12 points). The higher the score, the higher the adherence to Japanese foods). Multivariable analysis was used to examine the association of mJDI with DAS28 remission (adjusted for sex, age, BMI, and RA medications). The associations of each component of mJDI with DAS28 remission were also examined. [Results] Of the 2,926 RA patients in this IORRA survey, 2,575 patients were the subject of this study. The numbers of the patients with

low (0-4), medium (5-9) and high group (10-12) mJDI points were 955, 1,479 and 141, respectively. Mean age/DAS28 in low, medium and high group were 57.4/2.3, 63.9/2.5 and 72.1/2.6, respectively. The mJDI was not significantly associated with the DAS28 remission (OR: 1.01 [95%CI: 0.98-1.05],  $p=0.41$ ). For each component of the mJDI (per 100 g daily), the intake of mushrooms, beef and pork, green and yellow vegetables, soy and white rice were significantly associated with DAS28 remission. [Conclusion] No significant association between mJDI and DAS28 remission was observed.

## W15-5

### Factors affecting patient satisfaction related to cost and treatment effectiveness in rheumatoid arthritis: results from the multicenter observational cohort study, FRANK registry

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Conflict of interest: None

[Objective] To improve treatment for rheumatoid arthritis (RA), it is necessary to understand each RA patient satisfaction. [Methods] This is a multicenter observational study of Japanese RA patients from the FRANK registry from March 2017 to August 2020. We collected data on clinical data, quality of life, which was assessed using the EuroQol 5-dimensional questionnaire (EQ5D), and patient satisfaction assessed by the four categories (i.e., cost, treatment efficacy, activities of daily living [ADL], and global treatment satisfaction). We analyzed the factors affected with each satisfaction. [Results] This study included 2,235 RA outpatients. "Very satisfied" and "Satisfied" were given for almost half of each satisfaction aspect (cost: 49%; efficacy: 72%; ADL: 58%; global treatment: 66%). Multivariate analysis has revealed that the use of b/tsDMARDs increased satisfaction of treatment effect and ADL, but decreased cost satisfaction. All aspects of patient satisfaction were elevated in those with lower disease activity and higher score of EQ5D. [Conclusions] Cost of satisfaction was increased with aging and having the history of musculoskeletal surgery, and decreased in lower EQ5D score, and the use of b/tsDMARDs.

## W15-6

### Impact of seasonal changes on patients with rheumatoid arthritis - ANSWER cohort study

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Conflict of interest: None

Rheumatoid arthritis is an autoimmune disease characterized by polyarthritis. Seasonal changes, one of the environmental factors, have influence on the disease activity in other areas. The Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort is a multicenter observation registry of rheumatoid arthritis patients in the Kansai region, where detailed clinical data such as disease activity and medication are longitudinally accumulated. In this study, we report the impact of seasonal changes on patients with rheumatoid arthritis using ANSWER cohort data. The clinical data on 8380 people from 2011 to 2020 were classified into spring (April, May, June), summer (July, August, September), autumn (October, November, December), and winter (January, February, March). The proportions (mean  $\pm$  standard deviation) of patients achieving remission in the Clinical Disease Activity Index (CDAI) were  $31.4\% \pm 6.5\%$  in spring,  $34.5\% \pm 5.9\%$  in summer,  $36.7\% \pm 6.1\%$  in autumn, and  $35.8\% \pm 4.7\%$  in winter. One-way ANOVA and post hoc tests showed significantly higher activity in rheumatoid arthritis in spring than in autumn and winter. It was considered that the deterioration of about 5% of patients in spring was a clinically significant result.

## W16-1

### The change of serum antibody titer and vaccination of BNT162b2 COVID-19 in patients with rheumatic diseases

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Conflict of interest: None

**Objective:** To evaluate antibody reactions by COVID-19 vaccination (BNT162b2 COVID-19) in Japanese patients with rheumatic diseases. **Methods:** Outpatients with rheumatic diseases (ORD) ( $n=20$ ), medical staffs (MS) ( $n=130$ ), outpatients with non-rheumatic diseases (ONRD) ( $n=47$ ) and inpatients with non-rheumatic diseases (INRD) ( $n=80$ ) were enrolled in this study. We quantitatively measured antibodies to spike protein by ElecsysR Anti-SARS-CoV-2 S kits (Roche diagnostics). Blood collection was performed before vaccination, 3 weeks after 1st vaccination, 3 weeks, 6 months and 12 months after 2nd vaccination. **Results:** On all adverse reactions of vaccine, 2nd vaccination was very significant but those diminished within 3 days. The elevation of antibody titer by vaccination in MS was significantly higher than ORD, ONRD and INRD. In ORD, 1 patient with MCTD that had significant deterioration of ADL and 2 patients with rituximab usage showed antibody-negative after 2-times vaccination. **Conclusions:** Antibody titer elevated after 2nd vaccination in most cases of rheumatic diseases. Similar to western reports, the elevation of antibody titer was not revealed in 2 cases with history of rituximab usage. Considering possible 3rd vaccination, we need to follow-up the future changes of antibody titer.

## W16-2

### Changes in treatment adherence and behaviour during the COVID-19 pandemic in Japanese patients with rheumatoid arthritis and characteristics of patients with COVID-19: results from cross-sectional study in the IORRA cohort

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Conflict of interest: Yes

[Objective] To evaluate treatment adherence and behaviour of Japanese patients with RA during the COVID-19 pandemic and the characteristics of RA patients with COVID-19. [Methods] In the IORRA survey conducted in October 2020, adherence to RA medications and self-reported changes in RA disease activity, behaviour including frequency of hospital visits, and self-reported COVID-19 status during the COVID-19 pandemic were cross-sectionally investigated. [Results] Of the 2,996 RA patients who participated in this survey, 2,785 (93.0%) continued to use RA medications as usual. RA medications were reduced in 96 (3.2%) patients, and were discontinued in 89 (3.0%) patients. Among 185 patients who reduced or discontinued RA medications, 30.3% of the patients experienced worsening of self-reported RA disease activity. The proportion of patients with RA who visited our clinic as usual and visited our clinic at a longer interval than usual was 70.4% and 23.1%, respectively. RA Patients with COVID-19 ( $n=46$ ) were young, had low disease activity, and had good physical function than those without COVID-19 ( $n=2,915$ ). [Conclusions] Most RA patients continued to use RA medications as usual during the COVID-19 pandemic. The characteristics of RA patients with COVID-19 were clarified.

### W16-3

#### Immunogenicity against BNT162b2 mRNA COVID-19 vaccine in rheumatic disease patients receiving immunosuppressive therapy

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Conflict of interest: None

[Objective] To investigate serum antibody titer to SARS-CoV-2 spike protein against BNT162b2 mRNA COVID-19 vaccine in Japanese rheumatic disease (RD) patients undergoing immunosuppressive therapy. [Methods] Serum antibody titer to SARS-CoV-2 spike protein was analyzed in 123 outpatients with RD at Kagawa University Hospital and 43 healthy volunteers who had received two doses of BNT162b2 mRNA vaccine and at least 14 days had passed since the second dose. [Results] Antibody titer in RD patients was lower than that in healthy subjects ( $587\pm949$  U/mL vs  $939\pm973$  U/mL,  $P=0.0439$ ). The mean antibody titers of 41 patients who received biologics or JAK inhibitors and 47 patients who received conventional immunosuppressive agents were  $407\pm1134$  U/mL and  $366\pm503$  U/mL, respectively, which were significantly lower than that of 35 patients who did not receive immunosuppressive agents ( $1096\pm1002$  U/mL,  $P=0.0014$  and  $P=0.0005$ , respectively). The mean antibody titer of 43 patients on methotrexate (MTX) was significantly lower than that of 80 patients not on MTX ( $294\pm508$  U/mL vs  $745\pm1087$  U/mL,  $P=0.002$ ). [Conclusions] Immunogenicity to the BNT162b2 mRNA vaccine in RD patients was found to be reduced under immunosuppressive treatment. Among other things, MTX seems to be associated with a decreased antibody response.

### W16-4

#### Examining COVID19 infection status in patients with rheumatoid arthritis at Konan Kosei Hospital

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Conflict of interest: None

[Objective] This study investigated the treatment status of patients with rheumatoid arthritis (RA) with the presence or absence of COVID19 infection along with patients with RA judged to be close contacts. [Methods] The study included 877 general patients and 14 patients with RA who presented with COVID19 between September 2020 and August 2021. The data collected comprised of the outcome of whether COVID-19 infection developed or not, retrospectively. Moreover, 14 patients with RA were

selected, including close contacts and investigated for changes in DMARDs before the onset of COVID19 infection. [Results] The general patients were 150 hospitalized patients who became severely ill and 727 patients waiting at home (or sanatorium). Conversely, patients with RA were 2 and 12 patients, respectively. It was unrelated to RA and aggravation of COVID19 ( $p = 0.78$ ). Approximately 14 patients with RA, and among the 10 patients with RA that received bDMARD, 3 were transmitted but mild. Furthermore, four patients with RA who received csDMARD occurred. Patients with RA who received bDMARD were results to be hard to occur ( $p = 0.02$ ). [Conclusions] It is unrelated to suffering from RA and aggravation of COVID19 infection. However, patients with RA received bDMARD may pass without occurring.

### W16-5

#### Immunogenicity after SARS-CoV-2 mRNA vaccination in rheumatoid arthritis patients

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Conflict of interest: None

[Objective] Although the evidence of vaccine efficacy of COVID-19 has been accumulated, there are few studies in RA patients. We investigated the immunogenicity of the mRNA vaccine in RA. [Methods] We measured IgG titers against the SARS-CoV-2 spike receptor binding domain in RA patients more than 2 weeks after two doses of vaccine. We analyzed whether there was an association between IgG titers and patient background. [Results] 81 patients (median age 71 years, 82.7% female) were included. The median duration of disease was 15 years, median DAS28-CRP 1.8, median post-vaccination period 42 days (IQR 25, 54), MTX, TNF inhibitors, tocilizumab, abatacept, JAK inhibitors use were 35.8%, 27.2%, 13.6%, 9.9% and 21%, respectively. IgG titers were above the reference level in 95.1% of patients, with a median of 909.1 AU/mL. In univariate logistic regression analysis, the only factor significantly associated with an increase in IgG titers above the median was the post-vaccination period (OR 0.974 (95%CI: 0.950-0.998),  $p=0.014$ ). In addition, there was no difference in IgG titers between patients with and without biologics or JAK inhibitors. [Conclusion] The immunogenicity of the vaccine in RA patients in this study was high, and IgG titers tended to decrease with time after vaccination.

### W16-6

#### Positivity of the antiphospholipid antibodies and its clinical features in Japanese patients with COVID-19

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Conflict of interest: None

[Background] Thrombosis is a unique complication in coronavirus disease 2019 (COVID-19). Although antiphospholipid antibodies (aPL) are frequently observed in COVID-19 patients, their clinical significance remains elusive. Therefore, we evaluated APLs as a risk of clinical outcomes in COVID-19. [Methods] Serum samples were obtained from 122 patients hospitalized in Tokyo Medical and Dental University Hospital. Seven types of aPLs consisted in classic aPLs (anti-cardiolipin IgG/IgM, anti- $\beta$ 2GPI IgG/IgM) and non-classic aPLs (anti-phosphatidyl serine/prothrombin complex IgG/IgM and anti- $\beta$ 2GPI IgA) were measured using solid-phase assays. [Results] Among the 122 patients, 48 (39%) patients were positive for one or more aPLs; 44 (36%) of them were positive for any non-classic aPLs, while only 11 (9%) patients were positive for any classic aPLs. Advanced age and lower BMI were associated with any positive aPL. The proportion of autoimmune diseases was statistically insignificant but higher trend ( $p=0.056$ ). The frequency of thrombosis and mortality was similar regardless of aPL positivity. The titer of anti- $\beta$ 2GPI IgG and IgM had a trend of positive correlation with disease severity. [Conclusion] We observed the prevalence and irrelevance of aPL positivity in



thrombosis in Japanese COVID-19 patients.

## W17-1

### Experience of establishing a home-visit nursing station as my rheumatism care nurse

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Conflict of interest: None

With the progress of the treatment of Rheumatic disease, the role of rheumatism care nurses has expanded in recent years. There are many problems such as cognitive decline in the elderly, ADL/higher function decline, difficult to go to the hospital, and problems that cannot be solved only by being involved in a limited place such as a medical institution. We have established a home-visit nursing station to provide rheumatism care nursing at home. After the establishment, I recognized the lack of my care for patients with rheumatic disease, and the problems of elderly patients in their daily life. It became clear that there are still many problems that can be improved, such as how to manage medicine, self-injection method, infection prevention with immunosuppressed state by treatment, how to adjust living environment, exercise habits, and so on. In addition, in patients with rheumatoid arthritis, I can evaluate the activity of arthritis and the changes in joint symptoms intermittently. Collaboration with a local rheumatology clinic not only enhances home-visit nursing for rheumatoid arthritis, but also improves the psychological safety of patients with rheumatoid arthritis and their families. Establishment of a home-visit nursing station by a nurse is a very valuable experience for me.

## W17-2

### A prospective study regarding incident associated with self-injection in patients receiving biologics

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Conflict of interest: None

[Objective] We retrospectively reviewed incident associated with self-injection in patients receiving biologics during 2012-2018 (JCR 2020). The major incident included technical issues and change in interval arbitrarily in older age and injection at sick days at younger age. Hence, we modified our instruction. Here, we prospectively evaluated that the change contributed to reducing incident. [Methods] The incidence (100 person-year) of enrolled 71 patients was analyzed by age [group A: age of <65, group B: age of 65-74, group C: age of >75] and compared to that in our previous study. [Results] Incidence rate (vs. previous study) was improved to 31 (vs. 144,  $P<0.0001$ ). Incident in Group A, B, and C were 33.8 (vs. 57.0,  $P<0.01$ ), 36.8 (vs. 55.6,  $P=0.01$ ), 7.5 (vs. 137.5,  $P<0.0001$ ), respectively. Major incident was; skipping injection 11 (vs. 18, ns), technical issue 2.1 (vs. 16,  $P<0.01$ ), and injection at sick days 6.15 (vs. 12.5, ns). Skipping was more frequently observed in group A with 15 (vs. 20, ns). Technical issue reduced in group C [7.5 (vs. 75,  $P<0.0001$ )] but still higher than other groups. [Conclusions] Our modified instruction contributed to decrease in incident. More intensive instruction is needed to reduce skipping in younger age and technical issues in older age.

## W17-3

### Significance of nurses' interventions in conducting musculoskeletal ultrasonography

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Conflict of interest: None

[Objective] In our hospital, the nurses carry out the real-time musculoskeletal ultrasonography in the examination room for them since 2018. The purpose of this study was to examine whether the implementation of the musculoskeletal ultrasonography for new patients by nurses could assist for the evaluation of the diagnosis and treatment or not. [Methods] From February 2019 to February 2021, we studied 178 patients diagnosed with RA and Psoriatic arthritis (PsA) in 199 new patients who were suspected RA for the first time at our hospital. Then, we studied the coherence findings of the musculoskeletal ultrasonography with disease activity and treatment state. [Results] We performed the musculoskeletal ultrasonography for 164 patients (92%). 155 patients (95%) were started treatment, and 102 patients (65.8%) had the bDMARD. The longer the period from onset to the first visit or from first visit to the start of treatment is, the worse the HAQ-DI is ( $\rho=0.359$ ,  $\rho=0.234$ ). Especially, earlier treatment of bDMARD improve DAS28-CRP ( $P=0.003$ ). [Conclusions] The shorter the disease duration is, the better the result of treatment. So, we need to diagnose the seriousness of the illness earlier as possible. The nurses carry out the real-time musculoskeletal ultrasonography, so it helps the diagnosis as a team.

## W17-4

### Current Status of ICT tool use by rheumatoid arthritis patients

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Conflict of interest: None

[Objective] The purpose of this study was to investigate the utilization of Information and Communication Technology (ICT) tools by patients with rheumatoid arthritis (RA) at our hospital. [Methods] A questionnaire survey was conducted on 169 RA patients (mean age: 67.6 years) seen at our hospital from January to September 2021. [Results] There were 116 patients (68.6%) who used the Internet, 68% in their 70s and 35% in their 80s. Line and search sites were highly used, but no patients used telemedicine. 64% of the patients were unaware of pharmaceutical company information sites, 23% did not use them, and 13% used them. The most common reasons for not using the sites were "the contents are difficult" and "difficult to use". 66% of the patients did not want to use telemedicine because "hospitals are better" and "difficult to use". [Conclusions] For patients who are anxious about coming to the hospital, telemedicine and pharmaceutical company information sites can be useful, but elderly patients are not familiar with the Internet and need support in using ICT tools.

## W17-5

### Experience of COVID-19 vaccination of 242 patients with collagen vascular disease in our hospital

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Conflict of interest: None

[Purpose] We investigate to the side reactions of COVID-19 Vaccination to patients with collagen vascular disease (CVD). [Materials and Method] 285 patients with CVD were selected from the 1816 patients COVID-19 vaccinated between May 2021 and August 2021 in our hospital. We investigated and examined the background, treatment details, and side reactions of 242 patients. [Result] 40 males, 202 females, average age 64 years. 151 RA, 14 PMR, 2 SPA, 17 SLE, 23 SjS, 8 MCTD, 10 SSs, 12 DM, 20 IP, 2 BD, 4 AOSD, 7 Vasculitis syndrome (4 MPA, 1 GPA, 1 EGPA, 1 TA), 5 IgG4RD, 2 JIA, 2 APS, 2 PAH, 1 UC. Adverse reactions after COVID-19 vaccination were observed in 78.1% for the first time and in 82.2% for the second time. Immunosuppressive therapy was adjusted in 95 cases. The frequency of side reactions, myalgia, arthralgia and arm dullness was high at 21.9% -38.4%. Fever was 0.8% and 6.6% was observed at 1<sup>st</sup> and 2<sup>nd</sup> vaccination, respectively. Most of them were com-

pletely improved with no medication, and anti-inflammatory analgesics were used in 59 cases (24.4%). [Discussion] Patients with CVD might have had anxiety about the COVID-19 vaccine stronger than the healthy person, but I would like to try to reduce the anxiety as much as possible by presenting these data concretely.

## W17-6

### Practice on survey about answers and questions for side reactions after vaccinations and evaluation of serum IgG antibody levels against SARS-CoV-2 spike proteins following to management of DMARDs on the use of the COVID-19 Vaccine which was provided by the American College of Rheumatology Clinical Guidance for RA patients by RA professional nurses

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Hikari-Chuo Clinic

Conflict of interest: None

[Objective] RA patients treated by immunosuppressants or biologics were reported as lower seropositivity rate groups for vaccination by mass media. THE ACR COVID-19 vaccine clinical guidance was showed not to reduce antibody levels against SARS-CoV-2 spike proteins to rheumatology providers. RA patients have been feeling anxiety for severe side reactions and lower seropositivity against COVID-19 vaccine. They have a desire to get any adequate consultations. [Methods] Medication schedules of RA patients were managed with their personal calendars by RA professional nurses. 322 RA patients and their 188 families were examined on survey about answers and questions for side reactions after vaccinations. 97 patients were measured serum IgG antibody levels against SARS-CoV-2 spike proteins on 2-8 weeks after 2 times vaccinations. [Results] RA cases had pain with more joints and lower fever than their families' symptoms. Serum antibody levels of all patients are  $7640.0 \pm 8463.3$  AU/ml ( $n=97$ ),  $<50$  AU/ml: 91/97 cases (93.8%), MTX group  $8797.0 \pm 8822.0$  ( $n=36$ ), Abatacept:  $4014.3 \pm 485$  ( $n=11$ ), MTX + Abatacept:  $2839.9 \pm 2989$  ( $n=9$ ),  $<500$  AU/ml, Abatacept: 6/20 cases (30%). [Conclusions] It's most important for RA teams to take care of them with low antibody levels and high anxieties in the era with COVID-19.

## W18-1

### The first nationwide epidemiological survey in Japan of Chronic recurrent multifocal osteomyelitis (CRMO) -the number of patients and the clinical picture-

Yukako Maeda<sup>1</sup>, Eitaro Hiejima<sup>1</sup>, Kazushi Izawa<sup>1</sup>, Ryuta Nishikomori<sup>2</sup>, Shuichi Ito<sup>3</sup>, Takahiro Yasumi<sup>1</sup>

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Conflict of interest: None

[Objective] Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disease of unknown etiology that presents as multiple, recurrent, aseptic osteomyelitis in bone throughout the body. We conducted the first nationwide epidemiological survey in Japan to investigate the number of patients and the clinical picture. [Methods] In the primary survey, we studied the number of patients diagnosed with CRMO who were examined in pediatrics, rheumatology, orthopedics, and dermatology between January 1, 2015 and December 31, 2019. Unifocal cases and clinically diagnosed cases without biopsy were also surveyed. Subsequently, we conducted a questionnaire on the clinical picture of the patients. [Results] In the primary survey, 1894 of 2681 selected facilities (70.6%) responded. And 117 institutions reported a total of 284 patients. The estimated number of patients nationwide (including those who didn't undergo biopsy) was 414 (95% confidence interval: 356-473). In the secondary survey, we also analyzed complications, treatments, and prognosis. [Conclusions] The first nationwide survey in Japan has revealed the number of CRMO patients and the clinical profile. This survey will contribute to early diagnosis and establishment of treatment protocol.

## W18-2

### Implication of increased procalcitonin in adult-onset Still's disease

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Conflict of interest: None

[Purpose] Serum procalcitonin (PCT) is a useful biomarker for diagnosis of sepsis. In Adult-onset Still's disease (AOSD), serum PCT levels are significantly increased in some patients during the active phase. We investigated the characteristics of patients with AOSD who indicate increased serum levels of PCT. [Methods] The medical records of 38 patients with AOSD, who had admitted in our hospital from January 2005 to June 2021, were reviewed. Epidemiological, clinical, and laboratory findings were analyzed in patients with increased PCT levels more than 0.5 ng/ml (PCT-positive group). These findings were compared to those in patients without increased PCT levels (negative group). [Results] Serum ferritin levels, frequencies of elderly-onset of AOSD, diabetes, and hypertriglyceride were significantly higher in PCT-positive group than those in negative group. There was no correlation between serum levels of PCT and those of ferritin or serum IL-6. [Conclusion] Increase in PCT levels may be associated with disease activity of AOSD because serum ferritin is a relevant biomarker of disease. Moreover, elderly-onset, diabetes, and hypertriglyceride were frequently found in PCT-positive group, suggesting that they may be implicated in the pathogenesis of AOSD.

## W18-3

### Point mutation in human-NLRP1 induced autoinflammatory disease with liver fibrosis

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Conflict of interest: None

[Objective] It was recently reported that NLRP1 mutations induce autoinflammatory diseases. Here we identified a novel point mutation in patient with a rare disease involving severe liver fibrosis. [Methods] We transiently transfected plasmids encoding NLRP1 wild-type (WT) or NLRP1-P1214L together with ASC, pro-caspase-1, pro-IL-1 $\beta$  in HEK293T cells to measure levels of released IL-1 $\beta$ . We also measured serum levels of IL-1 $\beta$  or IL-18 in this patient. We analyzed immortalized cells derived from this patient's liver tissues. [Results] NLRP1-P1214L induced the release of substantially large amounts of IL-1 $\beta$  (or IL-18) in HEK293T cells. We found extremely high levels of serum IL-18, but not IL-1 $\beta$ , in this patient; however, liver transplantation substantially reduced serum levels of IL-18. Liver tissue sections from this patient displayed high levels of IL-18 expression in hepatocytes. Immortalized hepatocytes derived from this patient released constitutively high levels of IL-18, which were dampened by siRNA-mediated knockdown of NLRP1. [Conclusions] These results suggested that NLRP1-Mt-mediated inflammasome hyper-activation in hepatocytes contributes to the pathogenesis of this rare autoinflammatory disease with liver fibrosis.

## W18-4

### The differential diagnosis of familial Mediterranean fever ~through patients eventually diagnosed with other diseases~

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Conflict of interest: None

[Objective] We aimed to examine diseases that need to be differentiated from familial Mediterranean fever (FMF). [Methods] We analyzed 32 patients initially suspected as having FMF but eventually diagnosed as

other disease. All patients were fulfilled Tel-Hashomer criteria. Clinical symptoms, final diagnosis, effectiveness of colchicine, and genetic mutations were retrospectively investigated. [Results] The final diagnosis of these 32 patients were as follows; Behçet's disease (n=7), inflammatory bowel disease (n=4), periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) (n=4), myelodysplastic syndrome (MDS) (n=4), infectious disease (n=3), malignant disease (n=2), and other disease (n=8). All patients had recurrent fever, and the percentage of patients with peritonitis, pleuritis, and arthralgia were 59.4%, 28.1%, and 50%, respectively. About half of the patients responded to colchicine treatment, but none of the patients with PFAPA, MDS, and infectious disease responded to colchicine. Although known *MEFV* gene variants were identified in 19 patients (59.4%), none of which were in exon 10. [Conclusions] Patients without pathogenic *MEFV* variants and refractory to colchicine treatment may need to be reexamined for other diseases, including malignancy and infection.

## W18-5

### Identification for novel inflammasome-binding proteins

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Conflict of interest: None

[Objective] Inflammasomes are protein complexes involved in the transduction of inflammatory signals and are composed of signal transducing molecules such as NLRP3, ASC, and Caspase-1. Although several proteins such as Pyrin and NEK7 are known as regulatory proteins that bind to inflammasomes, other factors are still unclear. In this study, we searched for novel NLRP3 inflammasome-binding proteins. [Methods] Protein fractions extracted from THP-1 cells primed with LPS (5 µg/mL) for 24 hours, followed by stimulation with uric acid crystal MSU (100 µg/mL), an NLRP3 inflammasome stimulator, for 6 hours and unstimulated respectively were co-immunoprecipitated by using anti-NLRP3 and anti-Caspase-1 antibody. After electrophoresis, silver staining was performed. The protein of about 18 kDa, which showed increased binding to both anti-NLRP3 and anti-Caspase-1 antibody in case with stimulated as compared to unstimulated, was identified by linear trap/electric field FT-MS/MS mass spectrometry (Tokyo Medical and Dental University). [Results] Ten proteins including Dermcidin, a kind of antimicrobial peptide, were found both in the co-immunoprecipitation products of anti-NLRP3 and anti-Caspase-1 antibody. [Conclusions] The novel proteins that bind to the NLRP3 inflammasome were found.

## W18-6

### Genetic analysis of Caspase-1 in patients with palindromic rheumatism

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Conflict of interest: None

[Objectives] We previously found a constitutive active form of inflammasome molecule ASC exon2-lacking splicing variant in patients with palindromic rheumatism (PR) (Suganuma et al. Asian Pac. J Allergy & Immunol. 2019). We also found aberrant splicing of ASC in THP-1 cells stimulated with IL-1β and ceramide. (Hattori et al. JCR2021). In this study, we examined the splicing variability of the inflammasome molecule Caspase-1 in patients with PR and stimulated THP-1 cells. We also analyzed whole genome sequence of Caspase-1 in patients with PR. [Methods] We analyzed Caspase-1 cDNA obtained from patients with PR whole blood cells and THP-1 cells stimulated with IL-1β, IL-18, ceramide and LPS. We also performed NGS analysis of genomic Caspase-1 in patients with PR. [Results] Full-length cDNA of Caspase-1 (Caspase-1α) was observed in all cases, and other previously reported splicing variants (Caspase-1β, γ, δ, ε, and ζ) were not found. We identified eight minor allele SNPs in patients with PR. [Conclusion] Our results suggest that aberrant

splicing of inflammasome related genes is ASC specific. Although the relationship with pathogenesis is unknown, we also identified novel Caspase-1 genomic SNPs in patients with PR.

## W19-1

### Systemic lupus erythematosus (SLE) patient profile classified by body mass index (BMI)

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Conflict of interest: None

[Objective] The effect of BMI on disease activity in SLE has been reported to be conflicting in cohort studies. This study aims to classify SLE patients based on BMI and examine differences in SLE-related profiles. [Methods] SLE patients in our hospital from September 2017 to June 2020 were compared between those with BMI less than 22 (lower-BMI) and with 22 or more (higher-BMI).  $P < 0.05$  was considered significant by the Mann-Whitney test. [Results] Thirty-four SLE patients were included, with a mean age of  $48.6 \pm 14.6$  years, a mean BMI of  $21.6 \pm 2.9$ , and a mean SLEDAI of  $11.8 \pm 7.6$ . In the lower-BMI group, SLEDAI, the frequency of fever and the serum IFNα was significantly higher, whereas serum TREM1 was lower. There were no significant differences in complement titer or anti-dsDNA antibody titer. [Conclusions] Several mechanisms can be estimated for the higher disease activity in the lower-BMI group: (1) the effect of wasting; (2) immune abnormalities concerning malnutrition such as insufficient Vitamin D intake. Unexpectedly, serum TREM1 level, which is associated with the activation of the myeloid cells, was higher in the lower-BMI group, which warrants further research. This study suggests that BMI may help consider the choice of SLE treatment such as anti-IFN therapy.

## W19-2

### Impact of health literacy on trust in physicians among patients with systemic lupus erythematosus: the TRUMP2-SLE project

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Conflict of interest: None

[Objective] Diversity in patients' health literacy (HL) could affect physician-patient relationships. We examined how trust in physician is affected by not only "functional HL" but also "communicative HL" and "critical HL". [Methods] This cross-sectional study enrolled 362 SLE patients at 5 centers between 6/2020 and 8/2021. HL were measured via the 14-item FCCHL scale (range: 1-4 points). Outcomes were "trust in doctors generally" and "trust in one's physician", measured via the 5-item WFPT scales (range: 0-100 points). General linear models adjusted for age, gender, education, income, SLEDAI, disease duration, depression, and time using Internet were fit. [Results] Trust in one's physician increased with higher functional and communicative HL (per 1-pt increase, 3.2 [95%CI 0.7 to 5.9]; 5.4 [95%CI 1.6 to 9.3]). Trust in doctors generally increase with higher communicative HL and reduced with higher critical HL (per 1-pt increase, 6.8 [95% CI 2.0 to 12]; -6.7 [95% CI -12 to -1.9]) [Conclu-



sion] Among patients with SLE, the better they could extract information from communication, the more they trusted in their physicians. On the one hand, the more critically they could think information, the less trust in doctors generally they had, while trust in their physicians preserved.

## W19-3

### Impact of hope and trust in one's physician on medication adherence in SLE: the TRUMP2-SLE study

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Conflict of interest: None

[Objective] In SLE, psychosocial aspects related with medication behavior is theoretically important. We investigated the impact of “hope” (a pursuit of fulfillment in life and goals in light of health status) and “trust” (in one's physician) on it. [Methods] This was a cross-sectional study involving 386 patients with SLE at five university hospitals. The exposures were each score (range: 0-100 pts) of the 18-item health-related hope scale and the 5-item trust in one's physician scale. The outcome was the total score of the 12-item medication adherence scale (range: 12-60 pts). A general linear model was used with age, gender, marital status, income, education, health literacy, SLEDAI, duration of SLE, experience of side effects, steroid dose, and use of six other medications as covariates. [Results] The mean (SD) scores for hope, trust, and medication adherence were 57 pts (20), 79 pts (16), and 49 pts (5.3). The greater levels of hope and trust were associated with higher medication adherence score (per 10-pt increase in each, 0.59 pts [95%CI, 0.3-0.9], 0.75 pts [95%CI, 0.5-1.2]). [Conclusions] Our results demonstrate the importance of clinical practice that involves a trustful relationship and an awareness of the patient's hope to maintain medication adherence.

## W19-4

### Impact of shared decision-making on trust in physician in clinical practice for systemic lupus erythematosus: the TRUMP2-SLE study

Ryusuke Yoshimi<sup>1</sup>, Chiharu Hidekawa<sup>1</sup>, Natsuki Sakurai<sup>1</sup>, Nobuyuki Yajima<sup>2,3,4</sup>, Yuji Yoshioka<sup>1</sup>, Daiga Kishimoto<sup>5</sup>, Noriko Kojitani<sup>1,6</sup>, Yumiko Sugiyama Kawahara<sup>1,6</sup>, Yosuke Kunishita<sup>1,6</sup>, Hiroki Mizuno<sup>1</sup>, Kana Higashitani<sup>1</sup>, Yuichiro Sato<sup>1</sup>, Soichiro Adachi<sup>1</sup>, Yuki Iizuka<sup>1</sup>, Ayaka Maeda<sup>1</sup>, Lisa Hirahara<sup>1</sup>, Takaaki Komiyama<sup>1</sup>, Yutaro Soejima<sup>1</sup>, Naoki Hamada<sup>1</sup>, Hideto Nagai<sup>1</sup>, Naomi Tsuchida<sup>1</sup>, Kaoru Minegishi Takase<sup>1</sup>, Yohei Kirino<sup>1</sup>, Noriaki Kurita<sup>7,8</sup>, Nao Oguro<sup>2</sup>, Yoshia Miyawaki<sup>9</sup>, Ken-ei Sada<sup>9,10</sup>, Yasuhiro Shimojima<sup>11</sup>, Shigeru Ohno<sup>5</sup>, Hideaki Nakajima<sup>1</sup>

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Conflict of interest: None

[Objective] To investigate the relationship between patients' involvement with the shared decision-making (SDM) and their trust in physicians through a multicenter cross-sectional study. [Methods] For SLE patients who visit outpatient clinics of five facilities, we collected data of SDM-Q-9, the score of SDM, and Trust in Physician scale (TIPS), the index of reliability with the physician, through a self-administered questionnaire, and analyzed their relationship. [Results] We analyzed the data from 351 SLE patients (age  $45.5 \pm 14.1$  years, 88% female). When patients were divided into two groups, those with SDM-Q-9 of 75 or more (high SDM group; 185 cases, median 87 [IQR 80-96]) and those with SDM-Q-9 less than 75 (low SDM group; 166 cases, median 60 [51-67]), the high SDM group had a significantly higher TIPS than the low SDM group (75 [68-82] vs 66 [59-68],  $p < 0.0001$ ). A multiple regression analysis with age, sex, disease duration, disease activity, annual income, final education, and marital status as covariates revealed a 2.79 (95% CI 2.37-3.20,  $p < 0.001$ ) increase of TIPS by a 10-point rise in SDM-Q-9. We found a positive correlation between SDM-Q-9 and TIPS ( $r_s = 0.64$ ,  $p < 0.0001$ ). [Conclusions] The SDM was associated with trust in physicians in SLE patients.

## W19-5

### Clinical characteristics of elderly-onset systemic lupus erythematosus (SLE)

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Conflict of interest: None

[Objective] To clarify the clinical characteristics of elderly-onset SLE compared with young-onset cases. [Methods] We retrospectively reviewed medical records of SLE patients in our hospital from October 2015 to September 2021. [Results] Sixty-five patients were classified as young group (<60 years), and 20 patients as elderly group (>60 years). The female to male ratio was higher in the elderly group than in the young group, 9:11 and 2:63, respectively. At the time of onset, mucocutaneous symptoms was more frequent in the young group. Interstitial pneumonia, cerebrovascular diseases, and psychological symptoms were more frequent in the elderly group. Antibody positivity rates of young and elderly groups were the following: anti-ds-DNA antibody (87% vs 85%), anti-Sm antibody (37% vs 0%), and anti-cardiolipin antibody (25% vs 38%). The average dose of prednisolone for induction therapy was 40 mg/day in the young group and 37 mg/day in the elderly group. Thirty-six patients in the young group and 5 patients in the elderly group used immunosuppressants. [Conclusions] Compared to the young group, there were more males in the elderly group. And there were many cases with atypical symptoms such as interstitial pneumonia and cerebrovascular diseases, making it difficult to diagnose.

## W19-6

### Characteristics of patients with late-onset systemic lupus erythematosus in our hospital

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Conflict of interest: None

[Objective] Late-onset systemic lupus erythematosus (SLE), that is less common than early-onset SLE, has increased recently for aging of the population. The aim of this study is to clarify the characteristics of late-onset SLE patients. [Methods] Late-onset SLE patients (between 2007 and 2021) and early-onset SLE patients (between 2015 and 2020), those who were visited our department, were included. We historically collected clinical information about organ damage, laboratory data, treatment, and complications, and statistically analyzed the results. [Results] The mean ages of the patients late-onset SLE ( $n=8$ ) and those with early-onset SLE ( $n=19$ ) were  $55 \pm 11$  years old and  $33 \pm 10$ , respectively. Late-onset SLE patients had significantly less prevalence of skin rash (25% vs 79%,  $p=0.03$ ) and

higher of serositis (75% vs 21%,  $p=0.02$ ). The positivity of anti-RNP antibody (Ab) in late-onset SLE was significantly lower (13% vs 63%,  $p=0.03$ ) and anti-Sm Ab positivity tended to be lower ( $p=0.09$ ). There were no differences in prevalence of arthritis, nephritis, anti-dsDNA Ab titer, hypocomplementemia, dose of steroids, or immunosuppressants. [Conclusions] Late-onset SLE patients have less prevalence of skin rash and specific autoantibodies, which might lead diagnostic delay.

## W20-1

### SLE Disease Activity Score (SLE-DAS) can reflect Lupus Low Disease Activity State (LLDAS) simply and accurately

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Conflict of interest: None

[Objective] LLDAS is defined as (1) SLEDAI-2K (SLEDAI)  $\leq 4$  with no activity in major organs; (2) no new disease activity; (3) Physician's Global Assessment (PGA)  $\leq 1$ ; (4) prednisolone (PSL) dose  $\leq 7.5$  mg/day; (5) Standard doses of immunosuppressive drugs. There is concern that PGA makes LLDAS arbitrary and that SLEDAI may not adequately reflect changes in disease activity because each item is a dichotomous variable. Thus, we attempted to develop a new LLDAS definition using SLE-DAS. [Methods] We studied 293 patients with SLE in our hospital from April 2019 to April 2021. [Results] The mean age, disease duration, and PSL dose were  $49 \pm 14$  years,  $17.9 \pm 12$  years, and  $4.5 \pm 6.9$  mg/day, respectively. The mean SLEDAI-2K, SLE-DAS, and PGA were  $3.3 \pm 5.1$ ,  $4.5 \pm 6.9$ , and  $0.56 \pm 0.54$ , respectively. The correlation coefficient between SLEDAI and SLE-DAS was 0.69. The cut-off for SLE-DAS corresponding to SLEDAI  $\leq 4$  & PGA  $\leq 1$  was 3.5 (sensitivity 77%, specificity 84%, AUC 0.85). When we defined low disease activity as (1) SLE-DAS  $\leq 3.5$ ; (2) PSL  $\leq 7.5$  mg/day; (3) immunosuppressive drugs of the standard dose, the Cohen's kappa compared with LLDAS was 0.72, indicating substantial agreement. [Conclusion] The new definition of LLDAS using the SLE-DAS may reflect the LLDAS status simply and accurately.

## W20-2

### Evaluation of the new 2021 DORIS remission in SLE patients

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Conflict of interest: None

[Objective] To evaluate the new definition of remission in SLE (DORIS) introduced in 2021 and relationship between DORIS remission, Lupus Low Disease Activity State (LLDAS) and assessments by patients. [Methods] The subjects were SLE patients who visited our hospital from July to October 2019. We measured and analyzed the new DORIS remission, LLDAS, patient global assessment (PtGA), and SLAQ, LupusPRO and LIT. The New DORIS remission was defined as a clinical SLEDAI = 0 and Physician Global Assessment (PhGA)  $< 0.5$ , both of which are achieved with PSL  $\leq 5$  mg, antimalarial, and maintenance dose of immunosuppressive agents. [Results] Analysis was performed on 180 subjects both DORIS and LLDAS data of whom were available. The mean age was 45.6 years, 89.4% were female, 79.4%, 78.9%, 55.0% of patients were

receiving HCQ, PSL, and immunosuppressive agents. Of the 132 LLDAS-achieved patients, 91 (68.9%) achieved DORIS remission. Compared patients with DORIS remission and LLDAS-achieved, LLDAS only, and none of the above, PtGA, SLAQ, LupusPRO (health-related QOL), and LIT tended to be better in the remission group. There were no differences in gender, age, or drug use between groups. [Conclusions] The new DORIS remission might be a realistic treatment goal and related to patient assessment.

## W20-3

### Investigation of minimally important differences for improving the interpretability of the health-related quality of life measures for SLE patients: baseline characteristics of a prospective cohort

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Conflict of interest: None

[Objective] The minimally important differences (MID) required to interpret the magnitude of changes in the health-related quality of life measures (Lupus Patient-Reported Outcome; LupusPRO), which is widely used in SLE, remains unclear. We describe the patient background at enrollment from a prospective cohort study to determine the MID of the Japanese version of LupusPRO. [Methods] This prospective study from three institutions has been conducted from September 2020. MID estimates for some domains in health-related quality of life will be determined at 3 and 12 months by the seven-point Global Rating of Change as an external anchor. The descriptive statistics were presented as the mean and standard deviation (SD) or percentages (%). [Results] Of 166 patients included, 93% were female, the mean age was 48 years and 36% were within 10 years of disease onset. The glucocorticoid dose was 4.6 (4.2) mg. The SLEDAI and SDI scores were 3.0 (3.9) and 1.1 (1.7), and the domain scores for Lupus PRO were 73.6 (26.4) for pain/vitality, 70.0 (34.6) for cognition, and 69.9 (25.4) for emotional health, respectively. [Conclusions] We hope that the future results of this prospective study will allow the LupusPRO to have additional interpretability for assessing the quality of life of SLE patients.

## W20-4

### Association between EQ-5D and disease specific measures in Japanese patients with systemic lupus erythematosus

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Conflict of interest: None

[Objective] We aimed to cross-sectionally investigate the health-related quality of life (HRQoL) in Japanese patients with systemic lupus erythematosus (SLE) using the EQ-5D, which is a standardized instrument developed as a measure of HRQoL that can be used in a wide range of health conditions and treatments and often used for cost-effectiveness analyses. [Methods] Japanese patients with SLE ( $n = 106$ ) completed the EQ-5D and other related demographic questionnaires, and physicians simultaneously completed the SLE Disease Activity Index 2000 (SLEDAI-2K) and the Systemic Lupus International Collaborating Clinics Damage Index (SDI). [Results] The mean age, SLEDAI-2K score, and

SDI score were 44 years, 2.0, and 0.7, respectively. The mean EQ-5D index score of the SLE patients was 0.84, which was significantly lower than the age- and gender-matched national norm score, 0.92. EQ-5D index scores were significantly associated with the SDI scores ( $\beta = -0.30$ ,  $p < 0.01$ ), but not with the SLEDAI-2K scores. [Conclusions] HRQoL measured by the EQ-5D was reduced in Japanese patients with SLE and associated with disease damage, but not with disease activity.

## W20-5

### Association between achievement of treatment goal and personal characteristics of attending physician

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Conflict of interest: None

[Objective] In clinical practice for systemic lupus erythematosus (SLE), the concept of “treat to target” has been introduced. This study aims to evaluate the relationship between attending physician personality characteristics and treatment goal achievements in the clinical practice for SLE. [Methods] A cross-sectional study was conducted on 291 patients with SLE in five referral hospitals in Japan to examine the relationship between the “perseverance” and “consistency” (scores 1-5) of the attending physicians, as measured by the Short Grit Scale, and the achievement of the Lupus Low Disease Activity Score (LLDAS). [Results] The mean age of the patients was 44 years, 90% were female, and the mean disease duration was 181 months. Thirty-six doctors were in charge of the patients (1-44 patients/each doctor). Of the enrolled patients, 119 (41%) had achieved LLDAS. The attending physicians with a consistency score of  $\geq 4$  were less frequent in the patients who achieved LLDAS (29% vs. 46%,  $p=0.004$ ). There was no association between the achievement of LLDAS and perseverance. [Conclusions] The personality characteristics of the attending physician may affect the achievement of treatment goals in patients with SLE.

## W20-6

### Quality of life and medical satisfaction of SLE patients due to gender of rheumatologists: A survey from the LUNA registry

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Conflict of interest: None

[Objective] To evaluate the quality of life (QOL) and medical satisfaction of SLE patients by gender of rheumatologists. [Methods] 744 SLE patients from the registry for SLE patients (LUNA), who answered the Lupus-PRO an index of QOL for SLE patients, and the Medical Interview Satisfaction Scale (MISS-26), an index of medical satisfaction, were enrolled, and mean scores were calculated for each domain and item. [Results] 670 patients were in the male rheumatologist group and 74 patients were in the female rheumatologist group. Female patients were 579 (86.4%) and 66 (89.2%), age was 47.5 (14.9) and 48.9 (15.5) years, disease duration was 15.3 (10.7) and 18.5 (12.6) years, and SELENA-SLEDAI score was 3.71 (3.68) and 4.74 (4.84), respectively. In the Lupus-PRO, the mean score was high in 6 out of 12 domains in both male and female physician groups, especially the male rheumatologist group had high score in the domain of emotional health (2.60 (1.16), 2.44 (1.28)) and the female rheumatologist group in the domain of body image (2.91 (1.27), 3.18 (1.07)). In MISS -26, all 26 items were higher score in the female rheumatologist group. [Conclusion] In the female rheumatologist group, the medical satisfaction was high, but the QOL had different results for each domain.

## W21-1

### Effect of molecular targeted therapy on glucocorticoid reduction in rheumatoid arthritis - the ANSWER cohort study-

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Conflict of interest: Yes

[Objective] The purpose of this study was to investigate the effect of biologics (Bio) and JAK inhibitors (JAKi) on glucocorticoid (GC) dose reduction. [Methods] 1826 treatment courses (TCs) of 1679 patients who were newly inducted with Bio or JAKi with concomitant GC by 12 months were included. We divided into Bio (TNFi, IL-6Ri, CTLA4-Ig) and JAKi group, and the concomitant GC dose after the start of treatment was inves-



tigated. [Results] The mean (SD) age was 50.3 (16.3) and 50.9 (15.5) years, and the disease duration was 9.4 (10.0) and 10.6 (9.5) years, The DAS28-ESR was 4.5 (1.5) and 4.4 (1.4), HAQ-DI 1.1 (0.8) and 1.0 (0.7), and 80.8% and 81.0% were female. The mean (SD) PSL doses (mg/day) were 5.7 (5.2) and 4.8 (3.7), concomitant MTX 54.5% and 50.0%, and iguratimod 5.6% and 20.0%. The mean dose of PSL in mg/day after 0, 1, 3, 6, 9, and 12 months was 5.68, 5.34, 4.78, 4.28, 4.22, and 4.18 in the Bio group, and 4.81, 4.55, 4.40, 4.68, 4.27, and 4.14 in the JAKi group. In the JAKi group, there was a statistically significant difference between the increased and decreased GC doses group at 3-6 months. [Conclusions] Bio and JAKi had a GC-reducing effect, while JAKi had a temporary increase at 6 months after the start of treatment.

## W21-2

### Efficacy and Safety of Baricitinib in b/tsDMARDs Naïve and b/tsDMARDs-IR Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] We analyze efficacy and safety of baricitinib in real-world data. [Methods] Cases were recruited to SHIN-yokohama Arthritis Register (SHARE) between 2015 and 2021 (n=3,869). 154 Patients were diagnosed according to ACR/EULAR 2010 classification criteria and treated with baricitinib over 52 weeks. 38 cases fulfilled EULAR definition for difficult-to-treat RA (D2T-RA). [Results] 79 (51.3%) b/tsDMARDs naïve and 75 (48.7%) b/tsDMARDs-IR patients were enrolled. There were no differences in RA duration time (11.4+/-7.8 vs. 12.9+/-8.3), anti-CCP2 positive (ave.242.6+/-158.9), and CDAI (20.2+/-12.4 vs. 17.8+/-11.3) at the beginning of baricitinib. Baricitinib withdrawal for inefficacy showed no difference between b/tsDMARDs naïve and b/tsDMARDs-IR patients in RA with/without MTX (logrank p=0.8589). In b/tsDMARDs group, predictors to detect patients who achieved LDA and/or remission were lower CDAI (20.6+/-11.1 vs. 33.4+/-11.1) and baricitinib 2 mg/day in multivariate logistic regression (OR 1.1 and 14.3, 95%CI 1.0075-1.1240 and 0.0145-0.3322, p=0.023 and p<0.0001, respectively). [Conclusions] Our data confirm the efficacy and safety profiles of baricitinib in RA. It also showed baricitinib 2 mg/day was effective in b/tsDMARD naïve patients.

## W21-3

### Efficacy and Safety of switching to another JAK inhibitors for RA patients who had inadequate response to JAK inhibitors

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Conflict of interest: None

[Objective] To elucidate another JAK inhibitors (JAKi) for RA patients who had inadequate response to JAKi. [Methods] Among RA patients had taken JAKi in our hospital, the medical records of 34 RA patients who had taken another JAKi due to inadequate response to JAKi and had been followed up for more than 24 weeks were retrospectively evaluated. [Results] Background features at the switching another JAKi were as follows; average age 64.0 years old, mean disease duration 13.7 years, stage 4 ratio 52.9%, the average pre-JAKi administration duration 19.9 months, and the average CDAI 18.3. The JAKi that were discontinued were as follows; TOF in 21 cases (62%), BAR in 7 cases (20%), and PEF in 6 cases (18%). Next JAKi after switching were as follows; TOF 2 (6%), BAR 14 (41%), PEF 4 (12%) and Upadacitinib (UPA) 14 (41%). LOCF analysis revealed that the changes of CDAI from baseline to week 12 and 24 were from 18.3 to 11.4 (P=0.022) and 10.9 (P=0.005). After the change, there were no serious adverse events. [Conclusions] In this study, the switching to another JAKi seems to be helpful in RA patients who had inadequate response to JAKi.

## W21-4

### A study of cases with relapsing tendency after the introduction of baricitinib

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Conflict of interest: None

[Objective] We examined patients who presented a trend of relapse when the disease course was uneventful after the introduction of baricitinib (BARI). [Methods] By October 2020, we introduced BARI to 61 patients. 19 patients that presented a trend of relapse after BARI introduction (relapse group) were compared with 17 patients in which the disease course was uneventful (uneventful group). The examination items were the age at the time of introduction, disease duration, CDAI, SDAI, RF level, MMP-3 level, number of prior biologics/JAK inhibitors (JAK i), and HAQ. The levels of ESR, CRP, RF, MMP-3, IgG, and IgM were also examined in the relapse group at 4, 8, 12, and 18 weeks prior to relapse. [Results] The examination items in the relapse group did not differ markedly from those in the uneventful group. A pre-relapse retrospective study revealed high RF and IgG levels in 9 (47.4%) and 6 (31.6%) patients, respectively, 8-12 weeks prior to relapse. [Discussion] Follow-up observation is needed after dose reduction of BARI. In addition, the levels of RF and IgG were useful indexes in predicting the trend of relapse. [Conclusion] We examined the patients who showed a trend of relapse when the disease course was uneventful.

## W21-5

### Examination of therapeutic effects on interstitial lung disease model mice of heparin-enhanced adipose tissue-derived mesenchymal stem cells

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Conflict of interest: None

[Objective] The therapeutic effects of ASCs co-cultured with heparin on ILD was investigated. [Methods] The cell functions of ASCs co-cultured with heparin were compared with ASCs without heparin, and the therapeutic effects were investigated using bleomycin-induced ILD (BLM-ILD) mice. [Results] Heparin significantly increased HGF protein secretion and gene expression of ASCs, and also enhanced migration ability. In addition, gene expressions of anti-inflammatory factor (IDO-1) and cell migration promoting factors (SDF-1, CXCR-7) were also significantly increased. After examining the heparin concentration that most enhanced the cell function of ASCs, in vivo therapeutic experiments were conducted on BLM-ILD mice. ASCs were administered as a single dose from the tail vein after the completion of BLM delivery (day 7). The treatment groups were set as follows: 1) disease control, 2) ASCs alone (100000 cells), 3) heparin co-cultured ASCs (100000 cells). Lung inflammation and fibrosis were significantly suppressed in the heparin co-cultured ASCs group as compared with the disease control group and the ASCs alone group at 28 days after BLM administration. [Conclusions] Heparin enhanced the cellular functions of ASCs, and enhanced the therapeutic effects of ASCs on BLM-ILD mice.

## W21-6

### Analysis of the mechanism of Baricitinib on pain developed in anti-collagen antibody arthritis mice

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Conflict of interest: Yes

[Objective] Baricitinib has been shown to improve pain scores more strongly than anti-TNF inhibitors in clinical trials for the treatment of rheumatoid arthritis, suggesting the existence of a pain regulation, not involved in the improvement of arthritis. In this study, we investigated the mechanism of the pain regulation by Baricitinib. [Methods] The Collagen

Antibody-induced Arthritis (CAIA) model was used. Baricitinib, Celecoxib, and vehicle (water) were administered intragastrically once a day, and we evaluated arthritis and pain (Grip strength test, von Frey test). On Day8 and 14, the dorsal root ganglia (DRG) and spinal cord were harvested to evaluate the expression of the pain-related molecules. [Results] Arthritis and the grip strength peaked around Day 8 and attenuated gradually, while allodynia peaked around Day 14 and sustained thereafter. Two drugs suppressed arthritis and the grip strength equally, but Baricitinib suppressed allodynia predominantly over Celecoxib. Baricitinib inhibited the phosphorylation of STAT3 in the DRG at Day 8, and inhibited the spinal glial activity at Day 14. [Conclusions] This study suggests that Baricitinib may ameliorate allodynia via suppression of the STAT3 phosphorylation in the DRG and the spinal glial activity.

## W22-1

### The effectiveness of baricitinib for elderly patients with rheumatoid arthritis

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Conflict of interest: None

**Object:** This study aimed to investigate the effectiveness of baricitinib for rheumatoid arthritis (RA) **Methods:** A total of 243 RA patients who were followed for at least 52 weeks were included. The patients were divided into  $\geq 65$  years and  $< 65$  years group. We investigated the change of DAS28-CRP and rate of discontinuation of baricitinib treatment. **Results:** 138 patients were aged  $< 65$  years, and 105 patients were aged  $\geq 65$  years. Mean DAS28-CRP significantly decreased in both groups ( $< 65$ : 3.44 to 2.25/  $\geq 65$ : 3.78 to 2.40). Multivariate logistic regression analysis revealed that lower DAS28-CRP scores at baseline and concomitant glucocorticoid were independently associated with the achievement of low disease activity at 52 weeks. The Multivariable Cox hazard model revealed that the hazard ratio (HR) of discontinuation of baricitinib due to adverse events (AEs) in  $\geq 65$  group was significantly higher than that of  $< 65$  group (HR: 2.57, 95%confidence interval [CI]: 1.08-6.10,  $p=0.033$ ). **Conclusion:** There were no significant differences in the effectiveness of baricitinib between age groups. On the other hand, the risks of discontinuation of baricitinib by AEs were higher in elderly than younger patients.

## W22-2

### Clinical efficacy of low-dose JAK inhibitors in elderly patients with rheumatoid arthritis

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Conflict of interest: None

**[Objective]** JAK inhibitors (JAKi) are an effective treatment for elderly patients with rheumatoid arthritis (RA), but their efficacy at low dose administration is unclear. We investigated the efficacy and retention rate of low-dose JAKi in elderly RA patients. **[Methods]** We selected RA patients who had a history of low-dose JAKi use and who were aged 60 years or older at the time of JAKi initiation and evaluated the retention rate and efficacy. For patients who had received 2 or more JAKi, the first drug was evaluated. **[Results]** Twenty-nine patients (7 males, 22 females; mean age at initiation 73.5 years) were enrolled in this study. JAKi included tofacitinib in 10 patients, baricitinib in 18 patients, and upadacitinib in 1 patient. The overall retention rate at 12 weeks was 48.3%, and the reasons for discontinuation were inadequate response in 13 patients (86.7%), nausea

in 1 patient (6.7%), and interruption of hospital visits in 1 patient (6.7%). Of the patients with inadequate response, 8 patients (61.5%) had subsequent dose escalation. The change in disease activity at 12 weeks showed significant improvement in SDAI from 13.1 to 7.6 and DAS28-CRP from 3.3 to 2.4, respectively. **[Conclusions]** JAKi showed improvement in disease activity even at low doses for elderly RA patients.

## W22-3

### Retention rate and efficacy of JAK inhibitors in elderly-onset rheumatoid arthritis patients

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Conflict of interest: None

**[Objective]** The number of elderly-onset RA (EORA) patients has increased. Due to decreased renal function, treatment with MTX is often difficult. We examined efficacy and retention rate of JAK inhibitors (JAKi) in EORA. **[Methods]** The study included 211 patients treated with JAKi in our hospital and related hospitals. The patients were divided into 60 years or older (EORA group) and under 60 (YORA group) at the onset of RA. We analysed retention rate and efficacy over 24 weeks. **[Results]** There were 56 EORA and 155 YORA patients. The average age of RA onset was 68.9/43.1 years, and JAK was started at 75.5/61.2 years old. In EORA group, the duration of RA (6.1/17.6 years) was significantly shorter, the eGFR (65.7/78.6 ml/min/1.73 m<sup>2</sup>) was worse, and the frequency of combined with MTX (41.1/65.2%) was significantly lower. While the retention rate over 24 weeks (78.6/76.1%) was no significant different, the abandon rate for adverse events was higher in EORA group. The changes of DAS28-CRP and SDAI in patients who continued over 24 weeks was no significant difference. **[Conclusions]** Although the EORA group was older and the rate or dose of MTX were lower, there was no significant difference in retention rate and efficacy of JAKi. It suggested JAK may be an effective option for EORA treatment.

## W22-4

### Clinical study of MTX dose when JAK inhibitor is administered in the elderly

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Conflict of interest: None

**[Objective]** The guidelines recommend doses above MTX 8 mg / week for treated patients. But in clinical practice, older people tend to have lower doses of MTX. The survey was conducted with the aim of considering the conditions for safely continuing JAK inhibitors in the elderly. **[Methods]** A retrospective study was conducted on all patients who received JAK inhibitors from 2016 to September 2021. **[Results]** The dose of MTX was divided into a group exceeding 8 mg / week and a group not exceeding 8 mg / week, and the test was performed on elderly and non-elderly people. In the continuation group, the proportion of elderly people who did not exceed 8 mg / week was significantly higher. In addition, when comparing only the elderly with the group discontinued due to adverse events and the continuous group, the proportion of patients who discontinued due to adverse events did not exceed 8 mg / week was significantly higher. Similarly, only elderly people were compared between the inadequate effect group and the continuous group, but there was no significant difference in the amount of MTX combined. **[Conclusions]** It was suggested that MTX above 8 mg / week may not always be required to safely continue JAK inhibitors in the elderly.

## W22-5

### Clinical results of JAK inhibitor with and without methotrexate in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] The purpose of this study was to investigate the clinical results of JAK inhibitors in patients with rheumatoid arthritis (RA) with and without methotrexate (MTX). [Methods] Seventy-eight RA patients (43 MTX group, 35 non-MTX group) who received JAK inhibitors were included in this study. Patient's backgrounds were compared between two groups (age, disease duration, eGFR, PSL status, history of treatment with JAK inhibitors or biologics agents, and disease activity (DAS28CRP, white blood cell count)). [Results] There were no differences between two groups in the mean age (67.4 and 69.1 years), the disease duration (15.6 and 15.0 years), eGFR (76.5 and 71.4 mL/min), and DAS28CRP (4.25 and 4.38), respectively. Overall, 58 patients (74%), 30 in MTX group and 28 in non-MTX group, had received biologics agents or other JAK inhibitors. Eleven (26%, MTX group) and 8 (23%, non-MTX group) patients had received PSL. There was no difference in white blood cell count between the two groups, although there was a slight downward trend. [Conclusions] In this study, we compared the clinical course of patients with RA treated with JAK inhibitors with and without MTX.

## W22-6

### Comparison of efficacy and safety of JAK inhibitors and biologics in elderly patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To compare the efficacy and safety of JAK inhibitors and biologics (Bio) in elderly rheumatoid arthritis (RA) patients. [Methods] We retrospectively collected data from medical records of RA patients aged 65 years or older who were treated with JAK inhibitors or Bio due to inadequate response to csDMARDs between June 2015 and October 2020. [Results] There were 56 patients in the JAK inhibitor group (16 with tofacitinib, 35 with baricitinib, and 5 with upatacinib) and 57 patients in the Bio group (15 with IL-6 inhibitors, 27 with CTLA-4 inhibitors, and 15 with TNF inhibitors). There were no significant differences in gender, disease duration, disease activity, methotrexate use, or interstitial pneumonia complications between the two groups. The mean  $\Delta$ DAS28-CRP at 24 weeks was not significantly different between the two groups (JAK inhibitor -1.245 vs. Bio -1.182,  $p=0.945$ ), and the retention rate at 52 weeks was 83.9% in the JAK inhibitor group and 87.7% in the Bio group. The Kaplan-Meier method was used to analyze the overall retention rate, and there was no significant difference between the two groups ( $p=0.311$ ). [Conclusion] There was no significant difference in efficacy and safety between JAK inhibitors and Bio in elderly patients with RA refractory to csDMARDs.

## W23-1

### Long term effect of abatacept on structural remission - Results from the Kyoto University RA Management Alliance cohort (KURAMA)

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Conflict of interest: None

[Object] To investigate the effect of long-term observation on the inhibition of joint destruction in patients treated with abatacept in rheumatoid arthritis (RA). [Methods] Joint destruction was assessed by van der Heijde modified Total Sharp Score (mTSS) at induction and at least 2 years after induction in RA patients treated with abatacept (ABT) at the Rheumatology Center, Kyoto University Hospital. Differences in background at the time of treatment introduction were examined by Fisher's exact test. [Results] Of the 111 patients treated with ABT for whom mTSS analysis was available, 63 patients who continued ABT were included in the analysis. Median age: 67 years; percentage of women: 83%; anti-CCP antibody positivity: 43%; methotrexate use: 64%; concomitant steroid use: 51%; median duration of ABT at radiographic evaluation: 3.1 years; median DAS28-ESR at induction: 4.6. ACPA-positive patients (63%,  $n=27$ ) were more likely to achieve mTSS annual progression  $<0.5$  than negative patients (36%,  $n=36$ ) ( $p=0.044$ ), and patients with steroids (31%,  $n=32$ ) were more likely to achieve mTSS annual progression  $<0.5$  than those without steroids (65%,  $n=31$ ) ( $p=0.0118$ ). [Conclusions] ABT may significantly reduce long-term joint destruction in the ACPA-positive and steroid unused patients.

## W23-2

### In Real World Data, factor analysis associated with structural remission in RA patients with abatacept therapy

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Conflict of interest: None

[Objective] Previous reports on structural assessments of abatacept (ABA) therapy were for bio-naïve patients and were younger than the current age of RA patients. Therefore, we decided to re-examine the factors for achieving structural remission from Real-World Data (RWD). [Methods] The analysis was performed 78 patients who were started with ABA therapy between 2012 and 2020. We evaluated the background data at ABA therapy start. In addition, we evaluated disease activity changes, treatment responsiveness, and functional assessments for a year from baseline, as well as joint structure assessments at week 52. [Results] The mean age of them was 75 years old. Achievement rate of SDAI remission continued to increase until week 52. The EULAR-response was bimodal, rising again from week 12, and the trend continued until week 52. Achievement of mHAQ  $\leq .5$  maintained about 50% after week 8. In the structural evaluation, mTSS  $\leq .5$  was achieved by more than 50% of them. We showed statistically significant differences in the time to drug use and in the control state of disease activity after 12 weeks to achieve structural remission. [Conclusions] We could suggest that early initiation and continuous good arthritis control are more important to prevent of joint destruction in ABA therapy.

## W23-3

### What are the factors associated with achieving low disease activity after 6 months of abatacept treatment in rheumatoid arthritis patients with pulmonary involvement?

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Conflict of interest: Yes

[Objective] The purpose of this study was to investigate the factors for achieving low disease activity (LDA) with abatacept (ABT) in patients with rheumatoid arthritis (RA) complicated by respiratory disease. [Methods] Among 100 patients with RA undergoing ABT treatment at our hos-



pital, 79 patients with respiratory disease (13 males and 66 females) were included in the study, and the factors contributing to the achievement of SDAI LDA after 6 months were examined by logistic regression analysis. [Results] After 6 months of ABT treatment, SDAI significantly improved from 21.21 to 9.10 ( $P<0.01$ ), and 66% (52/79) of patients achieved SDAI LDA. In univariate analysis, the group of patients who achieved SDAI LDA had significantly lower tender joint count, patient pain VAS, patient general VAS, physician general VAS, HAQ-DI, and SDAI at induction (all  $P<0.01$ ). In multivariate analysis, low patient general VAS was extracted ( $P=0.047$ ). [Conclusions] To achieve LDA after 6 months of ABT treatment for RA patients with pulmonary lesions, a lower patient general VAS at induction is recommended.

## W23-4

### The necessity of methotrexate combination with IL-6 receptor antagonist for rheumatoid arthritis

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Conflict of interest: None

[Objective] To evaluate of MTX combination with IL-6 receptor antagonist for rheumatoid arthritis (RA). [Methods] This agent was administered to 1430 RA patients among 15553 patients enrolled in NinJa2020. We compared age, sex, disease duration, the value of ACPA, RF, and e-GFR, disease activity scores (DAS28-CRP, CDAI, Boolean remission) and concomitant use of steroid, NSAIDs, and other csDMARDs between MTX- combination group (500 patients, 35.0%) and non- combination group (930 patients). [Results] The mean age of non- combination group (66.8) was significantly older than that of MTX- combination group (62.4). The rate of men per women of non- combination group (0.23) was significantly higher than that of MTX- combination group (0.17). The mean disease duration of non- combination group (17.1) was significantly longer than that of MTX- combination group (14.9). There was no difference in the mean value of ACPA, DAS28-CRP and CDAI scores, and Boolean remission rate between two groups. The mean RF value of MTX- combination group (128.5) was lower than that of non- combination group (220.2). There was no difference in the rate of usage and the mean dose of steroid. [Conclusions] MTX combined with IL-6 receptor antagonist for RA might have poor effect on disease activity score.

## W23-5

### The efficacy and safety of shortening the duration of subcutaneous Tocilizumab administration in rheumatoid arthritis patients

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Conflict of interest: None

Purpose: To elucidate the efficacy and safety of shortening the duration of subcutaneous Tocilizumab (TCZ sc) administration in RA patients in our hospital. Methods: Using the MiRAi database, we extracted patients who received shortening the duration of TCZ sc administration between June 2017 and May 2021 and who were observed for at least 3 months and examined the following. 1) patient characteristics, 2) 1-year continuation

rate, 3) reasons for discontinuation, 4) changes in disease activity, 5) parameter comparison between successful and unsuccessful treatment groups. Results: 1) 28 patients, age 60 [48, 69] years, BMI 22 [21, 26], disease duration 71 [34, 263] months, DAS28ESR 3.3 [1.9, 4.2], CDAI 13 [5, 18], PSL/MTX use 57/43%, past TNF $\alpha$ /ABT failure rate 57/14%. 2) 45% 3) inadequate effect: 11, pregnancy: 1, patients were able to return to 2 weeks: 5, malignancy: 1, cellulitis: 1. 4) The total percentage of patients with low disease activity and remission was 46% (13/28) for DAS28ESR and 43% (12/28) for CDAI at the time of shortening, but 82% (9/11) for both after 1 year. 5) The factor that was significantly different between the groups were ACPA, DAS28ESR, etc. Conclusion: There are few reports of shortening the duration of TCZ sc administration in clinical practice and we report here as valuable data.

## W23-6

### Medium term persistence of sarilumab in rheumatoid arthritis patients with chronic kidney disease

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Conflict of interest: None

[Objective] To investigate the impact of chronic kidney disease (CKD) on the persistency of sarilumab (SRL) in patients with rheumatoid arthritis (RA). [Methods] 42 patients with RA who started SRL between May 2018 and May 2021 were divided into two groups: CKD group with eGFR-Cr  $< 60$  mL/min/1.73 m<sup>2</sup> (n=12) and non-CKD group with eGFR-Cr  $> 60$  mL/min/1.73 m<sup>2</sup> (n=30). [Results] There were no differences in age, disease duration, number of bDMARDs/tsDMARDs used in the past, PSL usage, rheumatoid factor positivity, anti-CCP antibody positivity, or CRP between groups, but there were more males in the CKD group ( $P<0.01$ ). The median follow-up period was 454 (IQR: 1145-783) days. During the follow-up period, SRL was discontinued in 14 patients, including 6 patients with invalidity, 2 patients with infection, 2 patients with allergy, and 4 patients with others. There was no significant difference in the persistency of SRL between CKD and non-CKD groups (HR: 0.8909 [95%CI: 0.279-2.845],  $P=0.8453$ ). There was no significant difference in persistency between the two groups after adjusting for age and number of bDMARDs/tsDMARDs used in the past (HR: 0.8801 [95%CI: 0.2743-2.823],  $P=0.8299$ ). [Conclusions] CKD was not a significant risk factor for SRL persistency in RA patients.

## W24-1

### The proportion of synovial fluid derived fibroblast subsets in rheumatoid arthritis

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Conflict of interest: None

[Objective] The aim of this study is to investigate the subsets of rheumatoid arthritis (RA) synovial fluid (SF)-derived fibroblasts and the difference of subsets proportion in clinical features. [Methods] We collected the SFs from RA patients at the onset or at the flare. The profile of cell surface markers expressed by SF-derived adherent cells were analyzed using flow cytometry performed by triple staining with PDPN, CD34 and THY1. [Results] We got the SFs from 37 patients. At the primary culture, PDPN<sup>+</sup> cells were 11.9 (5.2-25.9) % of total adherent cells. The major subset in the PDPN<sup>+</sup> cells in the onset group were CD34<sup>+</sup>THY1<sup>-</sup> and the major subset in the PDPN<sup>+</sup> cells in the flare group were CD34<sup>+</sup>THY1<sup>+</sup>. By passage, PDPN<sup>+</sup> cells were increased, of which the proportion of CD34<sup>+</sup>THY1<sup>+</sup> cells and CD34<sup>+</sup>THY1<sup>-</sup> cells were increased but CD34<sup>+</sup>THY1<sup>-</sup> cells were decreased. The CD34<sup>+</sup>THY1<sup>+</sup> cells increased well in the flare group significantly. The subsets of 4 patients who were collected SFs and STs at the same time were similar. [Conclusions] These data show that the proportion of SF-derived fibroblast subsets were different between at the initial onset and at

the flare. The difference proportion of SF-derived fibroblast subsets may be involved in clinical features in RA.

## W24-2

### WDR5 inhibitor suppresses the expression of chemokines in Rheumatoid Arthritis Synovial Fibroblast

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Conflict of interest: None

[Objective] Trimethylation of histone 3 lysine 4 (H3K4me3) in RA synovial fibroblasts (SF) may be involved in pathological conditions through abnormal hyperactivity of gene expression. Histone methyltransferase including MLL1 forms a complex containing WDR5 and exerts enzymatic activity. MM-102, a WDR5 inhibitor, treatment on RASF was performed to investigate changes in the expression of cytokines and chemokines. [Methods] We collected synovial tissue from knee. Changes in H3K4me3 and mRNA of each gene were evaluated by ChIP method and quantitative RT-PCR, respectively. Protein expression was analyzed by WB method. The siRNA method was used for knockdown of the target gene. [Results] The expression of MLL1 in RASF was increased as compared with that in OASF. MLL1 siRNA suppressed the expression of mRNA of several cytokines and chemokines, H3K4me3 of the promoter of the gene, and the expression of these genes. When RASF was treated with MM-102, among these cytokines and chemokines, decreased expression of H3K4me3 and gene expression of CCL2, CCL5, CXCL9, CXCL10, and CXCL11 promoters were observed. [Conclusions] MM-102 suppressed RASF activation via regulation of the histone methylation, and this type of medicine may be a candidate of a novel therapeutic drug for RA.

## W24-3

### Vascular endothelial cadherin reduces inflammation in rheumatoid arthritis

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Conflict of interest: None

[Objective] ADAM-15 is a protein expressed in the cell membrane surface, and we have reported that it is concerned with angiogenesis in RA. VE-cadherin is a protein concerned with the adhesion formation of vascular endothelial cells. We found that ADAM-15 and VE-cadherin were elevated in serum and joint fluid in RA. In this study, we more investigate the relation between RA and VE-cadherin. [Methods] To determine VE-cadherin expression on RA synovial tissues, immunohistochemistry was performed. RA-FLS and HUVEC were stimulated with VE-cadherin, and we measured cytokines in its serum. Then, We analyzed whether there was a correlation between pre-treatment serum VE-cadherin and pre-treatment disease (DAS-28ESR) and between pre-treatment serum VE-cadherin and pre- and post-treatment disease activity ( $\Delta$ DAS-28ESR). [Results] We found that VE-cadherin was expressed on RA synovial tissues. VEGF stimulated VE-cadherin in RA-FLS was decreased compared with control. CXCL16, ICAM and IL-8 stimulated VE-cadherin in HUVEC was decreased compared with control. There was a negative correlation between serum VE-cadherin and DAS-28ESR. No correlation was found between serum VE-cadherin and  $\Delta$ DAS-28ESR. [Conclusions] VE-cadherin may suppress inflammation in RA by inhibiting cytokine production.

## W24-4

### Significance of Inter alpha trypsin inhibitor heavy chain 4 (ITIH4) in arthritis

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Conflict of interest: None

[Background] Inter alpha trypsin inhibitor heavy chain 4 (ITIH4) is fluctuating protein at the onset of rheumatoid arthritis, but its detailed function in arthritis is unknown. [Objective] To clarify the role of ITIH4 in arthritis. [Methods] 1) K/BxN serum transfer was performed in C57BL/6 mice, and the expression and changes of ITIH4 in major tissues of naïve mice and serum-transferred arthritis (K/BxN-STA) were examined by western blot and quantitative PCR. 2) ITIH4-deficient (KO) mice were generated by CRISPR/Cas9, and the presence of each organ damage was investigated. 3) Collagen-induced arthritis (CIA) was induced in wild-type (WT) mice and ITIH4-KO mice, and arthritis scores and incidence rates were compared. [Results] 1) ITIH4-mRNA was expressed in the lung and liver of naïve mice, and its expression in the liver was increased in K/BxN-STA. ITIH4 localized in the plasma of naïve and STA mice and the synovial fluid of STA mice. Citrullinated ITIH4 was found in plasma in K/BxN-STA. 2) ITIH4-KO mice showed no developmental or growth problems and no obvious organ damage as arthritis. 3) ITIH4-KO mice tended to have a lower incidence of CIA and arthritis scores compared to WT mice. [Conclusions] ITIH4-KO mice tended to have improved CIA, suggesting that it might be involved in the aggravation of CIA.

## W24-5

### ACPA positivity has distinct relations with earlier onset and higher disease activity of RA

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Conflict of interest: None

[Background] ACPA and RF are characteristic antibodies found in patients with RA, and these antibodies revealed to be associated with pathogenesis and clinical course of RA. [Patients and Methods] We investigated impacts of these antibodies using National wide RA database NinJa 2020. [Results] Positivity of ACPA and RF are 73.1% and 73.0% each other. In ever or current smoking patients, ACPA positivity is 84%, while 73.6% in no-smoking ones (female), 59.4/70% (male). ACPA positive patients showed earlier onset of RA, higher disease activity according to CRP, ESR, TJC, SJC, DAS28ESR and DAS28CRP than negative ones. mHAQ score of positive patients was also higher than negative ones. [Conclusions] Smoking is thought to be associated with ACPA production. And ACPA positivity would be associated with pathogenesis and clinical course of RA.

## W24-6

### Examination of bone structure (bone density, geometry, microstructure) in anti-CCP antibody-positive cases using HR-pQCT

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Conflict of interest: None

[Objective] The bone structure of ACPA-positive cases was examined using HR-pQCT. [Methods] Early group was 43 ACPA-positive females (39  $\pm$  9 years) who were not with past arthritis. EstRA group was 39 ACPA-positive established RA females (43  $\pm$  9 years) who maintained remission. And Negative group was 43 arthritis-free ACPA and RF-negative females (44  $\pm$  7 years) as controls. Bone mineral density (BMD), bone microstructure, and geometry of the distal radius were measured by HR-pQCT. [Results] Total and cortical (Ct.) and trabecular (Tb.) BMD was

significantly lower in both the early group and EstRA group than in the negative group. Total and Tb. areas were significantly higher in the early group than in the negative group. Ct. bone thickness was significantly lower in both the early group and the EstRA group than in the negative group. Ct. porosity tended to be lower in the early group than in the other group. Tb. width was significantly lower in the early group than in the negative group. [Conclusions] The decrease in BMD in the early group compared to the group suggests the effect of ACPA on systemic bone. Cortical expansion observed in the early group, but not in the EstRA group. Furthermore, it is possible that cortical bone porosity was suppressed in the early group.

## W25-1

### Effect of temporary drug discontinuation on disease activity of rheumatoid arthritis in COVID-19 vaccination

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Conflict of interest: None

[Objective] The guideline of American College of Rheumatology recommends temporary drug discontinuation such as MTX, JAK-inhibitor (JAK), Abatacept (ABT) in COVID-19 vaccination for patients with rheumatoid arthritis (RA). However, flare of RA was concern due to temporary drug discontinuation. The purpose of this study was to investigate flare of RA due to temporary drug discontinuation in COVID-19 vaccination. [Methods] 176 RA patients (44 male, 132 female, average age 70.2, average duration of illness 15.1 years) were included in this study. 139 patients used MTX, 44 patients used PSL, 82 patients used biologics, and 12 patients used JAK-inhibitor. After second vaccination, disease activity (DAS28-CRP, CDAI, SDAI) and self assessment by the questionnaire were used for evaluation of flare of RA compared with before vaccination. [Results] 103 patients temporarily stopped MTX, 17 patients stopped ABT and 9 patients stopped JAK. Before and after vaccination, symptom by self assessment was not changed and average disease activity was improved 0.1 by DAS28-CRP, 0.3 by CDAI and 0.2 by SDAI. However, flare of RA was observed in 17 patients (14.5%). [Conclusions] In temporary drug discontinuation for COVID-19 vaccination, care should be taken for flare of RA symptoms in some cases.

## W25-2

### Lifestyle-related diseases has impact on MTX retention rate? -Kansai consortium for well-being of rheumatic diseasepatients (ANSWER cohort)-

Takaichi Okano<sup>1</sup>, Yo Ueda<sup>1</sup>, Hirotaka Yamada<sup>1</sup>, Iku Shirasugi<sup>1</sup>, Yuzuru Yamamoto<sup>1</sup>, Sadao Jinno<sup>1</sup>, Keisuke Nishimura<sup>1</sup>, Wataru Yamamoto<sup>2</sup>, Yasutaka Okita<sup>4</sup>, Kosuke Ebina<sup>3</sup>, Takayuki Fujii<sup>6</sup>, Kosaku Murakami<sup>5</sup>, Hideki Amuro<sup>7</sup>, Yonsu Son<sup>7</sup>, Hideyuki Shiba<sup>8</sup>, Tohru Takeuchi<sup>8</sup>, Ryota Hara<sup>9</sup>, Masaki Katayama<sup>10</sup>, Shinsuke Yamada<sup>11</sup>, Motomu Hashimoto<sup>11</sup>, Jun Saegusa<sup>1</sup>

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Conflict of interest: Yes

Risk factors for coronary heart disease such as hypertension, dyslipidemia, and diabetes mellitus (CHD risk factors), was reported to increase the disease activity of rheumatoid arthritis. We firstly examine the effect of CHD risk factors on the MTX retention rate using the Kansai multicenter ANSWER cohort. [Method] MTX naive patients were extracted from the

Kansai multicenter ANSWER cohort. 2973 MTX naive cases were included. And we selected 1751 cases who can be clearly detected to have or not have CHD risk factors. 1185 patients were analyzed, excluding bDMARDs user during observation period to eliminate the effects of bDMARDs. [Results] There were also no significant differences in the initial dose of MTX and PSL, in CDAI. SDAI was significantly higher in the MTX continued group ( $18.4 \pm 11.9$  vs  $15.8 \pm 10.6$ ). Logistic regression analysis showed that patients with dyslipidemia had a lower MTX retention rate after 1 year (Odds ratio 0.71,  $p = 0.014$ ). Diabetes mellitus did not affect MTX retention. Patients with hypertension had significantly better MTX retention (Odds ratio 1.5,  $p = 0.0018$ ). [Conclusion] It was suggested that dyslipidemia may worsen the MTX continuation rate after 1 year.

## W25-3

### Relationship between methotrexate metabolism-related gene polymorphisms and erythrocyte MTX-polyglutamate concentration and clinical effects in Japanese patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To clarify determine the relationship between gene polymorphisms related with methotrexate (MTX) metabolism, and MTX-polyglutamate concentrations and the effectiveness and safety of MTX. [Methods] In RA patients who had taken stable dose of MTX, 15 gene polymorphisms related to MTX metabolism (RFC1 80G>A, ABCB1 3435C>T, ABCB1 1236C>T, ABCC2 1058G>A, ABCC2 1249G>A, GGH 16T>C, GGH 452C>T, FPGS 1994D>A, MTHFR 677C>T, MTHFR 1298A>C, ATIC 347C>G, TYMS 5'UTR, TNFα 308G>A, TNFα 238G>A, IL-6 174G>C) were measured. The MTX-PG concentrations in erythrocytes were measured with a liquid chromatography-mass spectrometer. The relationship between each SNP and clinical parameters was analyzed. [Results] A total of 266 RA patients were included. The mean age 61.7 years, the mean disease duration 8.2 years. The mean duration of MTX usage was at 4.9 years and the mean MTX dose was 8.5 mg/week. FPGS 1994G>A was associated with MTX-PG3-5 concentrations (GG+GA 2.1 nmol/L vs AA 2.9 nmol/L,  $p=0.04$ ). MTHFR 1298A>C was associated with Boolean remission achievement rates (AA 41.5% vs AC 27.3% vs CC 11.1%,  $p=0.02$ ), while it was associated with liver injury (AC+CC 20.4% vs AA 9.6%,  $p=0.01$ ). [Conclusions] The polymorphisms related with MTX metabolisms in Japanese with RA were clarified.

## W25-4

### Study of iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPD) cases in patients (PAs) with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objective and Methods] The definitive diagnosis of LPD is based on the pathological diagnosis of biopsies, but if the biopsies taken after withdrawal of immunosuppressive drugs (ISDs) often making the diagnosis of LPD impossible. Between 2010 and 2020, 22 PAs with RA were clinically diagnosed with LPD. Biopsies were performed in 21 PAs, 2 of them died early. The aim of this study is to investigate the clinical course of LPD, and 19 PAs (excluding these two) were divided into two groups, in which biopsies were performed after (group A: 10 PAs) or before (group B: 9 PAs) withdrawal of ISDs. [Results] 6 PAs in group A and all PAs in group B were pathologically diagnosed with LPD. After withdrawal of ISDs, LPD disappeared in 5 PAs in group A and 3 PAs in group B, but recurred in 2 PAs in group A and 1 PA in group B. The 5 PAs in group A and 6 PAs in group B whose LPD did not disappear received CHEMO at 1.76 months (MO) and 0.87 MOs, after withdrawal of ISDs. 3 PAs in group A died at 28.5 MOs and one patient in group B (non-LPD related death) died at 37.4 MOs after the onset. [Conclusions] In this study, Group B PAs tended to receive CHEMO earlier than Group A PAs, and had a better prognosis. It is important to perform a biopsy to confirm the diagnosis of LPD before withdrawal of ISDs.



## W25-5

### Treatment of RA patients with a history of discontinuation of MTX due to adverse events

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Conflict of interest: None

[Objective] To evaluate the subsequent treatment and disease activity of RA patients with a history of discontinuation of MTX due to adverse events (AEs) [Methods] From the 2020 database of RA patients visiting our hospital, patients with a history of discontinuation of MTX due to AEs in the past are extracted, and the current treatment, disease activity, and physical function are evaluated. [Results] 86 RA patients had a history of discontinuation of MTX due to AEs, including gastrointestinal symptoms in 24, ILD in 19, LPD in 16, CKD in 8, cytopenia in 8, infection in 4, cancer in 3, liver cirrhosis in 2, gynecomastia in 1 and cough in 1 case. The average age was 72.7 years, 81.4% were women, 14.9 years of illness, 62.8% of RF positive, 59.3% of ACPA positive, 22.1% with interstitial lung disease, and 60.4% with CKD. Current treatments are TAC 37.2%, IGU 30.2%, SASP 16.3%, BUC 2.2%, MZR 1.2%, PSL 19.8%, mean PSL 4.4 mg, TNF inhibitor 16.3% (ETN 10.5%, GLM 3.5%, CZP 1.2%, ADA 1.2%), Non-TNF inhibitor 19.8% (TCZ 11.6%, ABT 8.1%), JAK inhibitor 1.2% and mean disease activity are DAS28-ESR3.12, SDAI7.26 and HAQ 0.73. [Conclusions] RA patients in our hospital who had a history of discontinuation of MTX due to AEs used other csDMARDs and biologics to maintain low disease activity and physical function.

## W25-6

### Clinical features of monoarticular rheumatoid arthritis

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Conflict of interest: None

[Objective] The 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) has made it possible to diagnose RA even in monoarthritis. In this study, we aimed to clarify the clinical characteristics of monoarticular RA. [Methods] We examined the sex, age, autoantibodies, imaging findings, course, and therapeutic interventions of patients with monoarticular RA in our outpatient department. [Results] Of the 50 cases, 39 were women and 11 were men. The mean age at onset was 46.5 years, and the mean age at initial diagnosis was 49.9 years. The site of arthritis was a large joint in 38 cases and a small joint in 12 cases. Anti-CCP antibody was positive in 44.7%, rheumatoid factor was positive in 64.6%, and serum negative was in 26.0%. 37 of 38 patients had synovitis detected by MRI or ultrasound, and 18 patients had bone erosion detected. In 44 patients, methotrexate and prednisolone were administered for treatment in 32 and 9 cases, respectively. [Conclusions] In monoarticular RA, large arthritis is common, the time lapse between onset and initial diagnosis is long, and bone destruction was already present in some cases at the first visit. It is necessary to diagnose RA at an early stage and intervene therapeutically, even in cases of monoarthritis, by utilizing imaging tests.

## W26-1

### Iguratimod vs. salazosulfapyridine in methotrexate inadequate response with the patients with rheumatoid arthritis. Final Report: A results from the rheumatology multicenter in the university, hospital, and clinic as the retrospective study (ARIES study)

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Conflict of interest: Yes

[Objective] The optimal combination of 2nd csDMARDs for MTXIR

is one of the most important evidence for the treatment of rheumatism, but it remains unclear. [Methods] In the present study, we compared the clinical efficacy and side effects of 2nd csDMARDs IGU and SASP as add-on therapy to 1st csDMARDs MTX-IR. [Results] At 24 months, the retention rate in the MTX+SASP and MTX+IGU groups was 33.3% vs.58.6%.  $\Delta$ DAS28-CRP from the baseline and the percentage of good responders were -0.6 vs. -1.3 and 14.8% vs. 45.1% in the MTX+SASP vs. MTX+IGU groups, respectively. Prednisolone dose reduction was  $0.3 \pm 5.6$  vs.  $-0.9 \pm 2.6$  mg/day. Conversely, the decrease in estimated glomerular filtration rate was reduced in MTX+IGU compared with baseline. [Conclusions] IGU is the second csDMARD for RA patients on MTX-IR and has demonstrated high retention rates and good clinical efficacy, being it a useful combination therapy for controlling disease activity. However, renal dysfunction should be noted during follow-up.

## W26-2

### Efficacy of adding iguratimod therapy in rheumatoid arthritis patients who had inadequate response to biologic DMARDs

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Rheumatology, Seirei Hamamatsu General Hospital

Conflict of interest: Yes

[Objective] Iguratimod was approved in June 2012 and recommended by guideline 2014 in the treatment of rheumatoid arthritis. Although there have been efficacy of monotherapy and concomitant MTX in clinical trials, however, there have been no reports of concomitant biologic DMARDs (Bio). Therefore, we investigated efficacy of concomitant IGU therapy in RA patients who had inadequate response to Bio at the author's institution. [Methods] Subjects were 151 patients adding IGU who had inadequate response to Bio from January 2014 to March 2021. Previous treatment Bio. was ADA. 143 patients received MTX and baseline mean concomitant MTX was 12.0 mg/week. And baseline characteristics were Mean age 55.3 years, mean duration of illness 68.2 months, corticosteroid use 9.3% (mean 3.3 mg/day). The course of DAS28, SDAI, CDAI and remission rates were analyzed. [Results] Mean DAS28-ESR, SDAI, CDAI were significantly decreased from the initiation of IGU treatment at 24 weeks ( $2.97 \rightarrow 2.3$ ,  $6.44 \rightarrow 2.23$ ,  $5.87 \rightarrow 1.94$ ), at 104 weeks ( $2.17$ ,  $2.71$ ,  $2.27$ ). Remission rates of DAS28-ESR, SDAI, CDAI were 74.8%, 76.8%, 76.2% at 24 weeks, 71.4%, 80.0%, 78.6% at 104 weeks. [Conclusions] IGU might be a new RA treatment option for aiming remission in patients who had inadequate response to Bio.

## W26-3

### Ultrasonographic evaluation of Iguratimod treatment 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 102 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 30 males and 72 females. The mean age was  $65.1 \pm 13.0$  years; the mean disease duration was  $7.8 \pm 10.5$  years; and the number of MTX combination, other DMARD excluded combination, IGU monotherapy and Biologics combination were each 44, 24, 17 and 17 cases. Clinical findings related to RA were as follows: tender and swollen joint count,  $3.5 \pm 2.7$  and  $3.0 \pm 2.0$ ; patient's and physician's global assessment of disease activity,  $36.5 \pm 23.6$  and  $36.2 \pm 22.3$  mm; CRP,  $1.1 \pm 1.4$  mg/dL; ESR,  $29.0 \pm 18.2$  mm/h; DAS28-ESR,  $4.08 \pm 1.12$  and CDAI,  $13.7 \pm 7.1$ . The mean GS score changed from  $15.9 \pm 10.2$  at baseline to  $14.9 \pm 10.1$  ( $p=0.040$ ) and  $14.1 \pm 10.2$  ( $p=0.003$ ) at week12 and 24. The mean PD score changed from  $8.4 \pm 6.0$  at baseline to  $7.0 \pm 6.6$  ( $p<0.001$ ) and  $6.4 \pm 6.4$  ( $p<0.001$ ) 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.

## W26-4

### Investigation of the risk factors for the side effects of iguratimod

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Conflict of interest: None

[Objective] To investigate the risk factors for the side effects of iguratimod (IGU). [Methods] We retrospectively evaluated 102 rheumatoid arthritis patients who started taking IGU in our hospital from January 2019 to March 2021 and were followed up for at least six months. [Results] 1) There were 56 patients in the IGU continuation group and 46 patients in the discontinuation group. The proportion of women was higher in the continuation group (71.4% vs. 55.3%), and the mean age was higher in the discontinuation group (67.9±14.5 years vs. 74.1±8.3 years,  $p=0.010$ ). More patients in the discontinuation group had adverse reactions to non-MTX csDMARDs (28.9% vs. 50.0%,  $p=0.027$ ). 2) In the discontinuation group, 23 patients had gastrointestinal adverse reactions: liver dysfunction or gastrointestinal symptoms. In this group, the number of patients with MTX was higher than that in the non-gastrointestinal adverse drug reaction group (30.4% vs. 4.3%,  $p=0.02$ ). The proportion of patients with a history of adverse drug reactions to non-MTX csDMARDs was higher in the non-gastrointestinal adverse drug reaction group (30.4% vs. 73.9%,  $p=0.003$ ). [Conclusion] Older patients with a history of adverse reactions to non-MTX csDMARDs were more likely to experience side effects of IGU.

## W26-5

### Effect of iguratimod on glomerular filtration rate

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Conflict of interest: None

[Objective] Iguratimod (IGU) is a drug that has been shown to be effective in combination with methotrexate (MTX). In clinical practice, renal dysfunction may be a cause for discontinuation of IGU, and its effect on glomerular filtration rate (GFR) should be investigated. [Methods] We used the Kaplan-Meier method to retrospectively analyze the continuation rate of rheumatoid arthritis patients newly started on IGU at our hospital from October 2018 to September 2021, treating dose reduction or discontinuation due to adverse events as event occurrence. We compared the rate of decline in eGFR (ml/min/1.73 m<sup>2</sup>/year; eGFR slope) before and after IGU treatment. eGFR slope was calculated using eGFR before, 1 month, 3 months, and 6 months after treatment. [Results] The continuation rate of IGU was 48.1%. The reason for discontinuation was decreased renal function in 6 patients (7.4%). 55 patients who were able to continue IGU for more than 6 months were compared. The pre-treatment eGFR slope was 1.97, and after 1, 3, and 6 months, the slopes were -0.25, -1.65, and 7.06 ( $p=0.0002$ ). [Conclusions] One of the reasons for the low continuation rate of IGU was the decrease in eGFR. It is necessary to pay attention to the occurrence of adverse effects of MTX, which is a concomitant drug.

## W26-6

### Adverse events differ between salazosulfapyridine and mesalazine

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Conflict of interest: None

[Objective] To examine differences of adverse events (AEs) between salazosulfapyridine (SASP) and mesalazine (5-ASA). [Methods] The numbers of AEs related to SASP and 5-ASA, reported from 2004 to 2020 and listed on the webpage of the Japanese Adverse Drug Event Report database (JADER) of Pharmaceuticals and Medical Devices Agency

(PMDA), Japan, were studied to find their major AEs. [Results] The total number of ADRs from 2004 to 2020 was 2493 cases for SASP and 2464 cases for 5-ASA. ADRs of SASP were more in skin disorders including rash (17% of total ADRs of SASP), hematopoietic disorders (15%), eosinophilia with systemic symptoms (10%), and infections (10%). Whereas, ADRs related to 5-ASA included interstitial lung injury (12% of total ADRs of 5-ASA), fever (9%), pancreatitis (7%), pericarditis/myocarditis (7%), and eosinophilic pneumonia (6%). [Discussion] The discrepancy might have been affected by the primary disease, the drug itself, or the maximum dose allowance such as 1000 mg of SASP for rheumatoid arthritis and 4000 mg for inflammatory bowel diseases, and 3000 mg to 4000 mg of 5-ASA for inflammatory bowel diseases. [Conclusions] The AEs reported in the real world much differed between the two similar drugs used for diseases with immune disorders.

## W27-1

### Homeodomain transcription factor Hhex negatively regulates osteoclast differentiation

Hisato Watanabe<sup>1</sup>, Kenta Makabe<sup>1</sup>, Yasunori Omata<sup>1</sup>, Takumi Matsumoto<sup>1</sup>, Takeshi Miyamoto<sup>2</sup>, Sakae Tanaka<sup>1</sup>

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Conflict of interest: None

[Objective] The cause of bone loss in patients with rheumatoid arthritis is that inflammatory cytokines produced in synovial tissue promote osteoclast differentiation by RANKL in osteoblasts. Therefore, elucidation of the mechanism of osteoclast differentiation is important for improving the prognosis of patients with rheumatoid arthritis. The purpose of this study is to identify genes that play an important role in osteoclast differentiation and reveal their functions. [Methods/Results] Using ChIP-seq and RNA-seq, Hhex genes whose expression epigenetically decreases in osteoclastogenesis was identified. Hhex overexpression cells inhibited osteoclastogenesis and Hhex suppression cells promoted osteoclast formation. In Hhex conditional knockout mice, cancellous bone mass decreased as the number of osteoclasts increased. These suggested that Hhex is negative regulator in osteoclast differentiation. In addition, Hhex induced the cell cycle of osteoclast precursor cells to the G1 arrest via Cdkn2a and promoted osteoclast differentiation. [Conclusions] Hhex is negative regulator of osteoclast differentiation and regulates skeletal homeostasis via cell cycle of osteoclast precursors.

## W27-2

### Functional roles of membrane-bound and soluble forms of RANKL in osteoporosis

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Conflict of interest: Yes

[Objective] RANKL is an essential cytokine for osteoclastogenesis. Excess RANKL signal leads to bone loss in rheumatoid arthritis (RA), osteoporosis and bone metastasis. Anti-RANKL antibody are now used for the treatment of these bone loss diseases. RANKL is synthesized as a membrane-bound molecule and cleaved into its soluble form by proteases. However, the functional difference between the two forms of RANKL had been poorly understood in vivo. Of note, serum soluble RANKL (sRANKL) level was reported to be associated with several clinical disease activities such as RA and postmenopausal osteoporosis. Therefore, we aimed to clarify the functional roles of two types of RANKL in pathological bone loss. [Methods] We have analyzed mice lacking sRANKL or membrane-bound RANKL (mRANKL) generated by genome editing. [Results] sRANKL-deficient mice exhibited normal bone phenotype, while mRANKL-deficient mice displayed severe osteopetrosis. In an ovariectomy (OVX)-induced model of postmenopausal osteoporosis, sRANKL-deficient mice and the control littermates lost a similar amount of trabecular bone. In contrast, mRANKL-deficient mice were resistant to OVX-induced bone loss. [Conclusions] We revealed that mRANKL mainly contributes to physiological bone metabolism and postmenopausal oste-

oporosis.

## W27-3

### Examination of bone structure related to the therapeutic effect of Romosozumab

Ikuko Tanaka<sup>1</sup>, Takashi Kato<sup>2</sup>, Motokazu Kai<sup>3</sup>, Kunikazu Ogawa<sup>3</sup>, Ryosuke Hibi<sup>1</sup>, Yusuke Suzuki<sup>1</sup>, Hidenao Imada<sup>1</sup>, Hitomi Nagasaka<sup>1</sup>, Hiroaki Mizuno<sup>1</sup>, Hisaji Oshima<sup>4</sup>, Shigenori Tamaki<sup>1</sup>

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Conflict of interest: None

[Objective] Romosozumab (ROMO) is indicated for severe osteoporosis patients. We investigated the relationship between the amount of change in bone mineral density (BMD) in DXA in patients who received ROMO and the bone structure in the distal radius (HR-pQCT) and proximal femur (3D-SHAPER). [Methods] The subjects were 48 patients (73 ± 8 years old) who were administered ROMO. Before ROMO administration and 12 months after, BMD of the lumbar spine and the proximal femur was measured by DXA, and the amount of change was calculated. Before administration, HR-pQCT measured bone structure (BMD, geometry, microstructure). DXA data was reconstructed in 3D by 3D-SHAPER, and BMD of cortical (Ct.) bone and trabecular (Tb.) bone was measured like QCT. [Results] In the study with HR-pQCT, the amount of change in lumbar spine did not correlate with any of the measured values. the amount of change in the proximal femur was positively correlated with the Tb. number and negatively correlated with the Tb. thickness. In 3D-SHAPER, BMD, Ct. bone thickness, Ct. surface BMD, and Tb. BMD were not correlated with the amount of change in DXA BMD. [Conclusions] It was considered that the effect of ROMO can be expected in the case where the trabecular structure is maintained.

## W27-4

### Comparison of bone strength using finite-element analysis between patients with and without ossification of the posterior longitudinal ligament

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Conflict of interest: None

[Objective] Patients with ossification of the posterior longitudinal ligament (OPLL) were often reported to be associated with increased bone mineral density (BMD). However, the bone strength in patients with OPLL remains unknown. This study aimed to compare bone strength measured by quantitative computed tomography-based finite element analysis (QCT/FEA) between patients with and without OPLL. [Methods] Eligible 157 patients were divided into the non-OPLL (68 patients) and OPLL groups (89 patients). We examined the BMD and the predicted bone strength (PBS) of the proximal femur and lumbar spine. We compared the BMD and the PBS between the non-OPLL and OPLL groups using the inverse probability weighting method. [Results] The BMD of the proximal femur and lumbar spine and the PBS of the proximal femur were significantly higher in the OPLL group than in the non-OPLL group. There were no significant differences in the PBS and BMD between the male subgroups. However, the BMD and PBS of the proximal femur and lumbar spine were significantly higher in the OPLL females than in the non-OPLL females. [Conclusions] Hyperostosis of the posterior longitudinal ligament in OPLL was associated with higher bone strength by QCT/FEA, especially in female OPLL patients.

## W27-5

### Effect of denosumab switched from bisphosphonates on prevention of joint destruction in postmenopausal rheumatoid arthritis patients

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of Medicine, Sendai, Japan

Conflict of interest: None

[Objective] The purpose of this study was to determine the effect of denosumab on joint destruction in Japanese women with rheumatoid arthritis (RA) who had anti-cyclic citrulline peptide (CCP) antibodies. [Methods] This retrospective study included 56 patients who received denosumab switched from bisphosphonates and 50 patients who continued to have bisphosphonates. All participants were positive for anti-CCP antibodies and were treated with subcutaneous injections of 60 mg denosumab every 6 months. Radiographs of the hands and feet were taken and the changes in the modified total Sharp score (mTSS), erosion score (ERO), and joint space narrowing score (JSN) were evaluated at 12 and 24 months. [Results] At 12 months, there was a significant difference in the amount of change in ERO ( $p=0.015$ ) and mTSS ( $p=0.01$ ). Similarly, there was a significant difference in the amount of change in ERO ( $p=0.013$ ) and mTSS ( $p=0.003$ ) after 24 months. On the other hand, there was no significant difference in the amount of change in JSN and clinical parameters. [Conclusions] The results suggested that denosumab might be effective in reducing the progression of bone erosion in RA patients who switch from bisphosphonates.

## W27-6

### The cumulative incidence of localized periosteal thickening and atypical femoral fractures in patients with autoimmune disease based on a ten-year observation period

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Conflict of interest: None

[Objectives] Femoral localized periosteal thickening (LPT) often precedes atypical femoral fracture (AFF). We previously reported based on a two-year observation period, the incidence of LPT was 8-10% in patients with autoimmune diseases taking prednisolone (PSL) and bisphosphonate (BP), and AFF occurred in one. This study was conducted to reveal the incidence of LPT and AFF in the subsequent observation period. [Methods] Four patients who were not examined follow up X-ray were excluded, and remaining 121 patients were included in this study. LPT was determined on X-ray of the bilateral femoral and hip joints. [Results] At the first examination, age was 55 (42-64) years, women were 108 (89%), daily PSL dose was 10 (8-12) mg, the duration of BP was 5.0 (3.0-6.3) years and the observation period was 9.0 (6.2-9.4) years. LPT was evident in 10 patients at the enrollment and 2 (1-3) patients/year were newly detected LPT in follow-up period. Finally, LPT was evident in 31 patients (26%), 45 femora, and AFF occurred in 5 patients (4%), 9 femora. The incidence of LPT after initiation of BP was 2,412 per 100,000 person-years and that of AFF was 383. [Conclusions] Long-term use of BP-related AFF is not rare and needs to be paid attention in patients with autoimmune disease treated with PSL.

## W28-1

### Refracture risks of the patients with rheumatoid arthritis with fragility fractures

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Conflict of interest: Yes

[Objective] Rheumatoid arthritis (RA) is known to be a risk factor for fragility fractures. Patients with fragility fractures tend to occur refracture. this study was to determine whether RA patients with fragility fractures have an increased risk of refracture. [Methods] Among 7,543 patients with fragility fractures treated surgically at ten hospitals from 2008 to 2017, 3,005 patients followed more than 24 months. Each 120 patients with and



without RA (controls) were matched using propensity score. The primary outcome was the refracture rate in the RA patients compared with the controls. Multivariable analyses were also performed to detect the risk factors. [Results] The refracture rates in the RA patients (12.5%) were significantly higher than in the controls (5.0%) ( $P=0.040$ ). The survival analysis also showed significantly high rates in the RA patients ( $P=0.040$ ). Patients with a long duration of RA were significantly associated with increased rates of refracture ( $P=0.030$ ). Only 10.5% of the RA patients switched osteoporosis treatments after surgery. [Conclusions] RA patients with fragility fractures tend to occur refracture, especially with a long duration of RA. It is important to review previous osteoporosis treatment considering fracture prevention and follow carefully.

## W28-2

### Evaluation of the accuracy of FRAX for the criteria of initiating pharmacotherapy for primary osteoporosis

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Conflict of interest: None

[Objective] The aim of this study was to evaluate the accuracy of FRAX against the criteria for initiating pharmacotherapy according to the 2015 Guidelines for the Prevention and Treatment of Osteoporosis (GL). [Methods] A total of 316 patients who were eligible for primary OP evaluation among those who underwent the bone mineral density test and FRAX evaluation were enrolled. The ROC curve was used to assess the accuracy of major fracture risk (Major%) and hip fracture risk (Hip%) against the GL criteria for initiating pharmacotherapy, and to compare the two. [Results] Major% showed a sensitivity of 0.825/specificity of 0.905 with 17% as the cutoff value, and Hip% showed a sensitivity of 0.848/specificity of 0.924 with 5.5% as the cutoff value. The area under the curve (AUC) was larger for Hip% (0.948) than for Major% (0.926) ( $p=0.02$ ). If the subject was limited to those aged 75 and over ( $n=202$ ), Major% showed a sensitivity of 0.853/specificity of 0.827 with 17% as the cutoff value, and Hip% showed a sensitivity of 0.887/specificity of 0.904 with 5.7% as the cutoff value. AUC was larger for Hip% (0.935) than for Major% (0.902) ( $p=0.03$ ). [Conclusions] A cutoff value of 5.5% in Hip% could be used to determine the criteria for initiating pharmacotherapy for OP, including secondary OP.

## W28-3

### FRAX® assessment in patients with rheumatoid arthritis predicted the real incidence of clinical fractures for 10 years -the results of the 10-year TOMORROW study-

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Conflict of interest: None

[Objective] To investigate if FRAX® in patients with rheumatoid arthritis (RA) can predict the incidence of new clinical fractures for 10 years. [Methods] We calculated ten-year probability of major osteoporotic fracture (FRAX) in 208 RA patients and 205 sex- and age-matched volunteers (Vo), and compared FRAX with the incidence of fractures for 10 years. [Results] The mean FRAX were 14.5 and 8.8% in 175 RA patients and 168 Vo, respectively, in whom we could calculate FRAX at baseline and complete to investigate the incidence of fractures. FRAX in RA was significantly higher than Vo ( $P<0.001$ ). The incidences of fractures were 33.9 and 22.9% in RA and Vo, respectively ( $P=0.031$ ). In both groups, the actual incidence of fractures was higher than FRAX prediction. Logistic regression analysis revealed that FRAX and  $FRAX \geq 15\%$  were the significant risk factors for fractures (Odds ratio (OR), 1.055,  $P<0.001$ , 2.943,

$P=0.043$ , respectively). The mean FRAX in RA with and without fractures were 18.5 and 12.5%, respectively ( $P=0.002$ ). In RA, FRAX was the significant risk factor for fractures (OR, 1.046,  $P=0.004$ ). [Conclusions] FRAX and the incidence of fractures for ten years were significantly higher in RA than Vo. We confirmed that FRAX was the risk factor for fractures in actual clinical practice.

## W28-4

### Achieving glucocorticoid free might decrease the risk for the clinical fractures in patients with rheumatoid arthritis - ten-year results from the TOMORROW study-

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Conflict of interest: None

[Objective] To reveal the correlation between decreasing dosage of glucocorticoid (GC) and the incidence of clinical fractures in patients with rheumatoid arthritis (RA) during ten years. [Methods] We investigated the effects of dosing of GC on the incidence of clinical fractures for ten years in 202 patients with RA from a prospective cohort named TOMORROW study. [Results] The incidence of clinical fractures in RA patients was 0.036/person-year. There were 89 patients (44.1%) treated with GC at least once during ten years. The incidences of fractures in RA patients treated with and without GC were 0.052 and 0.026/person-year, respectively. Cox proportional hazard model revealed that GC dose of  $\geq 2$  mg/day at entry was a significant risk factor for fractures (Hazard ratio [HR]: 2.430; 95%CI, 1.040-5.675,  $p=0.040$ ). Although the risk for fractures did not decrease by just reducing GC (HR: 4.505; 95%CI, 0.589-34.457,  $p=0.147$ ), it was significantly lower if the dose of GC could be reduced to zero during ten years (HR: 0.407; 95%CI, 0.194-0.857,  $p=0.018$ ). [Conclusions] If the dose of GC was reduced to free during ten years, the fracture risk could become lower. In conclusion, after controlling disease activity of RA we should decrease the dose of GC to free.

## W28-5

### Even low dosage of glucocorticoid is risk factor for clinical fracture in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To reveal the incidence of clinical fractures and associated risk factors in patients with rheumatoid arthritis (RA) who participated in the TOMORROW study. [Methods] We evaluated bone mineral density (BMD), RA medication, and the incidence of clinical fractures over a ten-year period in 202 RA patients and 206 age- and sex-matched healthy volunteers (Vo). We analyzed associated risk factors for fractures. [Results] The incidences of fractures were 0.036 and 0.024/person-year in RA and Vo, respectively. Cox proportional hazard model revealed that low BMD at the thoracic vertebrae ( $< 0.7$  g/cm<sup>2</sup>) and history of fractures were significantly associated with the incidence of fractures (Hazard ratio [HR] 1.737,  $p=0.020$  and HR1.514,  $p=0.047$ , respectively) in all participants. RA morbidity, however, was not (HR1.398,  $p=0.112$ ). In RA patients, medication with GC at entry was a significant risk factor for fractures (HR1.898,  $p=0.017$ ). Additionally, GC dose of  $\geq 2$  mg/day at entry and during the ten-year period increased risk for fractures (HR 2.189,  $p=0.004$ ,

1.866,  $p=0.022$ , respectively). [Conclusions] It was revealed that even low-dose GC use at entry and during ten years were significantly associated with an increased frequency of fractures among patients with RA.

## W28-6

### Effects of sleeve gastrectomy on bone mineral density and muscle mass

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Conflict of interest: None

[Objective] Sleeve gastrectomy is increasingly used in patients with morbid obesity to reduce weight and to treat comorbidities. However, there are some reports that the effects on the bone and muscle mass appear harmful. These data are lacking and only used dual-energy X-ray absorptiometry (DXA). The aim of this study was to evaluate the effects of the bone and muscle mass using computed tomography (CT). [Methods] Between March 2012 and May 2019, we retrospectively reviewed patients with morbid obesity who were treated by sleeve surgeries. Thirty-nine patients were male (mean age: 44 years) and fifty-four were female (mean age: 48 years). The present study evaluated the Hounsfield units and psoas muscle mass index (PMI). [Results] Body weight and body mass index (BMI) decreased significantly ( $p<0.0001$ ). Although Hounsfield units were not significantly decreased, PMI decreased significantly ( $p<0.0001$ ). [Conclusions] We must acknowledge the effects on the bone and muscle mass patients with morbid obesity who were treated by sleeve gastrectomy.

## W29-1

### Clinical significance of serum levels of IL-18 in adult-onset Still's disease -IL-18 reflects remaining rash in inactive patients-

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Conflict of interest: None

[Objective] Serum levels of IL-18 are useful for diagnosis and evaluation of activity in adult-onset Still's disease (AOSD). This study investigated the clinical significance of high IL-18 levels in AOSD. [Methods] Ferritin, C-reactive protein (CRP), and IL-18 levels were measured 131 times at the same time of day in 34 AOSD patients treated at our hospital between April 2014 and August 2021. Pouchot's score  $\geq 3$  was taken to indicate high disease activity, while score  $< 3$  indicated low. The latter group was divided into subgroups with and without rash. [Results] The study population consisted of 34 patients (13 men) with a mean age of 38.6 years, 71/131 of whom were treated with tocilizumab. Ferritin, CRP, and IL-18 levels were significantly different between low and high disease activity groups ( $p<0.001$ ). However, only IL-18 was significantly different between the low disease activity patients with and without rash ( $p=0.003$ ; sensitivity, 70.4%; specificity, 81.8%; cutoff, 11066 pg/mL). In the low disease activity group with rash, 7/12 subsequently relapsed, while 2/12 did not relapse without reducing steroid. [Conclusion] In AOSD patients with low disease activity, IL-18 levels were significantly elevated in patients with rash, even when ferritin and CRP were not elevated.

## W29-2

### Analysis for clinical features and cytokine profiles of elderly onset adult Still's disease

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Conflict of interest: None

[Objective] To clarify the clinical features and cytokine profiles of elderly onset adult Still's disease. [Methods] We examined patients with definite adult Still's disease based on Yamaguchi's criteria, who developed the disease between Jan 2006 and Sep 2021. We retrospectively compared 1) patient background and symptoms, 2) laboratory data including IL-6 and IL-18, and 3) treatment and prognosis, between young onset (YO) group ( $<65$  years old) and elderly onset (EO) group ( $\geq 65$  years old). [Results] 48 patients (46.5 $\pm$ 19.8 years old, 14 males/34 females) were examined (YO group: 38/EO group: 10 patients). 1) Atypical rash was significantly more frequent, while typical rash and splenomegaly were significantly less frequent in EO than in YO group. 2) WBC count was significantly higher and serum IL-6 was significantly lower in EO than in YO group. Serum IL-18 and ferritin was comparable between two groups. Initial PSL dose, concomitant immunosuppressants and biologics, and relapse were comparable between two groups, whereas infections were significantly more frequent in EO than in YO group. [Conclusion] In EO group, atypical rash was more frequent, typical rash and splenomegaly were less frequent, WBC count was higher, serum IL-6 was lower, and infections were more frequent than in YO group.

## W29-3

### Hypocomplementemia and IL-18 in adult onset Still's disease (AOSD)

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Conflict of interest: None

[Objective] In this study, we elucidate the patients' characteristics in AOSD with hypocomplementemia. [Methods] Ninety-nine patients with AOSD (male; 4 cases, female; 15 cases) who were admitted to our hospital from 2011 to 2020 were included. They were divided into low CH50 and low C4 (low complement group; LCG) and high CH50 and high C4 (high complement group; HCG). We evaluated the laboratory findings, cytokine profile, and treatments. [Results] Seven patients were classified into LCG. Titers of C3 were significantly lower in LCG. Hemoglobin levels [11.0 (10.7-11.5) vs 12.1 (11.8-12.8) g/dL,  $p=0.016$ ] and platelet counts [12.0 (8.6-25.5) vs 30.6 (17.6-43.3) $\times 10^4/\mu\text{L}$ ,  $p=0.028$ ], were lower, and ferritin titers [19990 (8868-34115) vs 3348 (2451-13197) ng/mL,  $p=0.043$ ] were higher. In LCG, the titers of IL-18 were higher [191239 (153626-336206) vs 117404 (69414-268790) pg/mL,  $p=0.043$ ]. The titers of IL-18 positively correlated with ferritin (Spearman's rank correlation coefficient  $r=0.807$ ,  $p<0.0001$ ), and negatively correlated with Hb ( $r=-0.616$ ,  $p=0.00497$ ) and platelet counts ( $r=-0.726$ ,  $p<0.0001$ ). [Conclusion] Hypocomplementemia and anemia, low platelet count and high ferritin levels are relevant to high disease activity in patients with AOSD.

## W29-4

### Characteristics and outcomes of 36 Adult-onset Still's disease patients

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Conflict of interest: None

(Background) Adult-onset Still's disease (AOSD) was proposed in 1971 after a childhood inflammatory disease that was recognized as still's disease. There are few established treatments other than steroids, and treatment may be difficult in severe cases. (Method) From December 2009 to June 2020, AOSD patients who required hospitalization were tabulated and examined for clinical features and treatment responsiveness. (Results) The total number was 36 (27 females, 9 males), with 23 initial cases, 9 recurrences, and 4 complications. The average age was 40.3 years, and the average age of the first case was 37.1 years, which was far below the national average (46.5 years). The recurrence hospitalization rate for patients who introduced initial remission at their own facility was 26.0%, which was also below the national average (39.1%). The complication hospital-

ization rate was 11.1% and the mortality rate was 2.8%. The administration rate of steroid pulse therapy was 55.6% (20/36 cases), which was higher in the initial remission group. Tocilizumab (TCZ) was performed in only 4 patients with recurrence. (Conclusion) Due to the expansion of adaptation, it is expected that the number of cases of introducing TCZ from the first time will increase in the future.

## W29-5

### The HScore is a potential indicator to diagnose complications of macrophage activation syndrome in adult-onset Still's disease

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Conflict of interest: None

[Objective] Adult-onset Still disease (AOSD) is associated with macrophage activation syndrome (MAS), which requires early diagnosis. HScore is an indicator developed for the diagnosis of secondary hemophagocytic syndrome. We investigated the usefulness of HScore for differentiating MAS complications in AOSD. [Methods] 46 patients with AOSD diagnosed according to Yamaguchi criteria were included. IL-18, IL-6, sIL-2R, ferritin, CRP, ESR, LDH, AST, ALT, triglyceride, fibrinogen, WBC, ANC, ALC, Hb, PLT, hepatosplenomegaly, and hemophagocytosis in bone marrow were assessed, and HScore was calculated based on them. AOSD-related MAS (MAS+ group) was defined as patients who fulfilled 5 or more of 7 the HLH-2004 criteria, and was compared with AOSD without MAS (MAS- group). [Results] IL-18, sIL-2R, Ferritin, LDH, AST, ALT, and the HScore were significantly higher in the MAS+ group. ROC analysis showed that the cutoff value of HScore was 169.5, AUC: 0.92 (95% CI 0.81-1.00,  $p=0.0002$ ), sensitivity: 88.9%, specificity: 90.3%. [Conclusions] HScore could be useful as a highly accurate diagnostic marker in the diagnosis of AOSD-related MAS as well as other secondary hemophagocytic syndromes in adults.

## W29-6

### Two Refractory Cases of macrophage activation syndrome associated with adult onset Still's disease successfully treated with liposteroid

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Conflict of interest: None

[Case 1] A 39-year-old woman was admitted with fever, sore throat, arthralgia, erythema. Leukocytosis and elevated liver enzyme and ferritin were noted. She was diagnosed with adult onset Still's disease (AOSD). Because intravenous methylprednisolone pulse therapy and following high dose prednisolone (PSL) had insufficient effect, oral cyclosporine was added. However, at 21 days after starting treatment, high fever recurred, and the blood tests showed pancytopenia. She was diagnosed with macrophage activation syndrome (MAS). After intravenous methylprednisolone pulse therapy, liposteroid was added. Then her disease became stable. [Case 2] A 47-year-old woman was admitted with fever, sore throat, rash. Leukocytosis and elevated liver enzyme and ferritin were noted. She was diagnosed with AOSD. Because high dose PSL and methotrexate was ineffective, intravenous methylprednisolone pulse therapy was added. However, high fever recurred, and the blood tests showed pancytopenia. She was diagnosed with MAS. After liposteroid was added, her fever and pancytopenia resolved. [Clinical significance] There are some reports about the clinical utility of liposteroid for the treatment of refractory MAS in pediatric rheumatology. Liposteroid may be effective for refractory MAS associated with AOSD.

## W30-1

### Clarify different points of cytokine profiles in adult-onset Still's disease (AOSD) and COVID19

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Conflict of interest: None

[Objective] AOSD and COVID-19 have a lot of similarities to have systemic inflammations, high fever, hyperferritinemia, and some occurrence of cytokine storms, but have some differences between two. This study showed the comparison of both diseases and similarities and different from the aspect of cytokine profiles. [Methods] To compare cytokine profile of acute phase (IL-18 and IL-6) and clinical presentation of active AOSD (included Systemic JIA) 5 cases and COVID-19 infection (references) [Results] AOSD patients have high IL-18 in acute phases, and they have higher IL-18 than that of s-JIA. In AOSD patients, there are two groups, IL-18 dominant and IL-6 dominant. Compare the group between IL-18 and IL-6 dominant, former group has MAS (macrophage activation syndrome), and latter have arthritis. In severe COVID-19 patients who have high IL-18, they tend to have ARDS and cytokine storm. AOSD patients don't have ARDS. [Conclusions] Our results indicated that there were two types of AOSDs to have IL-18-dominant group and IL-6 dominant groups. And two have some different from clinical presentations. There are IL-18 elevation related to ARDS in COVID-19, which was not seen in AOSD.

## W30-2

### A case of subcutaneous sarcoidosis after vaccination with Covid-19 vaccine (BNT162b2)

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Conflict of interest: None

We report a 74-year-old female, who received the first dose of COVID19 vaccine (BNT162b2) on June 7 and the second dose on June 28. In early July, she started to have redness, swelling, and heat sensation on her extremities without any particular trigger. MRI of her thighs showed findings suggestive of fasciitis, and eosinophilic fasciitis was suspected, so she was admitted to our hospital for further investigation and treatment. The clinical findings were very similar to those of eosinophilic fasciitis, but blood tests did not show an increase in eosinophils, but did show increases in ACE, Ca, and sIL2-R. A chest CT scan showed multiple lymphadenopathy in the hilar region of the lungs and uveitis, so a skin biopsy was performed to investigate the possibility of sarcoidosis. The results were consistent with subcutaneous sarcoidosis. Prednisolone 20 mg oral treatment was started, and the symptoms of the extremities improved markedly in a few days. There are existing reports that cutaneous sarcoidosis is difficult to differentiate from eosinophilic fasciitis, and this case was no different. Therefore, when eosinophilic fasciitis is suspected, cutaneous sarcoidosis should also be considered. The causal relationship of the COVID19 vaccine needs to be carefully examined.

## W30-3

### A comparison of two cases of polyarthritis caused by mRNA vaccination suggesting an association between pleurisy and serum IFN- $\gamma$

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Conflict of interest: None

Case 1: A 96-year-old woman without history of rheumatic diseases developed polyarthritis and chest pain the day after the second dose of



BNT162b2. Musculoskeletal ultrasonography showed bilateral tenosynovitis of the long head tendon of the biceps brachii (LHB) and she had bilateral exudative pleural effusion. After confirming that there was no evidence of infection or malignancy, prednisolone 20 mg/day (0.5 mg/kg/day) was started and the pleural effusion and arthritis improved immediately. Case 2: A 72-year-old man without history of rheumatic disease developed polyarthritis after BNT162b2 vaccination. Musculoskeletal ultrasonography showed bilateral tenosynovitis of LHB. There was no pleural effusion and no evidence of infection or malignancy. All symptoms improved with 20 mg/day (0.3 mg/kg/day) of prednisolone. Discussion: Although myocarditis and thrombosis are widely known adverse reactions after mRNA vaccination, we have experienced two cases of polyarthritis that developed after mRNA vaccination. Analysis of serum cytokines in the two cases revealed markedly elevated serum IFN- $\beta$  levels in case 1. No elevation of serum IFN- $\beta$  was found in case 2, suggesting that IFN- $\beta$  may be associated with pleural effusion after mRNA vaccination.

### W30-4

#### A case of nivolumab-related tracheobronchial chondritis that developed during immune checkpoint inhibitor treatment for hypopharyngeal cancer

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Conflict of interest: None

[Background] Immune checkpoint inhibitors (ICIs) for advanced cancers are known to cause immune-related adverse events (irAEs) including rheumatic diseases. We report a case of tracheocondritis that developed during ICI treatment. [Case] A 66-year-old man was initiated ICI treatment for multiple lymph node metastases after surgical resection of hypopharyngeal cancer since May X-1. Cervical lymph nodes shrunk by ICI, however he had a fever and increased sputum with CRP elevation after the 24th course administration of ICI in June X. Antibiotics had no effect with negative sputum and blood cultures. FDG-PET in July X showed accumulation of trachea and bronchus, and contrast enhanced CT showed tracheal and bronchial wall thickening. Therefore, he was clinically diagnosed as ICI-related tracheobronchial chondritis. Treatment with high-dose steroids was initiated, but relapse was observed during tapering. The combined use of immunosuppressants was added in August X, and the condition has improved. [Discussion] We experienced a case of tracheobronchial chondritis as irAE after ICI administration. As irAE, tracheal cartilage lesions are extremely rare, and we review a few similar previous reported cases with literature consideration including comparison with relapsing polychondritis.

### W30-5

#### Intravesical BCG therapy induced reactive arthritis successfully treated using tumor necrosis factor-alpha inhibitor

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Saiseikai Kanazawa Hospital

Conflict of interest: None

A 76 year-old Japanese man presented to our department with multiple joint pains during intravesical BCG therapy for bladder cancer. He was diagnosed with bladder cancer in situ 5 months prior to presentation, and intravesical BCG instillation therapy was initiated a month before his visit. He developed left upper arm pain after the fourth course and edema in his left dorsal hand, bilateral wrist pain, and difficulty with making a fist after the fifth course of treatment. NSAID therapy was ineffective. His condition worsened, and laboratory test revealed a high CRP level; therefore, he was referred to our department for evaluation. The patient's clinical course and physical examination suggested reactive arthritis (ReA). We initiated prednisolone (PSL, 20 mg/day). Tacrolimus (TAC) was added to the regimen owing to his prolonged symptoms; however, PSL taper was associated with a flare of symptoms, and methotrexate (MTX) was empirically administered for refractory ReA. PSL+TAC+MTX therapy was ineffective, and high CRP levels persisted; therefore, we initiated Etanercept. ReA is known to occur after BCG therapy; however, most patients respond

to NSAID. We report a case of ReA in a patient who required treatment using multiple immunosuppressive agents and TNF-alpha inhibitor.

### W30-6

#### A Case of SLE with Drug Allergy Associated with Aseptic Meningitis Caused by trimethoprim-sulfamethoxazole (TMP-SMX)

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Conflict of interest: None

TMP-SMX is frequently used to prevent PCP in immunosuppressed patients. It has many side effects, drug allergy and aseptic meningitis are also known. Case: 41-year-old female, diagnosed as SLE at age 26. TMP-SMX was started to prevent PCP. After 12 days, headache was noticed. 14 days later, back pain appeared. Exacerbating tendency was observed, she visited our hospital on day 15. Her conjunctive was hyperemia. Spontaneous pain in the lumbar region was strong, but there was no tapping pain. TMP-SMX and TAC was stopped. On the day after admission, headache, fever, nausea, and nuchal rigidity appeared. The spinal fluid examination showed 620/ $\mu$ l of nucleated cells (25% mononuclear cells, 75% polygonal cells), 127 mg/dl of protein, and findings of meningitis. Laboratory abnormalities also worsened, Ferritin 3781 ng/ml, D-Dimer 241.7  $\mu$ g/ml, steroid was started for fear of hemophagocytic syndrome. Symptoms improved quickly, and CSF examination showed normalization. We thought she was allergic to the TMP-SMX. Consideration In the case reports of aseptic meningitis caused by TMP-SMX, conjunctival hyperemia and hyperferritinemia have also been reported. Drug allergy should be considered in the case of headache and conjunctival hyperemia during the first or second week of TMP-SMX administration.

### W31-1

#### Retention rate and efficacy between JAK inhibitors switch cases in patients with RA

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Conflict of interest: None

[Objective] We investigated the efficacy and retention rate between JAK inhibitors (JAK) switch cases in patients with RA. [Methods] The subjects were total 211 patients who started JAK. The patients were divided into 3 groups, the 1st JAK group (58 patients) who had never used biological DMARDs (BIO) or JAK, the BIO switch group (116 patients) who had BIO usage history and no JAK usage history, and the JAK switch group (37 patients) who had JAK usage history. The retention rate and efficacy were investigated up to 24 weeks. [Results] The retention rate of 1st JAK group, BIO switch group and JAK switch group at 24 weeks were 87.9% (51/58 cases), 74.1% (86/116 cases) and 67.6% (25/37 cases). Changes in DAS28-CRP were that 0 w: (4.4, 4.1, 4.1), 4 w: (3.0, 3.1, 3.8), 12 w: (2.5, 3.0, 3.3), 24 w: (2.5, 3.0, 3.4), SDAI changes were that 0 w: (22.9, 21.2, 21.1), 4 w: (11.8, 12.5, 17.2), 12 w: (8.1, 10.9, 14.0), 24 w: (8.5, 10.8, 14.7). [Conclusions] This results suggest that the retention rate and effectiveness of JAK in switching cases between JAKs are not so low.

### W31-2

#### Evaluation of persistence and effectiveness of JAK inhibitor in treatment of difficult-to-treat rheumatoid arthritis

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Conflict of interest: None

[Objective] The aim of this study was to evaluate the persistence and effectiveness of JAKi in treatment of difficult-to-treat rheumatoid arthritis (D2TRA). [Methods] This study included 211 RA patients treated with JAKi. Fifty-eight patients were treated with JAKi as a 1st bio/JAKi (1st group), 55 patients were treated with JAKi as a 2nd bio/JAKi (2nd group), 23 patients who did not correspond to D2TRA were treated with JAKi after third bio/JAKi (nonD2TRA group), 75 patients corresponded to D2TRA were treated with JAKi after third bio/JAKi (D2TRA group). Continuation rate and clinical efficacy were evaluated at baseline, 4, 12 and 24 weeks. [Results] Continuation rate at 24 weeks were 87.9% in 1st group, 80% in 2nd group, 91.3% in nonD2TRA group, 61.3% in D2TRA group. DAS28-CRP in 1st group, 2nd group, nonD2TRA group and D2TRA group were 4.4, 4.0, 4.0, 4.3 at baseline, 3.0, 2.9, 3.3, 3.5 at 4 weeks, 2.5, 2.9, 2.7, 3.3 at 12 weeks, 2.5, 3.0, 3.0, 3.1 at 24 weeks. SDAI in 1st group, 2nd group, nonD2TRA group and D2TRA group were 22.9, 19.9, 18.8, 23.6 at baseline, 11.8, 11.9, 13.3, 14.6 at 4 weeks, 8.1, 11.5, 8.6, 13.0 at 12 weeks, 8.5, 11.7, 10.0, 12.4 at 24 weeks. [Conclusions] Continuation rate and clinical efficacy of JAKi in treatment of D2TRA were a little lower than that of nonD2TRA.

### W31-3

#### Short-term 12-week observational study of Filgotinib for RA including D-to-T RA at our center in clinical practice

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Conflict of interest: None

[Object] In 2021, JAK inhibitors and bDMARDs are considered equivalent in JCR Guidelines in 2021, and EULAR proposed the definition of D-to-T RA. In this study, we analyzed the efficacy of short-term 12-week FIL for RA in clinical practice. [Methods] Of the 24 patients with RA who underwent FIL at our center, 20 patients were observed for 12 weeks. 17 patients (85%) met the definition of D-to-T RA. Disease activity by DAS28-CRP and other measures were observed, and the continuation rates of patients with and without previous use of JAK inhibitors or IL-6R inhibitors, as well as elderly and non-elderly patients. [Results] Of the 20 patients followed for 12 weeks, 15 patients (75%) continued for 12 weeks. There was a significant improvement in DAS28CRP, DAS28ESR, CDAI, SDAI, and HAQ-DI after 12 weeks in the 15 patients in the continuation group ( $p < 0.05$ ,  $p < 0.01$ ). There was no significant difference in the 12-week continuation rate between patients with and without prior other JAK inhibitors use, nor prior IL-6R inhibitors use, nor between elderly and non-elderly patients. [Conclusions] Although it is a limitation of short-term, small number of observational studies, this observational study implicate that filgotinib is a useful one of the option for RA including D-to-T in clinical practice.

### W31-4

#### Impact of past use of disease modifying anti-rheumatic drugs on JAK inhibitor treatment for rheumatoid arthritis - Data from the Fukui Ishikawa Toyama Database of Rheumatoid Arthritis

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Conflict of interest: None

Objective: To clarify the impact of past use of disease modifying anti-rheumatic drugs on JAK inhibitor (JAKi) treatment for rheumatoid arthritis (RA) Methods: From 303 JAKi-treated RA cases in the Fukui Ishikawa Toyama Database of RA, we extracted 30 cases who switched from one JAKi to another (JJ group), 214 who switched from biologics to JAKi (BJ group), and 47 who were biologics/JAKi-naïve (NJ group). We compared the baseline factors, treatment response, and JAKi continuation rate among the three groups. Factors affecting JAKi discontinuation were also investigated. Results: No significant differences were found among the three groups in treatment response and JAKi continuation rate, except for the 6-month treatment response between the JJ and NJ groups. Cox regression analysis of the 303 cases revealed only past JAKi use as a significant factor associated with JAKi discontinuation. The Kaplan-Meier method showed that the group with past JAKi use had a significantly shorter median JAKi duration than that of the group without (20.9 vs. 54.7 months;  $p = 0.012$ ). Treatment response was significantly poor in the group with past JAKi use, mainly 6 months after starting treatment. Conclusions: Past JAKi use may contribute to decreased response and continuation rate of JAKi treatment.

### W31-5

#### Efficacy and Safety of Upadacitinib in b/tsDMARDs Naïve and b/tsDMARDs-IR Patients with Rheumatoid Arthritis

Masaomi Yamasaki

Shin-Yokohama Arthritis and Rheumatology Clinic

Conflict of interest: None

[Objective] We analyze efficacy and safety of upadacitinib in real-world data. [Methods] Cases were recruited to SHIN-yokohama Arthritis Register (SHARE) between 2015 and 2021 ( $n = 3,869$ ). 73 Patients were diagnosed according to ACR/EULAR 2010 classification criteria and treated with upadacitinib over 26 weeks. [Results] 15 b/tsDMARDs naïve, 58 b/tsDMARDs-IR and 16 D2T RA patients were enrolled. Upadacitinib withdrawal for inefficacy showed no difference between b/tsDMARDs naïve and b/tsDMARDs-IR patients in RA with/without MTX (logrank  $p = 0.8902$ ). There were no significant changes from baseline CDAI between MTX+/MTX- in phase II patients. There were no significant changes from baseline CDAI between pre-treatment group, TNFi, IL-6i and JAKinib, in phase III patients. In phase III group, predictors to detect patients who achieved LDA and/or remission were  $2.80 \leq \Delta CDAI$  at 4 weeks (ROC analysis,  $p = 0.0001$ , AUC = 0.96914). [Conclusions] Our data confirm the efficacy and safety profiles of upadacitinib in RA. It also showed upadacitinib was effective in all treatment phases including D2R RA.

### W31-6

#### Retention rates and factors associated with discontinuation of JAK inhibitor due to insufficient effect in rheumatoid arthritis

Takuya Matsumoto, Seiji Tsuboi

Shizuoka Welfare Hospital

Conflict of interest: None

[Objective] To explore retention rates and factors associated with discontinuation due to insufficient effect of JAK inhibitor (JAKi) in rheumatoid arthritis (RA) [Methods] The subjects were 65 RA patients who administered with JAKi from April 2015 to March 2021 and followed up for at least 6 months. The retention rates of JAKi were assessed and factors associated with discontinuation due to insufficient effect of JAKi were

identified using Cox regression analysis. [Results] The average age was 66.8 years and the average disease duration was 10.8 years. Concomitant MTX was used in 40% and oral corticosteroid was in 38.5%. In the past, 67.7% of subjects have used bio agent and 30.8% have used two or more bio agents. The 1-year retention rate of JAKi was 0.81 overall, 0.92 vs 0.73 ( $p = 0.02$ ) with and without MTX, and 0.74 vs 0.94 with bio use vs. without (n.s.) and 0.59 vs 0.90 ( $p < 0.01$ ) with 2 or more bio vs. without. Treatment without MTX, oral steroid use, 2 or more bio use, and non-TNF inhibitor use were identified as independent related factors for discontinuation of JAKi. [Conclusions] Although those factors were detected as risk factors for JAKi discontinuation, bio use (including one bio agent) was not associated with JAKi discontinuation.

### W32-1

#### **Efficacy and safety of Ozoralizumab (OZR; Novel anti-TNF-alpha multivalent NANOBODY® compound) in patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX): 52 weeks results of phase II/III study**

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Conflict of interest: Yes

[Objective] To assess the efficacy and safety through 52 weeks treatment with subcutaneous administration of OZR 30 or 80 mg with active RA despite MTX therapy. [Methods] 381 patients were randomized to Placebo (PBO), OZR 30 or 80 mg, administered every 4 weeks with MTX for 52 weeks with a 24-week double-blind followed by a 28-week open-label treatment period. At week 24, all remaining PBO patients were re-randomized (1:1) to OZR 30 or 80 mg. Efficacy assessments included ACR20, DAS28-CRP, SDAI, and HAQ-DI. [Results] The OZR groups showed good clinical improvement, with high ACR response rates at week 52. The OZR groups also showed good improvements in other endpoints, and these improvements were observed from day 3 maintained through week 52. Furthermore, the OZR groups showed a high remission rate in clinical and functional remission at week 24 and 52. Patients who switched from PBO to OZR, also showed good clinical improvements. A total of 23 serious adverse events occurred in the OZR groups, and there was no difference in incidence between doses. [Conclusions] OZR demonstrated significant therapeutic effects and efficacy was maintained for 52 weeks. The safety profile was consistent with the results evaluated in interim analysis at week 24, and OZR was well tolerated up to week 52.

### W32-2

#### **Efficacy and safety of Ozoralizumab (OZR; Novel anti-TNF-alpha multivalent NANOBODY® compound) without methotrexate (MTX) co-administration in patients with active rheumatoid arthritis (RA): 52 weeks result of phase III study**

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Conflict of interest: Yes

[Objective] To assess the efficacy and safety through 52 weeks treatment with subcutaneous administration of OZR 30 or 80 mg without MTX with active RA. [Methods] In this randomized, open-label, multicenter phase III trial, 140 patients were randomly allocated 2:1 to OZR 30 or 80 mg, and subcutaneous OZR injections were administered every 4 weeks without MTX for 52 weeks. Efficacy assessments included ACR20, DAS28-CRP, SDAI, and HAQ-DI. [Results] The OZR groups showed good clinical improvement. ACR response rates were high at week 24, and maintained through 52 weeks. The OZR groups also showed good improve-

ment in other endpoints, and these improvements were observed from day 7 maintained through week 52. The OZR groups also showed a high remission rate in clinical and functional remission at week 24 and 52. The improvements in many efficacy assessments were similar between doses. No death was reported through week 52, and a total of 20 serious adverse events occurred in the OZR groups. The adverse event with the highest incidence was infection. [Conclusions] OZR demonstrated significant therapeutic effects without MTX, and the efficacy was maintained for 52 weeks with active RA. OZR showed an acceptable tolerability profile over 52 weeks.

### W32-3

#### **Long time clinical course after the initiation of adalimumab in our hospital**

Eriko Hasegawa<sup>1,2</sup>, Satoshi Ito<sup>2</sup>, Yoichi Kurosawa<sup>1</sup>, Ayako Wakamatsu<sup>1</sup>, Hiroe Sato<sup>3</sup>, Daisuke Kobayashi<sup>1</sup>, Takeshi Nakatsue<sup>1</sup>, Takeshi Kuroda<sup>3</sup>, Hajime Ishikawa<sup>2</sup>, Ichiei Narita<sup>1</sup>

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Conflict of interest: None

[Objective] To evaluate the course of treatment after the initiation of adalimumab (ADA). [Methods] We retrospectively investigated the progress of 163 patients (37 males and 126 females) who were able to be followed among 197 patients who were newly introduced ADA at the Niigata Rheumatology Center from 2008 to 2018. [Results] As of September 2021, 116 patients had discontinued ADA (discontinued group), 47 patients were continuing ADA (continuing group). In discontinued group, 40 patients discontinued ADA due to bio free (BF) after achieving remission or low disease activity (BF group). In continuing group, the duration of ADA was 81.1±31.2 months, and methotrexate (MTX) use (10.4±3.0 vs. 7.9±3.4 mg/week,  $p < 0.001$ ), and prednisolone (PSL) use (3.2±3.4 vs. 0.3±0.8 mg,  $p < 0.01$ ) were significantly reduced. When comparing BF group and continuing group at the time of initiation of ADA, the duration of disease (39.7±47.5 vs. 119.5±136.6,  $p < 0.001$ ) was shorter, and Steinbrocker's Stage (1.9±0.98 vs. 2.46±1.12,  $p = 0.01$ ) was lower in BF group. [Conclusions] It may be a useful therapeutic strategy with ADA to aim for BF in patients with short disease duration and mild joint destruction, and to promote MTX and PSL reduction while continuing ADA in patients with longer disease duration.

### W32-4

#### **In adalimumab treatment, Remission induction and treatment continuation at 368 weeks in 229 patients**

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Conflict of interest: Yes

[Objective] Clinical usefulness and treatment continuation following 368 weeks of adalimumab (ADA) in rheumatoid arthritis (RA) patients were investigated. [Methods] Subjects were 186 analyzable patients introduced to ADA at the author's institution from May 2009 to Oct. 2014. Mean age was 54.3 years, mean duration of illness 6.8 years. 188 received MTX  $\geq 10$  mg/week ( $\geq 10$  group) and 34 MTX  $< 10$  mg/week ( $< 10$  group). The course of DAS28 (ESR), HAQ and remission rate were analyzed. [Results] Overall DAS28 (ESR) remission rate showed clinical remission in 51% of patients from 12 weeks, and achieved 69% from 52 weeks, after that this condition continued. Overall HAQ remission rate at 368 weeks was 83%; treatment continuation rate was 56.6%, and those of  $\geq 10$  group was 58.1%. [Conclusions] ADA plus an adequate dose of MTX with early escalation in early-stage RA and Bio Naïve patients is the best approach to maximally exploit the ADA potential.



### W32-5

#### Research on treatment continuity by switching from originator to etanercept biosimilar-Observational study with enrolled data of patient whose treatment was switching to etanercept biosimilar- From results of JET study

Tsukasa Matsubara<sup>1</sup>, Kou Katayama<sup>2</sup>, Akira Sagawa<sup>3</sup>, Masaaki Yoshida<sup>4</sup>, Takeshi Mitsuka<sup>5</sup>, Keisuke Hashimoto<sup>6</sup>, Tomomaro Izumihara<sup>7</sup>, Masakazu Kondo<sup>8</sup>, Tomomasa Izumiyama<sup>9</sup>, Nobumasa Miyake<sup>10</sup>, Motohiro Oribe<sup>11</sup>, Shigeki Momohara<sup>12</sup>

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Conflict of interest: Yes

**Objective:** Usefulness of etanercept biosimilar switching from its originator in daily practice by rheumatologist in Japan was evaluated and possibility of nocebo effect was examined. **Methods:** Total of 165 outpatients from 14 rheumatology clinics with low disease activity for 12 weeks or more under etanercept originator were analyzed. The evaluation items were DAS28-CRP, DAS28-ESR, and the components of each index including visual analogue scale (VAS). **Results:** There was no significant difference between the change in DAS28-CRP during 12-week before switching ( $0.03 \pm 0.581$ ) and the change during 12-week after switching ( $-0.09 \pm 0.507$ ) ( $P = 0.24$ ). Similarly, no significant difference was observed in DAS28-ESR ( $0.03 \pm 0.642$ ,  $-0.10 \pm 0.495$ ,  $P = 0.28$ ). The increase in the patient VAS and tender joints counts, which was pointed out as a feature of the nocebo effect in previous reports, was not observed. Furthermore, significant improvement in DAS28-CRP was observed at 24 weeks ( $1.78 \rightarrow 1.64$ ) and 52 weeks ( $1.62$ ) after switching ( $P < 0.01$ ). **Conclusion:** In daily practice by rheumatologist, no nocebo effect was observed by switching BS from the etanercept originator. As one of the reasons, providing careful explanation to the patient was considered to improve patient acceptance.

### W32-6

#### Usefulness as a Predictor of Therapeutic Response in Blood Trough Levels 14 Weeks after Infliximab

Yuji Nozaki<sup>1</sup>, Toshihiko Hidaka<sup>2</sup>, Daisuke Tomita<sup>1</sup>, Tetsu Itami<sup>1</sup>, Toshihiko Shiga<sup>1</sup>, Kazuya Kishimoto<sup>1</sup>, Koji Kinoshita<sup>1</sup>, Itaru Matsumura<sup>1</sup>

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Conflict of interest: Yes

**[Objective]** Infliximab (IFX) is the only biologic that can be easily measured in the blood using the RemicheckQ (RemiQ) kit. However, the clinical significance of RemiQ positivity/negativity does not necessarily correlate with disease activity depending on the time of measurement, making interpretation difficult. In the present study, we measured RemiQ at 14 weeks after new IFX introduction and investigated its usefulness as a predictor of treatment response. **[Methods]** We measured the RemiQ after 14 weeks of IFX introduction from September 2015, and evaluated the continuation rate, IFX dose escalation, and DAS28 disease activity in 29 patients with follow-up available. **[Results]** The results of RemiQ measurement after 14 weeks of IFX introduction were positive in 14 cases and negative in 15 cases. Treatment response was evaluated by  $\Delta$ DAS28 (14 weeks after IFX introduction: RemiQ positive:  $-1.8$  vs. negative:  $-0.9$ , 6 months:  $-1.3$  vs.  $-0.6$ , 12 months:  $-1.5$  vs.  $-2.0$ ), percentage of patients with dose increase within 12 months (RemiQ positive: 25.0% vs. negative: 78.6%), and continuation rate at 12 months (100% vs. 64.3%). **[Conclusions]** RemiQ qualitative assessment should be performed after 14 weeks, and if negative, early dose escalation should be actively considered.

### W33-1

#### A Survey in Rheumatoid Arthritis on Treatment Goals and Mutual Understanding between Patients and Physicians

Shigeki Momohara<sup>1</sup>, Kei Ikeda<sup>2</sup>, Masahiro Tada<sup>3</sup>, Toshiaki Miyamoto<sup>4</sup>, Mitsumasa Kishimoto<sup>5</sup>

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Conflict of interest: Yes

**[Objective]** To identify the gaps in treatment goals for rheumatoid arthritis (RA) between patients and physicians, it is necessary to analyze challenges in communication between the two and the patients' understanding of the disease to improve treatment satisfaction. **[Methods]** From June 16th to 30th, 2021, a cross-sectional survey was conducted via the Internet. Several panel networks were utilized for the enrollment of patients with RA and physicians. The factors associated with physician-patient communication and patient's satisfaction with their treatment goal were analyzed. **[Results]** Responses were collected from 502 patients and 216 physicians. In the primary endpoint that "Gap in treatment goals between patients and physicians", there was no significant difference in the distribution of means for short-term treatment goals (3-6 M); however, there was a significant difference in the distribution of means for long-term treatment goals (5-10 Y) ( $p < 0.0004$ ). In addition, there was a significant difference in patient's goals between physician's perspective and patient's for both short-term and long-term treatments (both  $p = 0.0067$ ). **[Conclusions]** This survey revealed that there was a gap in the treatment goals between RA patients and physicians, depending on the time frame of the treatment.

### W33-2

#### Usefulness of RAPID3 in assessing unmet needs in patients with rheumatoid arthritis-multicenter study from T-FLAG study-

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Conflict of interest: None

**[Objective]** RAPID3 is a patient-reported outcome (PRO) assessment that requires only a short interview and is useful as a simple method for assessing disease activity. In the treatment of rheumatoid arthritis (RA), there is an unmet need for patients who are in remission but have low satisfaction with their treatment. The purpose of this study was to investigate the relationship between DAS28-CRP and RAPID3 in RA patients. **[Methods]** The RAPID3 was divided into disease activity categories (remission:  $\leq 3$ , low disease activity: 3.1-6, moderate activity: 6.1-12, high disease activity:  $> 12$ ), and the DAS28-CRP disease activity category and RAPID3 disease activity category. **[Results]** In the disease activity category, the group with RAPID3 worse than DAS28-CRP (31.3%) vs. the group with the same RAPID3 and DAS28-CRP (59.5%) did not differ significantly in age, gender, and tender/swollen joints. There were significant differences in disease duration (14, 11 years), patient general assessment (36, 14 mm), HAQ-DI (0.84, 0.29), Kihon Checklist for frailty (9, 6 points). **[Conclusions]** We found that when RAPID3 was worse than DAS28-CRP, a typical method of assessing disease activity, the overall patient assessment was clearly worse in RAPID3. This unmet need may be related to frailty.

### W33-3

#### Discrepancies between patients and physicians global assessment in rheumatoid arthritis disease activity

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Conflict of interest: None

[Objective] to assess the factors which affect the discrepancies between patients and physicians global assessment in rheumatoid arthritis. [Methods] 145 patients with rheumatoid arthritis (male 46, female 99, 69 years old av) were divided into three groups by the difference between patients global assessment: VAS (G) and physicians global assessment: VAS (D). group A: difference  $\geq 4.0$ , group B:  $2.0 < \text{difference} \leq 4.0$ . Group C: difference  $< 2.0$ . We also examined pain score with VAS: VAS (P), we examined correlation coefficient between both VAS (G) and VAS (P), VAS (G) and VAS (D). We examined 16 factors, such as age, sex, disease period, stage, class, CRP, ESR, RF, anti-CCP antibody, morning stiffness, TJC, SJC, dose of methotrexate and prednisolone, usage of biologics and JAK inhibitors, and fibromyalgia among three groups. We analyzed the difference by statistically. [Results] Correlation coefficient (r) group A: VAS (G)-VAS (P):  $r=0.249$ , VAS (G)-VAS (D):  $r=0.577$ , Group B: VAS (G)-VAS (P):  $r=0.789$ , VAS (G)-VAS (D):  $r=0.855$ , Group C: VAS (G)-VAS (P):  $r=0.875$ , VAS (G)-VAS (D):  $r=0.825$ . [Conclusions] There were significant differences in age, disease period, class and morning stiffness between group A-C, in class between booth group A-C, group B-C and frequency of fibromyalgia among those three groups.

### W33-4

#### Clinical goals for elderly patients with established rheumatoid arthritis to maintain functional remission

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Conflict of interest: None

[Objective] The proportion of elderly patients with established rheumatoid arthritis (RA) is increasing. The purpose of the present study was to examine factors involved in maintenance of functional remission in elderly patients with established RA. [Methods] RA patients age  $\geq 65$  years receiving usual care without specific protocols were included. DAS28-CRP, SDAI, and HAQ-DI were calculated every 3 months for 1 year. Patients were divided into the HAQ-DI remission (REM) group and the HAQ-DI non-remission (NO-REM) group, time-averaged values of these parameters were compared between groups. [Results] Of the 118 patients, 76 fulfilled the remission criteria. Time-averaged DAS28-CRP and SDAI scores were significantly lower in the REM group than in the NO-REM group, (1.61 vs 2.65, 2.91 vs 11.15, respectively;  $p < 0.001$ ). Subsequent ROC analysis for estimation of remission indicated a cut-off value of 1.66 for time-averaged DAS28-CRP. [Conclusions] Our previous report showed that fulfillment of deep clinical remission increases the possibility of functional remission, but sustained functional remission may be obtained in elderly established RA without strict control. RA patients who maintained longitudinal HAQ remission had few complications and little history of RA-related surgery.

### W33-5

#### Advances in RA treatment have outweighed the effects of aging in improving quality of life

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Conflict of interest: None

[Objective] Advances in rheumatoid arthritis (RA) treatment have improved the quality of life (QOL) of patients. We investigated the effect of increasing elderly patients on improving QOL due to advances in treatment. [Methods] We registered EQ5D (EuroQol 5 Dimensions) and related data from 2011 to 2020, and examined the annual changes by age group. [Results] During the 10 years covered, methotrexate usage decreased from 67.8% to 54.9%, and b-, ts-DMARDs usage increased from 27.6% to 29.0%. Among 9324 patients registered (A: 2464 patients under 60 years old, B: 2626 in their 60s, C: 2933 in their 70s, D: 1267 over 80 years old), the overall EQ5D score was improved from 0.749 to 0.785. By

age group, the baseline EQ-5D score was A: 0.786, B: 0.766, C: 0.716, D: 0.655, which deteriorated with aging, but the improvement over 10 years was 0.041, 0.062, 0.055, 0.028, respectively. Improvements of the score were seen in all age groups. Similar analyzes were performed on JHAQ and DAS28-CRP, and similar results were obtained. [Conclusions] The QOL of RA patients has improved in 10 years, and improvement was confirmed even in super-aged RA over 80 years old, although it was lower than that of younger patients. Advances in RA treatment have outweighed the effects of aging in improving of QOL.

### W33-6

#### Differences in Treatment Satisfaction, Patient Preferences, and Treatment Patterns Between European, South American, and Japanese Patients With Suboptimally Controlled Rheumatoid Arthritis: A Subgroup Analysis of the SENSE Study

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Conflict of interest: Yes

**Objectives:** To explore differences in treatment satisfaction (TS), patient preferences, and treatment strategies between patients (pts) from Europe (EU), South America (SA), and Japan (JP) with suboptimal control of rheumatoid arthritis (RA). **Methods:** This is a subgroup analysis of SENSE, a non-interventional cross-sectional study. **Results:** Of 1234, 272, and 118 pts enrolled from EU, SA, and JP, respectively, 13.9%, 15.4%, and 5.9% reported good TS. In all regions, pts reported impaired quality of life and good treatment adherence, and around one-third of pts received ts/bDMARDs. ts/bDMARD monotherapy was most common in SA (45.3%) [26.3% (EU), 18.8% (JP)]. More than 80% of JP pts preferred oral treatments ( $< 60\%$  in EU/SA). DMARD switches were planned in 51.8% (EU), 57.4% (SA), and 38.1% (JP) of pts, most commonly to a TNF inhibitor. Predictors for good TS included treatment with ts/bDMARDs and the presence of psychiatric disorders in EU and SA, while current disease activity was not a common predictor. Reluctance to switch treatments was predicted by LDA (all regions) and current treatment with ts/bDMARDs (EU/SA). **Conclusion:** Current disease control was a common determinant of treatment switches. Predictors for good treatment satisfaction revealed region-specific patient attitudes.

### W34-1

#### Characteristics of neutralizing antibody-negative patients after COVID-19 vaccination in ANCA-associated vasculitis (AAV)

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Conflict of interest: None

[Objective] To clarify the characteristics of patients with AAV who were negative for neutralizing antibodies after COVID-19 vaccination. [Methods] In AAV patients who visited our department from July to October 2021, those who had received the second vaccination were included in this study. The spike protein antibodies (S antibodies) in the blood were measured using a commercial kit developed by Roche Diagnostics. Clinical features of patients with negative for antibodies (group N) (S-antibody  $< 0.8$  U/ml) were analyzed by comparison with S-antibody-positive AAV (Group P). [Results] Group N consisted of 9 patients (six with MPA and three with EGPA) and eligible for this study. The mean age was 72, and the average disease duration was 5.0 years. Their treatment at the time of second vaccination included prednisolone (n=9, mean dose: 7.4 mg/day), azathioprine (n=5), methotrexate (n=1), and mepolizumab (n=1), rituximab

(RTX) (n=7). After adjusting the patients' age, Group P consisted of 21 patients as the control group of this study. Group N received RTX more frequently ( $p<0.003$ ) and more dose of prednisolone ( $p<0.020$ ) than Group P. [Conclusions] In AAV patients, RTX and the prednisolone dose at the time of vaccination were the possible risks for inhibition of developing neutralizing antibody.

### W34-2

#### Reduced antibody response to SARS-CoV-2 mRNA vaccine in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To compare antibody responses to SARS-CoV-2 mRNA vaccine in patients with rheumatoid arthritis (RA) and those with hypertension, dyslipidemia or diabetes mellitus as controls. [Method] 99 RA patients and 84 in controls of 30 years old or older in our outpatient clinic gave us written informed consent. RA patients were being treated with either bDMARDs (TNF inhibitors, IL-6 inhibitor or T cell specific co-stimulation modulator), methotrexate, conventional DMARDs, glucocorticoids or a combination thereof. Serum antibody levels were measured using ARCHITECT SARS-CoV2 IgG II® (Abbott) 14~80 days after the second mRNA vaccine (Comirnaty®). [Result] In RA and control groups, age and time from the second injection to the antibody measurements were inversely correlated with the antibody titers. RA patients showed lower levels of antibodies than those of controls. Although the patients with biological DMARDs, methotrexate or glucocorticoids showed lower responses than those of controls, methotrexate showed the strongest effect. Among three biological DMARDs, T cell specific co-stimulation modulator seemed to have a greater inhibition than TNF inhibitors. [Discussion] Patients with RA showed lower levels of antibodies against SARS-CoV-2 mRNA vaccine and need boosters.

### W34-3

#### Efficacy of COVID-19 vaccination to the patients with rheumatic disease

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Conflict of interest: None

[Objective] To research the efficacy of COVID-19 vaccination to the patients with rheumatic disease. [Methods] Check the titer of antibody after COVID-19 vaccination. [Results] Antibody titer was measured in 100 cases. 79 females, 62.5±17.5 years old. The average period from the second vaccination to the antibody titer evaluation was 45.4±31.7 days, and the average antibody titer was 5828.9±9497.7 AU/mL. There were 47 cases in which antibody titers were measured during the period of 15-45 days after the second vaccination. 39 females, an average age of 60.1±16.3 years old. The average period from the second vaccination to the antibody titer evaluation was 28.9±8.0 days, and the average antibody titer was 6574.9±8296.6 AU/mL. In 18 cases, the antibody titer was 2150 AU/mL or less. The use of glucocorticoid or antimetabolites influenced the titer significantly. [Conclusions] The use of glucocorticoid or antimetabolites may influence the efficacy of the vaccine.

### W34-4

#### Functional immunophenotyping by using immune response to SARS-CoV-2 vaccine in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Patients with rheumatoid arthritis seem to have various immune pathologies. To evaluate the immune response in humans, it is necessary to analyze the population exposed to the antigen under the same conditions, and vaccination against SARS-CoV-2 is considered to be a valuable opportunity. We analyzed quality and quantity of cell-mediated and humoral immune responses to the SARS-CoV-2 vaccine in patients with rheumatoid arthritis to reveal the relationship with various background factors. [Methods] We performed PBMC isolation from 500 patients with rheumatoid arthritis 1-2 months after vaccination, and analyzed after cryopreservation. We analyzed lymphocyte subsets, cytokine production ability of antigen-specific T cells by using Flow Cytometry, and the SARS-CoV-2 spike protein antibody by ELISA, and then conducted statistical analysis with clinical information. [Results] Reactivity analysis using Flow Cytometry showed that antigen-specific CD4+ T cells mainly produced Th1-type cytokines such as TNF $\alpha$  and IFN $\gamma$ , while Th2 / Th17-type cytokines did not appear to be produced much. [Conclusions] Going forward, we will continue to analyze a lot of cases and clarify the patient background that affects the antigen-specific immune response to the SARS-CoV-2 vaccine.

### W34-5

#### A prospective study of the influence of therapeutic agents on the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with rheumatoid arthritis (RA) by NinJa data for 18 years

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Conflict of interest: None

[Objective] To evaluate the incidence of therapeutic agents on the SIR of TB in patients with RA prospectively. [Methods] We calculated the SIR of TB from the clinical data on National Database of Rheumatic Disease by iR-net in Japan (*NinJa*) prospectively from 55 facilities for 18 years. [Results] Among 186,853 RA patients registered from 2003 to 2020, 80 patients newly developed TB and the SIR of TB was 1.64 (95%CI: 1.28-2.00). 24 patients (30%) and 14 patients (17.5%) were treated with MTX and biologic agents, respectively. The SIR of TB in RA patients treated with biologic agents was 0.44 (0.18-0.69), and the SIR of TB in patients treated without biologic agents was 2.93 (2.24-3.62). [Conclusions] The SIR of TB of RA patients tended to decrease, and it was reconfirmed by prospective studies that there was no increase due to administration of biologic agents. No new cases of tuberculosis were observed in patients using JAK inhibitors during 2017-20, but the number of JAK inhibitors used (persons)/usage rate (%) increased from 2017 to 2020, 307/2.0, 454/2.9, 617/4.2, 798/5.1. Since it is increasing year by year, it is necessary to continue to investigate the effects of JAK inhibitors on the onset of TB.

### W34-6

#### A case of rheumatoid arthritis (RA) with organized pneumonia (OP) after COVID-19 pneumonia

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Conflict of interest: None

[Objective] We report a case of RA with OP after COVID-19 pneumonia. [Current medical history] RA developed 3 years ago and he was treated with SASP and MTX. There was COVID-19 patients at work, and a voluntary PCR test revealed positive. Shortness of breath appeared, he was admitted to the university hospital with SpO<sub>2</sub> 79% at the online medical examination. He was treated with TCZ, steroid-pulse, remdesivir, dexamethasone, etc. and was treated in ICU under mechanical ventilation.



Transferred to a general ward, PSL was gradually reduced to 7.5 mg, he was transferred to our hospital. Due to poor oxygenation, the patient was referred to the pulmonologist, and the dose of PSL was re-increased to 35 mg under the diagnosis of post-COVID-19 OP. Oxygenation gradually improved and rehabilitation was started. PSL was gradually reduced to 20 mg/day, HOT was introduced, and the patient was discharged. Currently he is being treated for outpatient RA and respiratory medicine with PSL tapering down to 15 mg. [Conclusions] This case was a case of chronic respiratory failure due to OP after COVID-19 pneumonia. In COVID-19 lung injury, steroid response may occur even in the chronic phase, and treatment opportunities should not be missed, and cooperation with a pulmonologist is important.

### W35-1

#### The effect of ixekizumab versus adalimumab on individual components of the ACR composite score, with and without concomitant methotrexate in patients with psoriatic arthritis: 52-Week Results from SPIRIT-H2H Study

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Conflict of interest: Yes

**Objectives:** To evaluate individual ACR score (ACR) components between ixekizumab (IXE)- and adalimumab (ADA)-treated patients (pts) with psoriatic arthritis (PsA), with and without methotrexate (MTX). **Methods:** bDMARD-naïve PsA pts were enrolled in an open-label, blinded assessor, Ph3b/4 trial. 566 pts were randomized to IXE or ADA for 52-week (wk) treatment. The proportion of pts achieving each efficacy measure was analyzed. **Results:** At baseline (BL), 167/283 IXE- and 169/283 ADA-treated pts had MTX use. For the overall population (566 pts), a significantly higher proportion of pts on IXE vs ADA (39% vs 26%) simultaneously achieved the ACR50+PASI100 at Wk 52, with similar efficacy of IXE and ADA for ACR50 (50% vs 50%). IXE demonstrated efficacy across all individual ACR components at Wk 52, specifically in PGA, PtGA and Joint Pain; ADA also demonstrated numerical efficacy. Improvements from BL for IXE and ADA were observed across ACR components, with or without MTX. The effect of MTX was notably different between IXE and ADA in TJC68, PGA, Joint Pain, and PtGA. **Conclusion:** There was improvement with IXE in all components of ACR, irrespective of MTX use. IXE showed comparable efficacy to ADA at Wk 52 in all components of ACR, demonstrating improvement across musculoskeletal domains.

### W35-2

#### Efficacy of Upadacitinib in Patients with Psoriatic Arthritis Stratified by Baseline Skin Severity: A Subgroup Analysis of Two Phase III Trials

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Conflict of interest: Yes

[Objective] This post-hoc analysis in SELECT-PsA 1 and 2 clinical trials is to assess the effects of baseline skin severity on upadacitinib (UPA) efficacy. [Methods] SELECT-PsA 1 and 2 enrolled patients (pts) with PsA and prior inadequate response (IR) or intolerance to  $\geq 1$  non-bi-

ologic disease-modifying antirheumatic drug (DMARD) or  $\geq 1$  biologic DMARD, respectively. In this analysis, pts were divided into subgroups based on the extent of psoriasis at baseline (body surface area [BSA] of  $\geq 3\%$ -<10% or BSA  $\geq 10\%$ ); efficacy endpoints were analyzed at Wk 56. [Results] In the UPA 15 mg and Adalimumab groups, respectively, 32% (138/429) and 31% (132/429) of pts had a BSA  $\geq 3$ -<10% at baseline in SELECT-PsA 1; 18% (76/429) in each treatment group had a BSA  $\geq 10\%$ . In SELECT-PsA 2, 38% (80/211) had a BSA  $\geq 3$ -<10% and 24% (50/211) had a BSA  $\geq 10\%$  at baseline in the UPA 15 mg group. Across pt populations, generally consistent results were observed between patients in both skin severity subgroups. A numerically greater proportion of UPA 15 mg pts with lower skin involvement compared with higher skin involvement achieved PASI100 and PASI  $\leq 1$ . [Conclusions] UPA can be a viable treatment option for pts with active PsA regardless of the extent of psoriasis at baseline.

### W35-3

#### Association Between Clinically Meaningful Improvements in Patient-Reported Outcomes and Stringent Measures of Disease Activity in Patients With Psoriatic Arthritis Treated With Upadacitinib Versus Placebo or Adalimumab: Results From a Phase 3 Trial

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Conflict of interest: Yes

[Objective/Method] This is to examine the association between clinically meaningful improvement in PROs) and stringent measures of disease control in SELECT-PsA 1 trial, which enrolled patients (pts) with PsA and prior inadequate response or intolerance to  $\geq 1$  non-biologic DMARD. The percentage of patients achieving stringent disease control (MDA, ACR70, DAPSA  $\leq 4.0$ , PASDAS  $\leq 1.9$ ) was determined among patients reporting vs not reporting PRO improvements  $\geq$  minimal clinically important differences (MCID) at Week 24. PROs included: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), 36-Item Short-Form Health Survey (SF-36), and Work Productivity and Activity Impairment (WPAI). [Results] The percentage of patients achieving MDA, ACR70, DAPSA or PASDAS remission at week 24 was significantly higher among patients who reported improvements  $\geq$  MCID for all PROs vs those who did not. Among patients reporting improvements  $\geq$  MCID across all PROs, more patients achieved ACR70 and MDA responses (29%-49%) with fewer patients achieving DAPSA or PASDAS remission (14%-19%). [Conclusions] PsA patients who reported clinically meaningful improvements in key PROs: fatigue, quality of life, and work productivity were more likely to achieve stringent measures of disease control.

### W35-4

#### An evaluation of the effects of psoriatic arthritis on anxiety and depression

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Conflict of interest: None

[Objective] Anxiety and depression are known to be typical comorbidities in patients with psoriatic arthritis (PsA). We evaluated the effects of arthritis and psoriasis on anxiety and depression. [Methods] Thirty-four patients with PsA were scored with the Hospital Anxiety and Depression Scale [HADS (anxiety disorder; HADS-A, depression; HADS-D)]. They were divided into two groups: HADS  $\geq 7$  and  $\leq 8$  (possible or probable clinical anxiety or depression). We compared patient's background, DAPSA, MASES, spinal VAS, BASDAI, ASDAS-CRP, and DLQI between the

groups. [Results] Among 34 patients with PsA, 15 (44.1%) had HADS-A  $8 \leq$  and 13 (38.2%) had HADS-D  $8 \leq$ . There were no significant differences in age, gender, comorbidities, smoking status, or BMI between the two groups. Spinal VAS, BASDAI, and ASDAS-CRP were higher in the group with  $8 \leq$  of HADS-A and HADS-D with highly significant differences ( $p < 0.01$ ). In addition, the number of tender joints, MASES, and DLQI were significantly higher in the group with HADS-D  $8 \leq$  ( $p < 0.05$ ). [Conclusions] Our data suggest that peripheral arthritis and enthesitis in PsA and decreased quality of life due to psoriasis had a significant effect on depression and that axial arthritis had a remarkable effect on both anxiety and depression.

## W35-5

### Consideration about patient's own health evaluation in psoriatic arthritis

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Conflict of interest: None

[Objective] A specific evaluation of PsA has not established. In this time, we focused on the health condition evaluation of PsA patients by themselves, and analyzed the factors involved in it. [Methods] The subjects were PsA patients who visited our hospital for more than 1 year and underwent joint evaluation. Using SF36, the health condition (Q1, general health, GH) by the patients themselves after treatment was classified into a good and a poor group, and the involvement of various evaluation was analyzed. [Results] At the first time, 57% of PsA patients ( $n=142$ , med 58 yrs) were in the poor group, and the proportion one year after treatment was 40%. There was no significant difference in the background. In poor group, except for evaluation of PASI, BASMI and dactylitis, DLQI, BASDAI, ASDAS, BASFI, TJ (68), SJ (66), LEI, DAS-CRP, painVAS, Pt-GVAS, E-GVAS, HAQ, PSDAS, DAPSA, MCS (mental health) were significantly higher. 70% of poor group did not achieve MDA, and 78% of the good group achieved MDA. Multivariate analysis considering each symptom extracted peripheral joint symptom (BASDAI: Q3), HAQ and MCS. [Conclusions] GH was highly correlated with each index, but there were still many GH poor groups even in one year of treatment. We need to pay more attention to the mental state.

## W35-6

### The significance of the detection of fatty acid (FA) profile in sera of patients with psoriatic arthritis (PsA)

Megumi Kurumizawa<sup>1</sup>, Naoki Dosoden<sup>1</sup>, Marika Sawada<sup>1</sup>, Natsuko Watanabe<sup>1</sup>, Masashi Suzuki<sup>1</sup>, Tatsuki Naganawa<sup>1</sup>, Ai Umeda<sup>1</sup>, Konomi Akamatsu<sup>1</sup>, Daisuke Hirano<sup>1</sup>, Takako Hashimoto<sup>1</sup>, Jo Nishino<sup>1</sup>, Shusaku Fukaya<sup>1</sup>, Kazumitsu Sugiura<sup>2</sup>, Hidekata Yasuoka<sup>1</sup>

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Conflict of interest: None

[Objective] To clarify the significance of the detection of FA profile in sera of the patients with PsA. [Methods] PsA who met the CASPAR criteria and visited Fujita Health University between January 2021 and April 2021 were consecutively included. Clinical information retrospectively collected was compared with each fraction of serum FA. Correlation was also examined. [Results] Twenty-eight cases were included. Mean age and disease duration were 54.3 and 5.6 years, respectively. 69% were male, 14% on PSL, and 57% on NSAIDs. As for the metabolic diseases, 5 were with dyslipidemia, 3 with diabetes mellitus and 12 had obesity. Each FA fraction was comparable between patients with or without metabolic diseases. As for the disease markers, no correlation was observed among CRP, MMP-3 and NRS. When each fraction was compared between pa-

tients with or without positivity of these markers and combined with the correlation analyses, no FA fractions were extracted by CRP or MMP-3, but eicosagenic acid and docosatetraenoic acid were significantly extracted by NRS. [Conclusions] Association between NRS and profile of FA fraction was observed. These results suggest that the FA fraction is the unique biochemical marker for PsA, which might be a clue to the pathogenesis.

## W36-1

### Ankylosis site in the spine with ankylosing spondylitis

Kenji Kishimoto, Shuji Asai, Mochihito Suzuki, Daisuke Kihira, Ryo Sato, Nobunori Takahashi, Kenya Terabe, Yoshifumi Ohashi, Kyosuke Hattori, Toshihisa Kojima, Shiro Imagama

Orthopedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: None

[Objective] To examine ankylosis site in the spine of ankylosing spondylitis (AS). [Methods] 21 patients with AS had evaluation for whole spine by CT between January 2004 and June 2021. We examined bridging syndesmophyte of anterior longitudinal ligament, posterior longitudinal ligament (PLL) and spinous process and ankylosis of facet in between C1/2 and L5/S. [Results] 21 patients (mean age 39.1 years), 81% men, the disease duration 11.7 years, 71% human leucocyte antigen B27 positive were included. 6 patients (29%) had ankylosis in cervical spine (C1/2-C7/Th1), 19 (90%) in upper thoracic spine (Th1/2-Th4/5), 15 (71%) in middle thoracic spine (Th5/6-Th8/9), 16 (76%) in lower thoracic spine (Th9/10-Th12/L1), and 11 (52%) in lumbar spine (L1/2-L5/S). 13 patients (62%) had ankylosis of facet in cervical spine. 16 patients (76%) had bridging syndesmophyte of PLL in thoracic spine. 9 patients (43%) had ankylosis of facet in lumbar spine. [Conclusion] Interbody ankylosis was predominant in the upper thoracic spine. The most common sites of ankylosis were PLL in the thoracic spine and facets in the cervical and lumbar spine.

## W36-2

### Relationship between spinal ankylosis and spinal alignment in ankylosing spondylitis

Kenji Kishimoto, Shuji Asai, Mochihito Suzuki, Daisuke Kihira, Ryo Sato, Nobunori Takahashi, Kenya Terabe, Yoshifumi Ohashi, Kyosuke Hattori, Toshihisa Kojima, Shiro Imagama

Orthopedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: None

[Objective] To demonstrate relationship between spinal ankylosis and spinal alignment in ankylosing spondylitis (AS). [Methods] 17 patients with AS had evaluation for whole spine by CT between January 2004 and June 2021. We examined bridging syndesmophyte of anterior longitudinal ligament and posterior longitudinal ligament and ankylosis of facet in between Th1/2 and L5/S. In addition, we measured thoracic kyphosis (TK), lumbar lordosis (LLs) and Sagittal vertical axis (SVA) as spinal alignment. [Results] 17 patients (mean age 39.8 years), 83% men, the disease duration 13 years, 73% human leucocyte antigen B27 positive were included. This study demonstrated positive correlation with TK and ankylosis between Th1/2 and Th12/L1 ( $r=0.64$ ,  $p=0.006$ ), negative correlation with LLs and ankylosis between L1/2 and L5/S ( $r=-0.49$ ,  $p=0.047$ ) and positive correlation with SVA and ankylosis between Th1/2 and L5/S ( $r=0.55$ ,  $p=0.022$ ). [Conclusion] Progression of thoracic ankylosis increased TK, and progression of lumbar ankylosis decreased LLs. In addition, progression of thoracolumbar ankylosis increased SVA. This study demonstrated that spine alignment deteriorated as progression of spinal ankylosis in AS.

## W36-3

### Efficacy and Safety of Upadacitinib in Patients With Active Ankylosing Spondylitis: 2-Year Results From a Randomized, Double-Blind, Placebo-Controlled Study Followed by Open-Label Extension With Japanese Subject Sub-analysis

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Conflict of interest: Yes

[Objective] To report efficacy and safety of upadacitinib (UPA) in active AS including Japanese patients (pts) through 2 years. [Methods] SELECT-AXIS1 (NCT03178487) enrolled pts with active AS who had an inadequate response to NSAID. At baseline (BL), pts were randomized to UPA 15 mg once daily (QD) or PBO; at wk 14, PBO pts were switched to UPA. [Results] Of 187 pts including 13 Japanese pts randomized at BL, 178 pts entered the open-label extension at wk 14; 144 pts (77%) including 9 Japanese completed wk 104. ASAS40 response was maintained through 2 years, 65.6% in continuous UPA and 63.8% in PBO to UPA pts at wk 104. A similar pattern of response was observed for other efficacy endpoints. The spinal progression based on mean change from BL to wk 104 in mSASSS was 0.68 in the total group. Overall UPA treatment-emergent AE rate was 242.7/100 patient-years (PY). Infections were the most common AEs while there were no serious infections. 5 herpes zoster (1.6/100 PY), 1 colitis (0.3/100 PY) and 16 uveitis (5.2/100 PY) were observed throughout the 2 years. Efficacy and safety were generally consistent in Japanese pts. [Conclusions] UPA 15 mg QD showed sustained and consistent efficacy over 2 years with low rate of spinal progression. No new safety findings were observed.

### W36-4

#### Work productivity and activity impairment among patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: 16-week results from ixekizumab clinical trials, COAST-V, COAST-W, and COAST-X

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Conflict of interest: Yes

**Objectives:** To evaluate the effect of ixekizumab (IXE) treatment on work productivity and activity impairment (WPAI) individual items in patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) and to determine how ASAS responses are associated with changes in WPAI. **Methods:** COAST-V, -W, and -X were phase 3 studies in bDMARD-naïve patients with AS (N=341), TNFi-experienced patients with AS (N=316), and patients with nr-axSpA (N=303), respectively. Patients were randomized to placebo (PBO), adalimumab, 80-mg IXE every 2 weeks (IXEQ2W) or every 4 weeks (IXEQ4W). Changes from baseline in WPAI at Week 16 were compared across treatment arms or between patient groups according to their level of treatment response at Week 16 (ASAS40 vs. ASAS40 - ASAS20 vs. ASAS<20). **Results:** Generally, AS and nr-axSpA patients treated with IXE showed significantly greater WPAI improvements compared to PBO (p<0.05). Patients achieving ASAS40 generally reported significantly greater WPAI changes, compared to ASAS20 responders who were ASAS40 nonresponders or to ASAS20 nonresponders (p<0.05). **Conclusion:** IXE-treated patients showed greater WPAI improvements compared to PBO. Achieving ASAS40 was associated with greater WPAI improvements compared to ASAS40 nonresponders.

### W36-5

#### Efficacy and safety of long-term treatment of ixekizumab in patients with axial spondyloarthritis

Tetsuya Tomita<sup>1</sup>, Rebecca Bolce<sup>2</sup>, David Sandoval<sup>2</sup>, Yves Schymura<sup>2</sup>, Ayako Konomi<sup>3</sup>, Jürgen Braun<sup>4</sup>

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Conflict of interest: Yes

[Objective] To study the efficacy and safety of ixekizumab (IXE) in the treatment of patients with ankylosing spondylitis (AS)/radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis (nr-axSpA) for up to 116 weeks. [Methods] COAST-V, -W, and -X were 52 week trials whose patients were eligible to enter into extension study COAST-Y. Here we present the 116 weeks results (52 of the original trials + 64 of COAST-Y). Patients receiving IXE at the end of the originating trial continued with the same dose; 80 mg IXE every 4 weeks (Q4W) or every 2 weeks (Q2W). [Results] Of the 773 (Japanese [JP]=22) patients enrolled in COAST-Y, 86% completed week 116. Among the patients continuously treated with IXE for 116 weeks (IXE Q4W: N=157, JP=3; IXE Q2W: N=195, JP=4), 47% achieved ASAS LDA, 20% achieved ASAS partial remission, and 56% achieved ASAS40 at 116 week. The mean change from baseline at week 116 was -1.7 for ASDAS, -3.0 for BASFI, and 9.2 for SF-36 PCS. For the 932 (JP=23) patients in the safety population, no new safety signals were identified. [Conclusions] IXE treatment led to consistent long-term improvements in disease activity and quality of life in patients with AS and nr-axSpA, with no new safety signals up to 2 years of treatment.

### W36-6

#### The incidence and HLA typing of reactive arthritis in Japanese patients with bladder cancer following intravesical BCG therapy: the prospective study

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Conflict of interest: None

[Objective] To prospectively evaluate the incidence and HLA typing of ReA in Japanese patients with bladder cancer following Intravesical instillation of Bacillus Calmette-Guerin (iBCG) therapy. [Methods] The clinical findings of Japanese patients who received iBCG (n = 45) for bladder cancer from January 2018 to December 2020 were prospectively assessed, with specific attention to patients with ReA. We also looked at HLA typing of patients with ReA. [Results] Patient age was 74 ± 9 and male/female ratio was 35/10. Of the 45 cases, ReA, uveitis and conjunctivitis were revealed in 1 (2.2%), 0 (0%) and 1 (2.2%), respectively. Notably, HLA-B27 was not detected in ReA patient. [Conclusions] Although this was 3-year prospective study, the incidence of ReA in Japan was 2.2% as same as that in previous study from Western countries and Japan. The frequency of HLA-B27 in Japanese is lower than Western countries, and therefore we need to assess the other genetic and environmental factors as large-scale and long-term prospective study.

### W37-1

#### Regional differences and clinical characteristics of patients with SpA and concomitant IBD: results from the ASAS PerSpA study

Keisuke Ono<sup>1,2</sup>, Mitsumasa Kishimoto<sup>1</sup>, Sho Fukui<sup>3,4</sup>, Satoshi Kawaai<sup>3</sup>, Haruki Sawada<sup>5,6</sup>, Kurisu Tada<sup>6</sup>, Naoto Tamura<sup>6</sup>, Yoshinori Taniguchi<sup>7</sup>, Ayako Hirata<sup>8</sup>, Hideto Kameda<sup>8</sup>, Shigeyoshi Tsuji<sup>9</sup>, Yuko Kaneko<sup>10</sup>, Hiroaki Dobashi<sup>11</sup>, Tadashi Okano<sup>12</sup>, Yoichiro Haji<sup>13</sup>, Akimichi Morita<sup>14</sup>, Masato Okada<sup>3</sup>, Yoshinori Komagata<sup>1</sup>, Tetsuya Tomita<sup>15</sup>, Shinya Kaname<sup>1</sup>

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Conflict of interest: Yes

[Objective] The purpose of this study is to clarify the clinical characteristics of spondyloarthritis (SpA) patients with inflammatory bowel disease (IBD), including regional difference. [Methods] Using observational ASAS-PerSpA data, we analyzed information, dichotomizing patients by IBD status. SpA patients with IBD were categorized by region, and categorized as IBD-associated SpA or other SpA with IBD by their rheumatologists. [Results] Among 4465 SpA patients included in the study, 287 were identified with IBD. Compared to those without IBD, the duration between the first symptom of SpA and the diagnosis of SpA (diagnostic delay) was longer in SpA patients with IBD. SpA patients with IBD in Japan had more diagnostic delay, lower HLA-B27 positivity and fewer axial symptoms than other countries. 111 of 287 patients were diagnosed with IBD-associated SpA by rheumatologists. Multivariable analyses showed that the absence of HLA-B27 positivity and psoriasis, the presence of IBD as the first symptom of SpA, and need for IBD-specific treatment led rheumatologists to diagnose IBD-associated SpA. [Conclusions] SpA patients with IBD had diagnostic delay, which was marked in Japan. Several clinical features were related to a rheumatologist-driven formal diagnosis of IBD-associated SpA.

### W37-2

#### Clinical characteristics of non-radiographic vs. radiographic axial spondyloarthritis in Asia and non-radiographic axial spondyloarthritis in other regions: results of the cross-sectional ASAS-COMOSPA study

Mitsumasa Kishimoto<sup>1</sup>, Keisuke Ono<sup>1</sup>, Sho Fukui<sup>2</sup>, Satoshi Kawaai<sup>2</sup>, Naomi Ichikawa<sup>3</sup>, Yuko Kaneko<sup>4</sup>, Taku Kawasaki<sup>5</sup>, Kazuo Matsui<sup>6</sup>, Mitsuhiro Morita<sup>7</sup>, Kurisu Tada<sup>8</sup>, Naoho Takizawa<sup>9</sup>, Naoto Tamura<sup>8</sup>, Atsuo Taniguchi<sup>10</sup>, Yoshinori Taniguchi<sup>11</sup>, Shigeyoshi Tsuji<sup>12</sup>, Shigeto Kobayashi<sup>13</sup>, Masato Okada<sup>2</sup>, Yoshinori Komagata<sup>1</sup>, Tetsuya Tomita<sup>14</sup>, Shinya Kaname<sup>1</sup>

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Conflict of interest: Yes

[Objective] To delineate characteristics of nr-axSpA in Asia. [Methods] Using ASAS-COMOSPA database, we compared clinical characteristics between nr-axSpA from Asia vs. elsewhere (Europe, the Americas, and Africa). Within Asian, we additionally compared characteristics of those with nr-axSpA vs. r-axSpA. [Results] Among 3984 SpA, 1094 were from Asia. Of 780 axial SpA in Asia, 112 (14.4%) had nr-axSpA, less than in non-Asia (486/1997, 24.3%). Nr-axSpA in Asia were predominantly male (75.9 vs. 47.1%), younger at onset (22.8 vs. 27.8 years) and diagnosis (27.2 vs. 34.5 years), and experienced less diagnostic delay (1.9 vs. 2.9 years) compared to nr-axSpA in non-Asia. Nr-axSpA in Asia exhibited higher +HLA-B27 (90.6% vs. 61.9%), fewer peripheral SpA features (53.6 vs. 66.3%), and similar extra-articular and comorbid disease rates. Disease activity, functional impairment, and MRI sacroiliitis were less in nr-axSpA in Asia, with higher rates of NSAID response and less MTX and bD-

MARDs use. Within Asia, r-axSpA showed higher disease activity and structural damage compared to nr-axSpA. [Conclusions] Among axial SpA, lower frequency of nr-axSpA was observed in Asia. Our results offer an opportunity to better understand clinical characteristics and optimize diagnostic strategies in Asia.

### W37-3

#### Cervical spine lesions in axial spondyloarthritis

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Conflict of interest: None

[Objective] The objective of this study is to examine the tonic sites and symptoms of the cervical spine in Axial spondyloarthritis (axSpA) patients. [Methods] Twenty-five patients who were diagnosed with axSpA from January 2005 to June 2021 and whose cervical spine could be evaluated by CT were included. C0 / 1 to C7 / Th1 were evaluated by CT, and those with bony bridges in the anterior or posterior vertebral bodies and between the spinous processes and those with bony ankylosis in the facet joints were considered to have tonicity. [Results] The patient background was 80% male, 40.4 ± 13.1 years old, 55% HLA-B27 positive, and 92% ankylosing spondylitis. There were 76% with ankylosis in one or more places. By element, ankylosis was observed in the order of 68% of facet joints, 56% of posterior and 44% of anterior vertebral bodies, and 28% between spinous processes. By level, C0 / 1 32%, C1 / 2 16%, C2 / 3 52%, C3 / 4 48%, C4 / 5 44%, C5 / 6 40%, C6 / 7 44%, C7 / Th1 52% was recognized as tough. All ankylosis observed on C0 / 1 was facet joints. Of the 17 patients who had no clinical symptoms, 12 had one or more tonic findings. [Conclusions] In axSpA patients, 76% had cervical spine ankylosis, and 70% had cervical spine ankylosis even if there were no clinical symptoms in the neck.

### W37-4

#### Image evaluation of sacroiliac joints using plain X-rays and CT in axial spondyloarthritis

Kenji Kishimoto, Shuji Asai, Mochihito Suzuki, Daisuke Kihira, Ryo Sato, Nobunori Takahashi, Kenya Terabe, Yoshifumi Ohashi, Kyosuke Hattori, Toshihisa Kojima, Shiro Imagama  
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Conflict of interest: None

[Objective] To compare the grade evaluation of the sacroiliac joint (SIJ) with axial spondyloarthritis (axSpA) by X-rays and CT. [Methods] 50 patients (100 joints) with axSpA had evaluation for sacroiliac joints by X-rays and CT between January 2004 and June 2021. Two rheumatologists independently evaluated the sacroiliac joints on a scale from grade 0 to grade 4 according to the Bennet grade criteria. This study examined the evaluation reliability between X-rays and CT, and inter-reader reliability for each modality. [Results] 50 patients (mean age 40.2 years), 84% men, the disease duration 11 years, 68% human leucocyte antigen B27 positive, 88% ankylosis spondylitis were included. The κ coefficient between grade evaluation on X-rays and CT was 0.52. The κ coefficient of inter-reader reliability was 0.41 by X-rays and 0.65 by CT. [Conclusions] The evaluation reliability between X-rays and CT was moderate. In addition, inter-reader reliability was substantial on the evaluation by CT, which was higher than the evaluation by X-ray. CT was useful for SIJ evaluation with axSpA.

### W37-5

#### Characteristics of radiographic findings of the hip joint in patients with axial spondyloarthritis in Japan

Daisuke Kihira, Shuji Asai, Mochihito Suzuki, Nobunori Takahashi, Kenya Terabe, Yoshifumi Ohashi, Kenji Kishimoto, Kyosuke Hattori, Toshihisa Kojima, Shiro Imagama  
Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: None

[Objective] Characteristics of imaging findings in large joints of axial spondyloarthritis (axSpA) have not been fully clarified. The purpose of this study was to investigate the imaging findings of the hip joint in patients with axSpA. [Methods] At our hospital from January 2005 to June 2021, 130 hips in 65 patients who could be evaluated with X-rays were evaluated for the presence of joint space narrowing, joint surface irregularity, and ankylosis. In addition, we focused on pistol grip deformity (PGD), referring to previous reports. [Results] The patient background was 92% Japanese, 74% male, mean age at the time of imaging evaluation 41.1 years, mean disease duration 12.8 years, 61% HLA-B27 positive. There were 66 hips with some findings on X-rays. Detailed imaging findings included narrowing of the joint space in 64 hips (49%), irregularity of the joint surface in 27 hips (21%), and ankylosis in 6 hips (5%). More patients with PGD had articular surface irregularities than those without PGD. [Conclusions] Joint space narrowing, PGD was more common than in the general Japanese population and was associated with joint surface irregularities, suggesting that PGD is a characteristic imaging change in ax SpA.

### W37-6

#### Evaluation of sacroiliac joints in patients with osteoarthritis and non-osteoarthritis by CT and examination of risk factors for fusion

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Conflict of interest: None

[Objective] There are few reports of HOA and sacroiliac joint fusion. We investigated whether HOA is a risk factor for sacroiliac joint fusion. [Method] We evaluated the state of sacroiliac joint fusion in 348 patients (mean age 67.1 years) by CT imaging in patients diagnosed with HOA, and that of 1113 non-HOA patients (mean age 69.0 years), according to the classification criteria of Yahara et al. A total of 1462 patients were subjected to multivariate logistic regression analysis with Type 4c fusion as the objective variable, the presence or absence of HOA, age, gender, rheumatic disease, induction of dialysis, and diabetes as explanatory variables. [Result] Type 4c fusion was 41 cases in HOA and 109 cases in non-HOA. As a result of multivariate logistic regression analysis, male (odds ratio 2.92 [95% CI: 1.99-4.29],  $p < 0.001$ ), age (1.024 [1.010-1.037],  $p < 0.001$ ), HOA (1.87 [1.23-2.85]),  $P = 0.0035$ ) was an independent risk factor for sacroiliac joint fusion. The sacroiliac joint fusion rates were 11.8% and 5.2%, respectively, in 348 HOA cases and non-HOA 348 cases adjusted for age and gender by propensity trend matching, which were significantly higher in the former ( $p = 0.002$ ). [Discussion] This result suggests that some HOA patients may contain Spondyarthritides.

### W38-1

#### Interim Tabulation Results of Post-marketing Surveillance (PMS) Study of Mepolizumab in Patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA)

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Conflict of interest: None

[Objectives] This study was conducted to collect the safety information of mepolizumab in EGPA patients. [Methods] This all-cases study started from May 2018. The observation period was 96 weeks. The safety endpoint was the occurrence of adverse events (AEs). [Results] As of Sep.23, 2021, 1,724 cases were enrolled and 492 completed case report forms for safety analysis (Observation completed: 492, 310, and 141 cases at Weeks 12, 48, and 96). In 492 cases, 57.1% were female, and the mean age was 59.6 years. The duration from EGPA onset (mean) was 3.7 years, and 94.1% had comorbidities, with an observation period (mean) of 340 days. At least one AE was reported in 31.5%. Regarding AEs defined as the safety specification, hypersensitivities (such as anaphylaxis), infections and malignant tumours were reported in 6.5%, 12.0% and 0.4%, respectively. Serious events of these were as follows: EGPA (exacerbation) as hypersensitivities occurred most commonly in 1.8%. As infections, pneumonia occurred most frequently in 1.6%, pneumonia bacterial in 0.8%, respiratory tract infection and urinary tract infection in 0.6%. Malignant tumours were reported in 2 cases. [Conclusion] Compared to the known safety profile of mepolizumab, no new concern is detected by now. (Funding: GSK, Study 208505).

### W38-2

#### Establishment of Japan's collaborative registry for ANCA-associated vasculitis (J-CANVAS): Temporal and international comparison study

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Conflict of interest: None

[Objective] To address the diversity and uncertainty of practice in ANCA-associated vasculitis (AAV), we started to establish a multicenter registry in Japan collaborating with an ongoing international study. [Methods] Patients with new-onset or severe relapse of AAV were retrospectively registered between January 2017 and June 2020 at 25 sites in Japan. The Japanese cohort (525 patients) was divided into two groups before and after January 2020 (the COVID-19 pandemic), and the international cohort (292 patients after the pandemic) was compared in three groups; Japan, Europe, and the US. [Results] The Japanese cohort included 312 MPA, 114 GPA, and 99 EGPA; there was no change in the severity before and after the pandemic, and the RTX usage increased slightly from 22% to 30%. The proportion of remission at 24 weeks was 73% for both before and after the pandemic, and the mortality at 48 weeks was 6% for both. The international cohort enrolled 101/147/44 patients from Japan, Europe, and the US. The use of CY or RTX in remission-induction was 63%/95%/98%, the proportion of remission at 24 weeks was 76%/86%/84%, and the mortality at 48 weeks was 6%/15%/7%, respectively. [Conclusions] Internationally, there is non-ignorable heterogeneity in treatment strategies and outcomes for AAV.

### W38-3

#### Efficacy and safety of intravenous glucocorticoid (IVGC) pulse therapy for the induction of remission in ANCA-associated vasculitis: Analysis by propensity score matching using the J-CANVAS registry

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Conflict of interest: None

[Objective] To evaluate the efficacy of IVGC pulse therapy in the induction of remission of ANCA-associated vasculitis (AAV). [Methods] The J-CANVAS registry, which is being established at 25 sites in Japan, is enrolling patients with AAV who had a first or relapse between January, 2017 and June, 2020. In the current study, total of 430 patients with microscopic polyangiitis (MPA) and polyangiitis with granulomatosis (GPA) were included. We conducted a propensity score-matched comparison of patients with and without IVGC pulse therapy using age, gender, MPA/GPA, smoking status, comorbidities, renal function, urinary protein level, presence of severe organ involvement, BVAS, acute type of interstitial pneumonia, and initial dose of prednisolone. [Results] Seventy patients each with and without IVGC pulse therapy were matched. The overall survival rates at 48 weeks were 90.1% and 93.0% ( $p=0.241$ ), and relapse-free survival rates were 80.0% and 81.7% ( $p=0.396$ ). Remission was achieved at 24 weeks (70.2%, 83.9%,  $p=0.117$ ) and 48 weeks (75.9%, 82.4%,  $p=0.484$ ), respectively. The incidence of severe infections by week 48 in each group was 27.2% and 21.1% ( $p=0.514$ ). [Conclusions] we found no evidence of efficacy of steroid pulse therapy in the treatment of AAV.

### W38-4

**Decreased IgG during remission induction is associated with the occurrence of severe infections in ANCA-associated vasculitis (AAV): a historical retrospective cohort study using the J-CANVAS registry data**

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Conflict of interest: None

[Objective] This study was to investigate the association between serum IgG reduction caused by remission-induction therapy of AAV and the development of severe infections. [Methods] The J-CANVAS registry, which is being established at 25 sites in Japan, enrolls patients with new-onset or severe relapse of AAV between January, 2017 and June, 2020. We conducted a historical retrospective cohort study of AAV patients enrolled in the registry. The minimum IgG levels during the remission-induction treatment period were collected, and the patients were classified into two groups using IgG 600 mg/dL as the cutoff. The cumulative incidence of severe infections up to 48 weeks after the start of treatment in both groups was compared. A Fine-Gray model was used to analyze the effect of low serum IgG on severe infection, with confounding adjustment for patient background, severity and treatment. [Results] A total of 523 patients were included, and there were 94 patients who developed severe infections. The adjusted hazard ratio of IgG for the development of severe infection was 1.76 (95% CI: 1.07-2.90,  $p=0.027$ ). [Conclusions] Decreased serum IgG in the remission induction period was associated with the development of severe infections.

### W38-5

**Status of clinical practice for ANCA-associated vasculitis in Eastern and Western Japan-from the Japan Collaborative registry of ANCA-associated VASculitis (J-CANVAS)**

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Conflict of interest: None

[Objective] J-CANVAS was established to register patients with AAV. This study aimed to retrospectively investigate the status of current practice for AAV in Japan. [Methods] The study included 448 patients in whom AAV onset was observed and who were enrolled between January 1, 2017, and June 30, 2020. Japan was divided into Eastern and Western regions in the Chubu and Kinki regions, and patient backgrounds and treatments were evaluated. [Results] The total number of AAV patients was 182 in Eastern Japan and 266 in Western Japan. The mean age was 70 years in both Eastern and Western Japan. The baseline BVAS in patients with initial-onset AAV was 14 in both Eastern and Western Japan. For treatment, the initial dose of glucocorticoids was 45 mg/day in both Eastern and Western Japan. But, at 12, 24, and 48 weeks, dose of glucocorticoids tended to be lower in eastern Japan. The frequency of use of immunosuppressants tended to be high in eastern Japan. There was no difference in the induction rate of remission after 24 and 48 weeks between Eastern and Western Japan. [Conclusions] When considering Japan as Eastern and Western Japan, significant differences were observed in the initial dose of steroids; however, no significant differences were noted in other parameters.

### W38-6

**Investigation of the pattern of improvement of urinary findings in patients with ANCA-associated vasculitis: Latent class trajectory modeling using the J-CANVAS registry**

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Conflict of interest: None

[Objective] To identify the pattern of changes in urinary findings after remission induction therapy for AAV and its impact on prognosis. [Methods] The J-CANVAS registry, which is being established at 25 sites in Japan, enrolls patients with new-onset or severe relapse of AAV between January 2017 and June 2020. Of the 353 patients with nephritis enrolled in the registry, 215 patients whose urinalysis could be obtained at the start of treatment and after 24 and 48 weeks were included. We performed group-based trajectory models and compared the remission achievement and survival at 48 weeks. [Results] We found two groups for the trajectories of proteinuria: "improved proteinuria" (78%) and "prolonged proteinuria" (22%). In each group, 90% and 69% of the patients achieved remission. We also found two groups for the trajectory of hematuria: "improved hematuria" (69%) and "prolonged hematuria" (31%) In each group, 89% and 78% of the patients achieved remission. There was no apparent difference in subsequent mortality in both comparisons. [Conclusions] We found distinct patterns of the trajectory of urinary findings after remission induction therapy. Whether these trajectories also affect long-term outcomes requires further study.

### W39-1

**A study on the risk of falls in elderly patients with rheumatoid arthritis-Clinical considerations on factors associated with falls during in-patient care-**

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Conflict of interest: None

[Introduction] In this study, we investigated factors associated with the occurrence of falls in elderly patients with rheumatoid arthritis (RA). [Methods] Eighty-three elderly RA patients (75.06±8.71 years) admitted to our hospital in 2020 were classified into two groups: fall group and non-fall group. Patient demographics (age, cognition, resting level), physical function factors (Frail CS-10, SIDE, 10-meter walk), daily living function factors (FIM, BI), and fall assessment (FRI-21, MFES) were evaluated and statistically analyzed. [Results] There was no difference in the FRI-21 between the two groups, but the fall group tended to have a lower Frail CS-10, SIDE, FIM, and BI, and a higher 10 m walking speed. In addition, 53% of patients in the falls group tended to have higher MFES. [Discussion] In addition to physical function factors, psychological factors such as fear of falling also influenced the risk of falling in elderly RA patients. In order to manage the risk of falling, it is necessary to combine the assessment of fall with the assessment of functional disability in RA. In addition, it is important to comprehensively evaluate narrative aspects such as compensatory movements and self-perception of activities.

### W39-2

#### Effect of an orthosis on foot center of pressure translation for treatment of hallux valgus in patients with rheumatoid arthritis: A report of 17 cases

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Conflict of interest: Yes

[Objective] We aimed to investigate the change in the center of pressure (COP) path and distribution with or without orthosis for hallux valgus (HV) in patients with rheumatoid arthritis (RA). [Methods] In total, 17 patients and 21 feet were enrolled. We measured the COP path using the COP path measurement device (F-Scan II system). The HV angle (HVA) and the peak planter pressure at the forefoot area were analyzed by comparing patients with RA with and without orthosis. The forefoot area was divided into medial third (medial 1/3), center third (center 1/3), and lateral third (lateral 1/3) of the forefoot width. [Results] Testing without and with the orthosis showed that the HVAs were  $31.8 \pm 9.3^\circ$  and  $25.2 \pm 6.8^\circ$  ( $p < 0.001$ ). The peak planter pressures at central 1/3 were  $683.5 \pm 486.4$  kPa and  $474.6 \pm 254.0$  kPa without and with the orthosis, respectively ( $p = 0.012$ ). The peak planter pressures at lateral 1/3 were  $470.4 \pm 299.1$  kPa and  $371.7 \pm 240.3$  kPa without and with the orthosis, respectively ( $p = 0.031$ ). [Conclusions] The results indicated that the orthosis for HV improved the walking path and should be considered as a therapeutic option in nonpharmacological treatment of RA.

### W39-3

#### Relationship between sarcopenia with rheumatoid arthritis and physical activity classified by daily living

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Conflict of interest: None

[Objective] Sarcopenia with rheumatoid arthritis (RA) is particularly influenced by physical inactivity. Although moderate-to-vigorous physical activity (MVPA) promotion is recommended, it is often difficult. In this study, we investigated the aspects of PA to establish sarcopenia treatment for RA patients. [Methods] Twenty-three female outpatients with RA were

included in the study. PA was measured by wearing the Actigraph GT3X BT monitor. The activity intensities were classified into “sedentary behavior” “very light-intensity” “light-intensity” and MVPA. The parameters of PA were compared between the sarcopenic and nonsarcopenic group. [Results] The mean age was 67.0 years, the mean duration of disease was 24.3 years. “Sedentary behavior” and “very light-intensity” did not differ significantly between the sarcopenic and nonsarcopenic groups. However, there were significant difference in “light-intensity” and MVPA with mean of 4.2% and 0.6%, mean of 8.6% and 3.0%, respectively ( $p < 0.05$ ). [Conclusions] For RA patients is necessary to establish a method to compensate for the decrease in MVPA from two aspects: a lifestyle change that leads to an increase in “light-intensity” PA, and the development of a new treatment method that is expected to increase skeletal muscle mass.

### W39-4

#### Walking habit positively influences disease activity and total spine alignment in elderly rheumatoid arthritis patients at 1 year

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Conflict of interest: None

[Objective] The purpose of this study was to evaluate the effects of walking on general health after one year in elderly RA patients. [Methods] Of the 87 elderly patients with RA who were able to complete the initial survey, 81 were able to complete the follow-up survey one year later. Gender, height, weight, BMI, incidence period, medication status (MTX, PSL, biological formulation, JAK), blood samples (anti-CCP antigen, creatinine, cystatin C, CRP, ESR, MMP-3, eGFR, Sarcopenia Index (serum creatinine/cystatin C)), diseases activity (DAS28-CRP, DAS28-ESR), thigh bone density (T-score), dysfunction index (HAQ) and Total spinal alignment (sagittal vertical axis (SVA), pelvic incidence-lumbar lordosis (PI-LL)) was assessed at the time of the initial survey and again at the time of the follow-up survey. [Results] The number of experiment group contained 40 subjects (49.4%). Between-group comparisons of change showed significant differences in DAS28-CRP (walking/control group:  $0.33 \pm 0.61 / 0.07 \pm 0.83$ ), SVA ( $-3.7 \pm 19.3$  mm /  $11.6 \pm 12.4$  mm), and PI-LL ( $-1.00 \pm 7.07^\circ / 2.83 \pm 6.98^\circ$ ). [Conclusions] When compared with the control group, it is proved that more favorable changes in disease activity and total spinal alignment.

### W39-5

#### Changes in SMI over one year of practicing T2T

Shinichiro Fujita<sup>1</sup>, Ryoza Harada<sup>2</sup>, Koji Takasugi<sup>3</sup>, Kazuhiko Ezawa<sup>3</sup>, Kie Inoue<sup>1</sup>, Rumi Inoue<sup>4</sup>, Sakiko Shinmyo<sup>5</sup>, Wataru Yamamoto<sup>6</sup>, Ryuichi Nakahara<sup>7</sup>, Yoshihisa Nasu<sup>7</sup>, Keiichiro Nishida<sup>7</sup>

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Conflict of interest: None

[Objective] Sarcopenia, a decrease in skeletal muscle mass and skeletal muscle strength, is a problem in the decline of physical function in patients with age-related rheumatoid arthritis (RA). In this study, we investigated the changes in skeletal muscle index (SMI) over a one-year period when T2T was practiced in RA patients. [Method] 81 patients (67 females, mean age 71 years, mean disease duration 17 years) with outpatient RA who underwent T2T within a 1-year period were evaluated for DAS28-CRP, HAQ-DI, Alb, BMI, SMI, and a number of sarcopenia were evaluated. [Result] The pre- and post-DAS28-CRP showed a significant improvement of  $3.45 \pm 1.22 / 3.18 \pm 1.17$  ( $p = 0.02$ ). The pre- and post BMI was  $23.2 \pm 3.9 / 23.3 \pm 4.3$  ( $p = 0.15$ ), SMI was  $5.76 \pm 0.96 / 5.77 \pm 1.12$  ( $p = 0.66$ ), sarcopenia was 42 (52%) / 44 (54%) ( $p = 0.88$ ), respectively and no significant improvement was observed. [Discussion] Even though T2T was practiced

and RA activity was controlled, SMI did not increase and the number of patients with sarcopenia tended to increase. As discussed in another chapter of the Rheumatoid Arthritis Clinical Practice Guidelines 2020, there is a need for some intervention and involvement with RA patients, such as exercise instruction and patient education.

### W39-6

#### The effect of music therapy on Patient Related outcomes and serological factors in patient with rheumatoid arthritis

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Conflict of interest: None

[Introduction] Reports on subjective assessment of the effect of music therapy on RA patients are scattered, but there were no reports on objective assessment such as serologic findings. [Objectives] Subjective and serological effects of music therapy in patients with rheumatoid arthritis were examined. [Participants and Method] 16 RA patients (3 men, 13 females) performed music therapy for about 45 minutes mean age of 75 years (65 to 83). We measured Pain-Visual Analogue Scale (P-VAS), General Health-VAS (GH-VAS), Feeling-VAS (F-VAS), CRP, MMP-3, and serum cytokines. The statistical method used the Wilcoxon rank order sign test for changes before and after music therapy. [Result] Before and after music therapy, the P - VAS changed from an average of 24±21 to 20±17 (p = 0.235), the F - VAS changed from an average of 22±18 to an average of 16±13 (p = 0.117). Serum MMP-3 and TNFα levels markedly decreased after music therapy. [Consideration] In this study we showed that music therapy on RA patients might reducing inflammation. Although the mechanism unclear, emotional experiences by music therapy may influence the immune system and affect cytokines. Music therapy may help non-medication therapy in RA treatment in the future.

### W40-1

#### Association of HLA-DRB1 and TSLP variants with eosinophilic granulomatosis with polyangiitis

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Conflict of interest: Yes

[Objective] Genetic factors may play a role in the etiology of eosinophilic granulomatosis with polyangiitis (EGPA), one of the subsets of ANCA-associated vasculitis. A recent genome-wide association study on EGPA in European populations identified *HLA* and *TSLP* as susceptibility genes for EGPA, and that susceptibility genes were different between MPO-ANCA positive EGPA (MPO+EGPA) and ANCA negative EGPA (ANCA-EGPA). In this study, we examined whether *HLA* and *TSLP* variants are associated with EGPA also in a Japanese population. [Methods] Association study of *HLA-DRB1* allele and *TSLP* rs1837253 with EGPA was conducted on 81 patients with EGPA. The patients' genotypes were compared with 786 healthy individuals in *HLA* analysis, and 8.3KJPN data obtained from jMorp (Japanese Multi Omics Reference Panel) in *TSLP*. [Results] *HLA-DRB1*\*07:01 and \*09:01 alleles were increased in total EGPA and MPO+EGPA, while association of these alleles was not detected in ANCA-EGPA. With respect to *TSLP*, rs1837253C allele was increased in total EGPA, confirming the result in European populations. The association of rs1837253 was detected both in MPO+EGPA and ANCA-EGPA. [Conclusions] *HLA-DRB1* and *TSLP* may contribute to susceptibility to EGPA also in a Japanese population.

### W40-2

#### The Bruton's tyrosine kinase inhibitor tirabrutinib suppressed the development of MPO-ANCA-associated vasculitis in rat model

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Conflict of interest: Yes

[Objective] MPO-ANCA-associated vasculitis (MPO-AAV) is an autoimmune disease characterized by MPO-ANCA and systemic necrotizing small-vessel vasculitis. Bruton's tyrosine kinase (Btk) inhibitors suppress the differentiation of B-cells into plasma cells. This study aimed to determine the effects of a Btk inhibitor tirabrutinib on the development of MPO-AAV in rat model. [Methods] WKY rats were immunized with human MPO and divided into disease group and low- or high-dose drug group. The drug groups were fed containing 0.0037% or 0.012% tirabrutinib from Day0 or 28. Blood was collected every 2 weeks, and urine was collected on Day40. All rats were euthanized on Day42 for histological evaluation. Furthermore, the effects of tirabrutinib on formation of neutrophil extracellular traps (NETs) were examined in vitro. [Results] Although MPO-ANCA titers were not different between the groups, the degrees of hematuria and pulmonary hemorrhage were decreased in the drug groups. Renal tubular erythrocyte casts were significantly decreased in the high-dose group given the drug from Day0. Tirabrutinib reduced the NET formation induced by MPO-ANCA immune complexes dose-dependently in vitro. [Conclusions] Tirabrutinib can suppress the development of MPO-AAV via reduction of NET formation.

### W40-3

#### A novel neutrophil-modifying compound suppressed development of MPO-ANCA-associated vasculitis in rat model

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Conflict of interest: Yes

[Objective] Glucocorticoids and immunosuppressive drugs as standard of cares lead remission in MPO-ANCA-associated vasculitis (MPO-AAV) patients. Because there are unmet medical needs such as severe side effects, resistance to the treatment and relapse, development of new therapeutic strategies is awaited. The aim of this study was to demonstrate the

efficacy of compound A, a novel neutrophil-modifying compound, against MPO-AAV in a rat model. [Methods] 4-week-old WKY rats were immunized with human MPO. The rats were divided into three groups (n=8 in each group), and vehicle (0.5% methylcellulose) or compound A (0.3 or 3 mg/kg bid) was orally administered every day for 42 days. All rats were euthanized at the end of the study for serological and histological evaluation. [Results] MPO-ANCA was induced in all groups at the same level. Neutrophil extracellular trap (NET)-forming neutrophils in peripheral blood, glomerular lesion, and glomerular neutrophil counts were significantly suppressed by compound A treatment. Furthermore, urinary NGAL and tubular erythrocyte cast counts were significantly decreased in the 3 mg/kg compound A-treated group. [Conclusions] Compound A suppressed the NET-formation, glomerular lesions and tubular damage in the MPO-AAV model rats.

#### W40-4

##### **Low serum complement C3 level as a risk factor for relapse and death of antineutrophil cytoplasmic antibody-associated vasculitis: A retrospective cohort study**

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Conflict of interest: None

[Objective] To analyze the clinical characteristics and outcomes of antineutrophil cytoplasmic antibody-associated vasculitis (AAV) patients with low serum C3 levels at the time of diagnosis. [Methods] We included 79 AAV patients. Serum C3 levels were measured at diagnosis. AAV included microscopic polyangiitis and granulomatosis with polyangiitis. Patients were divided into low- and high-C3 groups (C3 < 100 and  $\geq$  100 mg/dL, respectively). We compared the clinical characteristics of the two groups and identified predictors of AAV relapse and death. [Results] Of the 79 patients, 19 (24%) were in the low-C3 group. The low-C3 group patients were older, and had a higher Five Factor Score (FFS) and a lower remission rate, than the high-C3 group. The log-rank test revealed that the relapse-free survival time was significantly shorter in the low-C3 group than in the high-C3 group (27 vs 82 months;  $p=0.001$ ). The overall survival was also shorter in the low-C3 group than in the high-C3 group (83 vs 120 months;  $p=0.046$ ). In the Cox proportional hazards model, a low C3 level (< 100 mg/dL) was independent predictors of AAV relapse (hazard ratio [HR], 3.42;  $p=0.005$ ) and death (HR, 2.28;  $p=0.031$ ). [Conclusions] AAV patients with low C3 levels at diagnosis were at higher risk of relapse and death.

#### W40-5

##### **Instability of regulatory T cells in ANCA-associated vasculitis: focusing on pathogenic mediators**

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Conflict of interest: None

[Objective] To investigate the plasticity and instability of regulatory T cells (Tregs) in antineutrophil cytoplasmic antibody-associated vasculitis (AAV). [Methods] Peripheral blood mononuclear cells (PBMCs) from 25 patients with AAV and 17 healthy controls (HC) were used. Intracellular expressions of effector cytokines, FoxP3, reactive oxygen species (ROS), and phosphorylated mTOR (p-mTOR) in Tregs were analyzed. The alterations in and functional ability of Tregs were compared before and after resveratrol (RVL) treatment of PBMCs in patients with AAV. [Results] The expression levels of interferon (IFN)- $\gamma$ , interleukin (IL)-17, IL-4, ROS, and p-mTOR in CD4+CD25+FoxP3+ cells were significantly higher in patients with AAV than in the HC. FoxP3 expression in CD4+CD25+ cells and suppressive function of Tregs were significantly lower in patients with AAV than in the HC. Tregs after RVL treatment demonstrated significant decreases in IFN- $\gamma$ , ROS, and p-mTOR levels, and increases in FoxP3 levels and functional activity. [Conclusions] Plastic changes and

impaired function of Tregs, as well as their decreased FoxP3 expression, were indicated in AAV. mTOR activation could be implicated in imbalance of Tregs. Furthermore, ROS is a key mediator for inducing instability of Tregs in AAV.

#### W40-6

##### **Clinical value of immunoglobulin E and rheumatoid factor in eosinophilic granulomatosis with polyangiitis**

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Conflict of interest: None

[Objective] To clarify the clinical significance of rheumatoid factor (RF) and Immunoglobulin E (IgE) in eosinophilic granulomatosis with polyangiitis (EGPA). [Methods] Our retrospective cohort included all new EGPA patients according to ACR criteria who visited our department between April 2012 and June 2021. We investigated the relationship between MPO-ANCA, eosinophil count, RF, and IgE and organ symptoms and recurrence-free survival. The correlation between the two immunological data was investigated. [Results] Twenty-two patients were included, and male: female ratio was 6:16. Higher levels of RF was associated with skin lesions in EGPA. A negative result of MPO-ANCA and higher levels of eosinophils and IgE tended to be associated with heart involvement, while a positive result of MPO-ANCA tended to be associated with renal involvement. No significant correlation was found in any combination of immunological data. None of the immunological data were associated with recurrence. [Conclusions] The clinical significance of the immunological data was not clear, despite the small number of cases studied.

#### W41-1

##### **Mortality risk stratification using cluster analysis in patients with myositis-associated interstitial lung disease receiving initial triple combination therapy**

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Conflict of interest: None

[Objective] To identify patients with myositis-ILD who benefit from triple combo therapy using cluster analysis in the JAMI cohort. [Methods] Two-step cluster analysis was done in 185 patients who received triple combo therapy using the known prognostic factors in myositis-ILD. The 284 patients who received dual combo/monotherapy were also categorized into the cluster subgroups defined in triple combo therapy. Cumulative survival rates were compared between two therapy groups using log-rank test. [Results] The patients with triple combo therapy were divided into 6 clusters. The clusters 1 and 2 consisted of anti-MDA5-negative younger age patients with low mortality rates (5% and 9%). The clusters 5 and 6 consisted of anti-MDA5-positive younger patients who require no oxygen with mortality rates of 35% and 36%. The cluster 3 included elderly classic DM patients who require oxygen with mortality rate of 50.0%. The cluster 4 had the worst mortality rate of 95%, and included elderly amyopathic DM anti-MDA5-positive patients who required oxygen. There was no cluster that showed the better cumulative survival rates in triple combo therapy group over dual/monotherapy group. [Conclusions] We failed to identify a subgroup who benefits from triple combo therapy in patients with myositis-ILD.

#### W41-2

##### **The prognosis of 7 cases with rapidly progressive interstitial pneumonia with anti-MDA5 antibody-positive dermatomyositis treated with tofacitinib**

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Conflict of interest: None

[Objective] To examine the cases treated with Tofacitinib (TOF) for rapidly progressive interstitial pneumonia with anti-MDA5 antibody-positive dermatomyositis (DM-RPIP) retrospectively. [Methods] The subjects were 7 cases of anti-MDA5 antibody-positive DM-RPIP hospitalized in our department from November 2018 to May 2021 and treated with TOF. [Results] The median ages of the subjects, AaDO<sub>2</sub>, KL-6, CRP, and serum ferritin were 55 years, 27.7 torr, 444 U/ml, 0.30 mg/dl, and 608 ng/ml, respectively. Prednisolone, calcineurin inhibitor, intravenous cyclophosphamide pulse therapy (IVCY), and TOF were used in all 7 cases. It was also used in 6 cases of plasma exchange, 1 case of PMX, and 2 cases of IVIgG. The median dose of IVCY was 6050 mg, and the initiation of TOF was 15 days (median) after the start of the treatment. There were 3 deaths, all cases were related to the primary disease. The characteristics of all deaths were age  $\geq$  57 years, AaDO<sub>2</sub>  $\geq$  33.2 torr, and serum albumin  $\leq$  2.9 g/dl at the start of treatment. Survivors were age  $\leq$  55 years, AaDO<sub>2</sub>  $\leq$  27.0 torr, and serum albumin  $\geq$  3.3 g/dl. [Conclusions] In order to further improve the prognosis of anti-MDA5 antibody-positive DM-RPIP, it is necessary to study more effective TOF usage and collect more cases.

### W41-3

#### A review of the criteria for the induction of apheresis therapy in clinically amyopathic dermatomyositis with interstitial pneumonia (CADM-IP) based on previous reports

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Conflict of interest: None

[Object] To review the criteria for the introduction of apheresis therapy in CADM-IP, we researched previous reports published reports last year. [Methods] The cases published since October 2020 were divided into two groups, survival and death, and analyzed by F test for significant differences in the points of clinical features, like as age, gender, specific autoantibodies, clinical indices, type of immunosuppressive agents. [Results] The total number of cases was 151, of which 61 were positive for anti-MDA5 antibody. The mean age was 58 years with a male: female ratio of 54:83. 80/134 patients were survival. Almost all patients were treated with three immunosuppressive agents. The total number of patients treated with therapeutic apheresis was 48 for simple plasma exchange (PE) and 34 for PMX. [Summary] Of the clinical indices, the P/F ratio tended to be significantly higher in the surviving patients. In addition, ferritin levels also tended to be significantly lower in them. The mean P/F ratio was low at 166 and the ferritin level was high at 1964 mg/dl, both of which were not life-saving. However, almost all of the analyses were case reports, and further examination of the registry data currently being conducted by the JSFA and other future reports is urgently needed.

### W41-4

#### A case of anti-MDA5 antibody-positive rapidly progressive interstitial pneumonia saved by multidisciplinary treatment including baricitinib and nintedanib

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Conflict of interest: None

A 54-year-old woman presented with erythema on her fingers after receiving COVID-19 vaccine. After the second vaccination, she visited her local doctor with persistent fever and respiratory distress. She was referred to another doctor, and she was admitted to the hospital with decreased oxygenation and frosted glass shadows on chest CT. She was treated, but the oxygenation worsened, and she was referred to our department. Based on inverse Gottron's sign, anti-MDA5 antibody-positive dermatomyositis associated with rapidly progressive interstitial pneumonia (IP) was suspected, and she was transferred to our department. Her respiratory

status worsened after transfer, and she was admitted to the ICU, and we started treatment with methylprednisolone pulse, cyclophosphamide, plasma exchange, and baricitinib (Bari) on ventilator management. Her chest X-ray showed improvement, and she was weaned from the ventilator on the 6th day and discharged from the ICU on the 9th day. The efficacy of tofacitinib in the treatment of anti-MDA5 antibody-positive IP has been reported, but the efficacy of Bari has not yet been reported. It has been revealed that anti-MDA5 antibody-positive IP and COVID-19 pneumonia are similar clinical manifestations, and Bari is expected to be a new treatment.

### W41-5

#### The characteristics of mediastinal emphysema in patients with inflammatory myopathy-related interstitial lung disease

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Conflict of interest: None

[Objective] The aim of this study is to clarify the clinical characteristics of the patients those who complicated mediastinal emphysema (ME) with idiopathic inflammatory myopathy associated interstitial lung disease (IIM-ILD). [Methods] We retrospectively investigated the patients with IIM-ILD who were admitted to our department between February 2014 to September 2021. The clinical information, such as physical examination, blood test, imaging test, pulmonary function test, and treatment history, were collected and compared between patients with and without ME. [Results] Thirty patients with IIM-ILD (16 dermatomyositis, 7 polymyositis, and 7 clinical amyopathic dermatomyositis) were included. Mean age was 57.3 $\pm$ 16.8 years, and 83.3% were female. Compared to the patients without ME (n=23), the patients with ME (n=7) showed higher KL-6 levels at initial diagnosis (1196 $\pm$ 1604 U/ml vs. 645 $\pm$ 903 U/ml, p=0.04), lower DLCO (48 $\pm$ 1.98% vs. 65 $\pm$ 20%, p=0.04) and higher rate of admissions to intensive care unit (28.6% vs. 0.0%, p=0.048). There was no difference in the type of myositis-associated autoantibodies, dose of steroids, or smoking history between the two groups. [Conclusion] Among the patient with IIM-ILD, the presence of ME is associated with the severity of ILD.

### W41-6

#### Fatal thrombotic microangiopathy in a patient with clinically amyopathic dermatomyositis; A case report

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Conflict of interest: None

[Case report] A 34-year-old man was referred for examination and treatment of facial and ear rash, and weakness and pain in lower limb. He was diagnosed as clinically amyopathic dermatomyositis (CADM) with full physical examination. It showed poor prognosis that computed tomography of the chest revealed the progressive ILD and his blood test showed a high ferritin level. The prednisolone (PSL) dose was increased to 60 mg combined with tacrolimus (Tac) on day 2, and intravenous cyclophosphamide (IVCY) was commenced on day 6. After he developed bacteremia which disturbed intensive immunosuppressive therapy, the serum ferritin and LDH level increased. Therefore, steroid pulse therapy and IVCY was administered. The diagnosis of thrombotic microangiopathy (TMA) was given based on the findings of thrombocytopenia, schistocyte, elevated LDH and creatinine levels, and a reduced serum level of haptoglobin. Therefore, we started plasma exchange on day 32. On day 37, consciousness disorder and lactic acidosis appeared. Tac which could induce TMA was discontinued and PSL was changed to dexamethasone. He developed multiple organ failure and died on day 39. [Discussion]. Here, we report a case that a patient with CADM developed fatal TMA, which was previously reported a poor prognosis.

## W42-1

### Four cases of dermatomyositis with abnormally high anti-MDA-5 antibody titers and almost normal ferritin levels

Daichi Umemoto<sup>1</sup>, Shuji Sumitomo<sup>2</sup>, Hideki Oka<sup>1,2</sup>, Hayato Shimizu<sup>1,2</sup>, Maki Kanamori<sup>1</sup>, Hiroaki Nishioka<sup>1</sup>, Koichiro Ohmura<sup>2</sup>

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Conflict of interest: None

Anti-MDA-5 antibody-positive dermatomyositis has a poor prognosis when the antibody levels and ferritin levels are high. Recently, we experienced four cases with abnormally high anti-MDA-5 antibody titers and with almost normal ferritin levels. All patients were female, aged 29-54 years, with anti-MDA-5 antibody titers of 2060-3040, ferritin of 87-294 ng/mL, KL-6 of 186-1806 U/mL. One patient had respiratory distress on exertion and all patients had relatively mild ground glass opacity/reticular shadows near pleura by CT. Three patients were treated with a combination of high-dose glucocorticoid, intermittent intravenous cyclophosphamide, and calcineurin inhibitor, and two of them required plasma exchange due to worsening of lung lesions. One patient with very mild pulmonary lesions was treated with moderate doses of glucocorticoid and calcineurin inhibitor, and the pulmonary lesions disappeared. In all cases, ferritin and KL-6 levels were elevated at the beginning of treatment. Plasma exchange therapy was effective. The final outcome was survival in all patients. The disease can become severe when anti-MDA5 antibody titers are very high even when ferritin is low. Early aggressive therapeutic intervention is recommended with close evaluation of CT chest images and biomarkers.

## W42-2

### Treatment of anti-MDA5-positive dermatomyositis (DM) diagnosed after insurance coverage of antibody testing

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Conflict of interest: None

[Objective] We investigated the treatment of anti-MDA5-positive DM diagnosed at Nagaoka Red Cross Hospital after anti-MDA5 testing had become covered by insurance. [Methods] We retrospectively examined the treatment of 11 patients with anti-MDA5-positive DM diagnosed at our hospital after October 2016. [Results] There were 2 males and 9 females (median age 62 (49-70) years, observation period 12 (3-23) months, ferritin 223 (203-1234) ng/mL, CRP 1.36 (0.11-1.73) mg/dL, KL-6 736 (499-990) U/mL, LDH 440 (321-515) U/L, anti-MDA5 3385 (610-3657) pg/mL). Of the 11 patients, 4 had skin ulcers and 10 had interstitial pneumonia. Almost all of the patients received triple-drug combination therapy comprising high-dose glucocorticoid, carcinulin inhibitor and intravenous cyclophosphamide, and among those showing an insufficient response, 6 received high-dose immunoglobulin therapy, 3 plasmapheresis, 1 rituximab, 2 tofacitinib, and 1 hydroxychloroquine. Nine survived and 2 died (13 and 14 days after diagnosis). In the survivors, it took 96 (76-106) days until no active organ lesions were evident. CRP and anti-MDA5 were decreased significantly 12 weeks after treatment. There were no relapses. [Conclusions] Intensive immunosuppressive therapy achieved a high survival rate.

## W42-3

### Idiopathic inflammatory myopathy with anti-nuclear matrix protein 2 (NXP2) antibody is characterized as atypical rashes, wide-spread muscular manifestations, and low anti-nuclear antibody titer

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Conflict of interest: None

[Objective] Anti-nuclear matrix protein 2 (NXP2) antibody is often detected in juvenile patients with dermatomyositis (DM) and adult patients with idiopathic inflammatory myopathies (IIMs) accompanied by

malignancies. However, the distinct clinical feature of IIMs with anti-NXP2 antibody were still not disclosed. [Methods] Seventy-six anti-NXP2 antibody-positive IIMs patients, including 29 juvenile patients, were enrolled in this study. Clinical manifestations and laboratory data were analyzed retrospectively from medical chart. [Results] Twenty-seven cases (35.5%) showed polymyositis (PM) phenotype, although 19 cases showed nonspecific skin manifestations except for DM-specific rashes, heliotrope rash and Gottron sign/papules. Muscle weakness extended to distal extremities addition to proximal extremities were observed in 36 cases (47.4%), moreover, dysphagia and neck muscle weakness were in 45 cases and 33 cases, respectively. Anti-nuclear antibodies (ANAs) were negative in 46 cases (60.5%). [Conclusions] Anti-NXP2 antibody-positive IIMs sometimes showed PM phenotype with atypical rashes, and frequently presented severe muscular involvements with low titers of ANA.

## W42-4

### Predict the characteristics of lung disease with myositis-specific and related antibodies in dermatomyositis / polymyositis

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Conflict of interest: None

[Objective] To clarify the relationship between MSA/MAA and the prevalence of interstitial lung disease (ILD) and HRCT. [Methods] From 2011 to 2018, the patient was diagnosed at our hospital according to Peter & Bohan's criteria, and 78 IIMs patients were included. 14 types of MSA / MAA (Jo1, PL12, PL7, EJ, OJ, KS, Mi2, MDA5, TIF1γ, SRP, PM-Scl70, 100, Ku, Ro52) were analyzed by ELISA and Line blot. The presence or absence of ILD and chest HRCT findings were identified from medical records and their association with MSA/MAA was examined. [Results] 53/78 patients (68%) had ILD. 60% of all ILD cases were Anti-ARS (+). Anti-MDA5 and ARS positive cases had ILD complication rates of 100% (3/3 cases) and 94% (32/34 cases), respectively. In Anti-ARS (+) ILD, there were many Anti-Ro52 (+) cases. The frequency of HRCT patterns of chronic ILD was in the order of fibrotic NSIP (fNSIP), fibrosing OP (fOP), and UIP, but MSA / MAA peculiar to each pattern was not observed, and Anti-ARS was more positive in all patterns. Anti-ARS (+) chronic ILD has a worse prognosis than other MSA / MAA (+) ILDs, and the frequency is fOP, fNSIP, UIP in that order. [Conclusions] Anti-ARS is associated with fibrosis of ILD and has a poor prognosis, so it is necessary to consider treatment including anti-fibrotic drugs.

## W42-5

### A case of anti-ARS antibody syndrome with a new anti-ARS antibody

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Conflict of interest: None

[Background] Anti-aminoacyl-tRNA synthetase (ARS) antibody syndrome is characterized by myositis, interstitial pneumonia, fever, Raynaud phenomenon, arthritis, and mechanic's hands. We report a case who showed anti-ARS antibody syndrome like symptoms with a new anti-ARS antibody. [Case] A 69 years old man showed 3 months effort dyspnea, mechanic's hands, fever and arthralgia. There was no loss of muscle strength, elevation of CK. The myositis specific antibodies including anti-ARS antibody covered by insurance were all negative. He was successfully treated with methylprednisolone pulse and PSL 60 mg and intravenous cyclophosphamide pulse as anti-ARS antibody syndrome like dermatomyositis with IP. He was affected with Stage I colon cancer. We confirmed the existence of anti-cysteine synthetase (CRS) by the immunoprecipitation with his serum and cell line lysate. [Discussion] There is no report of anti-CRS antibody as an anti-ARS antibody syndrome associated antibody. Though this case lacked myositis and Raynaud symptoms, there were typical mechanic's hand and IP with good response to therapy. We

need to elucidate the relationship with cancers by the accumulation of the cases. Anti-CRS antibody will be a new marker of anti-ARS syndrome and a clue of mechanism elucidation.

## W42-6

### Autoantibody against ADAR in myositis; presence and its clinical features

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Conflict of interest: None

[Objective] In this study, we tried to measure anti-adenosine deaminase acting on RNA (ADAR), antibodies in patients with myositis, in which type I interferon plays important role, and to examine the clinical features of patients with the antibody. [Methods] The subjects were 117 patients with dermatomyositis/polymyositis who were admitted to our department from December 2008 to September 2020 and whose serum samples were available. To detect anti-ADAR antibodies, ELISA was developed using recombinant ADAR as an antigen. [Results] Of the 117 cases, 13 cases (11.1%) were positive for anti-ADAR antibody (male /female: 5/8, average age; 61.8 years, 8 ADM; 2 DM; 2 PM, and 1 ARS syndrome). Of 13 patients with anti-ADAR antibody, anti-MDA5 antibody and anti-ARS antibody was positive in 8 and 4 cases, respectively. Anti-ADAR antibody was frequently found in anti-MDA5 antibody-positive cases (8/27; 29.6%) compared to others such as anti-ARS antibody-positive cases (4/39; 10.2%) ( $P=0.017$ ). Arthritis was a common symptom and interstitial lung disease was found in all patients with anti-ADAR antibody. [Conclusions] Anti-ADAR antibody was present in 11.1% of patients with myositis. Anti-ADAR antibody positivity was associated with anti-MDA5 antibody positivity.

## W43-1

### Trends in orthopedic surgery in patients with rheumatoid arthritis: An observational cohort study using the National Database of Rheumatic Diseases in Japan from 2004 to 2020

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Conflict of interest: None

[Objective] The purpose of this study was to evaluate the trend and background of rheumatic surgeries using a large database. [Methods] We extracted data from the National Database of Rheumatic Diseases by iR-net in Japan (NinJa) from 2004 to 2020. The number of surgeries for each year were shown in chronological order. The background of rheumatoid arthritis patients were compared as well. [Results] The total number of surgeries has decreased over time. Especially, knee and hip prosthetic joint surgeries has declined until 2012. Spine surgery showed a gradual upward trend. The patient background showed an aging of population and an improvement in disease activity. As for drugs, use of methotrexate and biologics has increased frequency. [Conclusions] Disease activity has been improving with changes in rheumatology treatment. The overall number of rheumatology-related surgeries has been decreasing accordingly. In addition, the trend of change differed depending on the type of surgery.

## W43-2

### Orthopedic surgery and postoperative ADL for patients with juvenile idiopathic arthritis at our hospital

Naoko Koenuma<sup>1</sup>, Tomohiro Kawabe<sup>2</sup>, Ayako Tominaga<sup>1</sup>, Takako Miyamae<sup>2</sup>, Katsunori Ikari<sup>1</sup>, Ken Okazaki<sup>1</sup>

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Conflict of interest: None

[Object] Juvenile idiopathic arthritis (JIA) lead to joint destruction, growth impairment and severe deformity. Orthopedic surgery is a common treatment for rheumatoid arthritis (RA), but we found few reports of intensive joint surgery for JIA. In this study, we examined the descriptive statistics of orthopedic surgery in patients with JIA at our hospital. [Methods] We selected JIA patients who had reported orthopedic surgery in the IOR-RA cohort study. And, we collected data on JIA patients who underwent orthopedic surgery at our institution from July 1993 to December 2020. We evaluated pre and postoperative ADL using the Barthel Index in patients who underwent TKA and THA. [Results] A total of 155 surgeries were performed. The mean age at the time of surgery was 36.8 years, and the mean disease duration was 24.9 years. 25 out of 52 patients with TKA/THA had evaluable Barthel Index, which showed significant improvement from 87.6 preoperatively to 93.6 postoperatively. [Discussion] The mean age and duration of orthopedic surgery for RA patients in our hospital from 2015 to 2019 were 65.3 years and 21.8 years. JIA patients tended to undergo surgery at a younger age than RA patients, but with a longer duration of illness. Orthopedic surgery for JIA is effective in improving ADL.

## W43-3

### Surgical repair of extensor tendon ruptures in the rheumatoid wrist under the selective sensory nerve block and monitored anesthesia care

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Toho Medical Omori Medical Center

Conflict of interest: None

[Objective] This paper explains the combined use of MAC and the selective sensory nerve block under us to induce intraoperative awareness to decide the tension of tendon and reports on its effectiveness. [Methods] The subjects are seven hands with RA which underwent the reconstruction of subcutaneous extensor tendon rupture in our department between 2020 and 2021. For all cases, we released tourniquet after S-K procedure. About ten minutes later, patients were instructed to spontaneously move fingers so that the operator can check the ROM. Geldmacher criteria for outcome assessment was used for the motion range of MP joint at survey, while HAND20 and Quick-DASH were used in clinical evaluation. [Results] Appropriate tension of tendon suture and early training resulted in no cases with limited inflection at survey, with five cases marking "good" and two cases "fair" in the Geldmacher criteria for outcome assessment. While the values at operation at HAND20 65.3 and Quick-DASH 59.2 improved to 28.8, 25.3 at survey respectively, no significant differences were observed. [Conclusions] Combined use of MAC and selective sensory nerve block in reconstruction of subcutaneous extensor tendon rupture due to RA seems to be effective in enabling decision on the tension of tendon suture.

## W43-4

### Relationship of the Patient-Reported Outcome between Japanese Version of the Decision Regret Scale and Patient Satisfaction for Lower Extremity Joint Surgery in Rheumatoid Arthritis

Takayuki Shimazaki<sup>1</sup>, Yuichi Mochida<sup>1</sup>, Kengo Harigane<sup>1</sup>, Akiko Nagaoka<sup>1</sup>, Naomi Kobayashi<sup>2</sup>, Yutaka Inaba<sup>3</sup>, Ken Kumagai<sup>3</sup>, Hyonmin Choe<sup>3</sup>, Taro Tezuka<sup>3</sup>, Shunsuke Yamada<sup>3</sup>, Shuntaro Nejima<sup>3</sup>, Gosuke Akiyama<sup>3</sup>, Hironori Yamane<sup>3</sup>, Naotsugu Nakajima<sup>3</sup>, Dan Kumagai<sup>3</sup>

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Conflict of interest: None

[Objective] The clinical significance of Japanese version of the Decision Regret Scale (DRS) as a patient reported outcome (PRO) was evaluated, then the relationship between DRS and patient satisfaction for lower extremity surgery in rheumatoid arthritis (RA) were analyzed. [Methods] A questionnaire was sent to RA patients who underwent primary knee or forefoot joint surgery. 93 patients (64 knees in 50 patients: K group, 72 feet in 47 patients: F group, included duplicates) answered the questionnaire that included DRS and patient satisfaction by visual analogue scale (VAS). VAS was scored for the subgroup of function, appearance and to-



tal. The relationship between DRS and each VAS was analyzed. [Results] The mean DRS (0-100 points, higher scores indicate greater regret) was 12.0 points in K group and 15.7 points in F group. 2 knees (3.1%) and 2 feet (2.8%) scored 50 or more that were assessed as regret. In K group, DRS had a negative correlation with VAS in function, appearance and total ( $P < 0.01$ ). In F group, although DRS had a negative correlation with VAS in function and total ( $P < 0.01$ ), no correlation was observed with appearance. [Conclusions] In K group, DRS was thought to be a useful PRO. From the result of F group, functional satisfaction may influence regret for surgery.

### W43-5

#### Efficacy of spinal endoscopic surgery for lumbar spinal stenosis in patients with rheumatoid arthritis

Shima Hirai

National Sagami Hospital

Conflict of interest: None

[Objective] Clarifying the Efficacy of spinal endoscopic surgery for lumbar spinal stenosis in patients with rheumatoid arthritis. [Methods] Performed by the same surgeon at our hospital from April 2020 to August 2021 Rheumatoid arthritis out of 152 cases of endoscopic laminoplasty (MEL) for lumbar spinal stenosis 14 (RA) patients were compared with age- and gender-matched patients without rheumatoid arthritis. Pre- and post-operative XP was used to compare the presence or lumbar slip, surgery time, bleeding volume, facet joint preservation rate on postoperative CT, and pre- and post-operative symptoms with healthy subjects. [Results] There was no difference in both group with surgery time, bleeding volume, facet joint preservation rate. Postoperative symptoms in both groups were significantly improved compared to preoperatively. There was no difference between the two groups. [Conclusions] It was found that MEL is a useful procedure in RA patients as well as in healthy subjects. It has been reported that there are many perioperative complications and reoperations in lumbar fusion surgery for RA patients, and MEL It is hoped that these complications will be reduced by responding.

### W43-6

#### Long-term surgical outcomes of cervical spine lesions caused by rheumatoid arthritis in the era of biologics use

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Conflict of interest: None

[Objective] This study aimed to evaluate long-term surgical outcomes of cervical spine lesions caused by rheumatoid arthritis (RA) in the era of biologics use. [Methods] The authors retrospectively extracted data for patients with RA cervical lesions who underwent atlantoaxial or occipito-cervical fixation and were followed for at least 5 years. The following data were recorded including the preoperative patient background, postoperative radiographic parameters, and neck pain. The Primary Outcome was the occurrence of subaxial subluxation (SAS). [Results] Mean age at initial surgery was 60.7 years, and mean follow-up period was 6.8 years (range, 5-10 years). Biologics use (30.0% vs. 35.3%) was comparable between patients with and without SAS. As a result of survival analysis, there was no effect of Biologics use on the occurrence of SAS, but the occurrence of SAS was higher after surgery in patients over 65 years at the time of surgery (Age  $\geq 65$  years vs.  $<65$  years: postop. 3 years, 25% vs. 7%; postop. 6 years, 61% vs. 14%;  $p=0.031$ ). [Conclusions] In patients with rheumatoid arthritis who have undergone spinal surgery for RA cervical spine lesions, SAS may occur secondarily, and long-term follow-up is important even in the era of biologics use.

### W44-1

#### Analysis of clinical features in ANCA-associated vasculitis treated with Rituximab: a single center experience

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Conflict of interest: None

[Objective] Rituximab (RTX) has been increasingly used in ANCA-associated vasculitis (AAV). Therefore, we analyzed our patients treated by RTX. [Methods] We therefore analyzed retrospectively the clinical database of 66 patients with AAV (MPO-MPA 32, MPO-GPA 17, PR3-GPA 17) in our hospital who were treated with RTX. [Results] The mean age of RTX induction was  $65.9 \pm 16.4$  years old. 62 patients had induction of remission at the time of initial onset / relapse. There were 21.2% (14/62 cases) of whom disease activity was suppressed without maintenance RTX. 57% (22/39 cases) of maintenance therapy were performed with on-demand administration. In addition, 35% (6/17 cases) of regular administration were switched from regular administration to on-demand within 1 to 2 years after the induction of remission. Relapses occurred more than 6 months after the last RTX administration (mean  $16.6 \pm 9.2$  months). RTX introduced re-remission. [Conclusions] These results showed that AAV treated by RTX is good tend. RTX treatment was tailored to each patient and was effective in improving prognosis.

### W44-2

#### A review of clinical features of patients with hypertrophic pachymeningitis (HPM) associated with ANCA-associated vasculitis (AAV)

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Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University

Conflict of interest: None

[Objective] To clarify the characteristics of clinical course and treatment of HPM associated with AAV. [Methods] We retrospectively reviewed the clinical characteristics of patients who were diagnosed and treated for HPM associated with AAV at our hospital from January 2010 to October 2021. [Results] We identified 10 patients (4 men and 6 women). The median age at the time of HPM diagnosis was 68 (32-83) years. 70% of patients had headache and cranial nerve involvement was detected in all patients. AAV classification was GPA 80%, mPA 10% and EGPA 10%. All patients had otitis media with ANCA-associated vasculitis. Detected ANCA was MPO-ANCA (90%) and PR3-ANCA (10%). 90% of the patients developed HPM after relapse AAV, and among them, CRP was elevated in all patients, however ANCA levels showed an upward trend in only 11%. In addition to glucocorticoids, 80% of patients were treated with immunosuppressive drugs. [Conclusions] In patients with AAV, contrast-enhanced MRI should be considered for the possibility of HPM if headache or central neuropathy is present, and the need for MRI increases if otitis media is present. In patients who develop HPM after AAV relapse, ANCA levels may not reflect the disease activity of HPM, although elevated CRP may be a clue.

### W44-3

#### Analysis of risk factors for relapse in ANCA-associated vasculitis: a single-center retrospective cohort study

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Conflict of interest: None

**Objectives:** We aimed to investigate risk factors for relapse in ANCA-associated vasculitis (AAV). **Methods:** We conducted a retrospective cohort study of 172 adult Japanese patients with newly diagnosed AAV at our department who were classified as microscopic polyangiitis (MPA), polyangiitis granulomatosis polyangiitis (GPA), or eosinophilic granulomatosis polyangiitis (EGPA) according to the classification algorithm proposed by Watts et al. The factors associated with AAV relapse were analyzed by Cox proportional hazard model. **Results:** Eighty males and 92

females were enrolled. The mean age was 65.9 years. There were 97, 57, and 18 patients classified as MPA, GPA, and EGPA, respectively. Twenty-nine patients had diabetes at the onset. Prednisolone and immunosuppressants were administered to 160 and 103 patients, respectively. In a median follow-up period of 30 months (IQR, 7-67.5), 144 patients achieved AAV remission (BVAS new/worse =0 for  $\geq 1$  month), and 46 had AAV relapse (BVAS new/worse  $\geq 1$  after the remission). Multivariate analysis revealed the presence of diabetes (HR=3.67; 95% CI 1.70-7.93) and GPA (HR=2.37; 95% CI 1.26-4.46) as independent risk factors for AAV relapse. **Conclusions:** Comorbidity of diabetes at onset or GPA could be risk factors for AAV relapse.

#### W44-4

##### **Assessment of renal risk score as a predictor of renal outcome for Japanese patients with ANCA associated vasculitis (AAV)**

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Conflict of interest: None

[Objective] Patients with AAV still reach end-stage renal disease (ESRD) or death despite aggressive treatments. Brix et al. suggested the usefulness of renal risk score to predict the renal outcome for AAV. We assessed the availability of renal risk score for Japanese patients with AAV. [Methods] We retrospectively reviewed the association between ESRD and renal risk score using 128 patients diagnosed with AAV and underwent renal biopsy from 1992 to 2019 in Nagasaki prefecture. [Results] The average age was 66.6 $\pm$ 13.3 year-old, the date of diagnosis was the 1990s; 8 patients, 2000s; 41 patients, 2010s; 79 patients. The average eGFR was 31.69 $\pm$ 23.65 mL/min/1.73 m<sup>2</sup>. The number of MPO-ANCA positivity was 113 (88.3%), and PR3-ANCA positivity was 10 (7.8%). The average BVAS was 14.58 $\pm$ 4.81; the average renal risk score was 4.25 $\pm$ 4.81. As a result of comparison between the groups with and without ESRD, significant differences ( $p < 0.05$ ) were found in the age of diagnosis, eGFR, and renal risk score. We performed a multivariate analysis that included the date of diagnosis and renal risk score. The renal risk score was still an important variable predicting outcome ( $p < .0001$ ). [Conclusion] The renal risk score was helpful as the predictor for the renal outcome of Japanese patients with AAV.

#### W44-5

##### **Clinical significance of ANCA subtypes and effect of immunosuppressive therapy in patients with granulomatosis with polyangiitis: a multicenter retrospective observational study**

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Conflict of interest: None

[Objective] We aimed to investigate the clinical significance of ANCA subtypes and the effect of immunosuppressive therapy in patients with granulomatosis with polyangiitis (GPA) for each organ lesion. [Methods] We retrospectively studied a total of 108 patients with GPA who attended three hospitals between 2000 and 2021. In severe or refractory cases, we used cyclophosphamide (CYC) or rituximab (RTX) as initial remission induction therapy in addition to glucocorticoid. We evaluated ANCA subtype characterization and treatment effect for each organ lesion. We used relative risk for analysis. [Results] After initial remission induction with CYC, PR3-ANCA positive patients were more likely to relapse than

MPO-ANCA positive patients. Compared to MPO-ANCA positivity, PR3-ANCA positivity carried a higher risk for mass extension from the paranasal sinuses to the orbits. Intraorbital masses and cerebrovascular lesions were more prone to recur or worsen even after initial remission induction with CYC, and remission re-induction therapy with RTX was effective. [Conclusions] PR3-ANCA positivity can be a risk factor for mass extension from the paranasal sinuses to the orbits. Intraorbital masses and cerebrovascular lesions are refractory, and RTX can be useful for remission re-induction.

#### W44-6

##### **The utility of the PEXIVAS protocol for the treatment of ANCA-associated vasculitis in Japanese patients**

Takehiro Suzuki, Kahori Ishida, Makiko Ikoma, Takeshi Kaneko, Takashi Hosokawa, Hiroshi Fujiwara

Division of Rheumatology and Allergy, Osaka General Medical Center

Conflict of interest: None

[Objective] To investigate the utility of the PEXIVAS protocol for the treatment of ANCA-associated vasculitis in Japanese patients. [Methods] We compared the course of treatment for half a year in patients who received conventional treatment in our hospital from April 1, 2019 to March 31, 2020 (C group) and those who were treated according to the PEXIVAS protocol in our hospital from April 1, 2020, to March 31, 2021 (P group). [Results] There were seven patients in each group. The average age at diagnosis was 74 years in the P group and 74.6 years in the C group. The average BVAS at diagnosis was 15.9 points in the P group and 9 points in the C group. The duration of hospitalization was 32.4 days in the P group and 54.4 days in the C group. After 6 months, remission (BVAS  $< 1$  point, and prednisolone [PSL]  $< 10$  mg/day) was achieved in three patients in the P group and four patients in the C group. The average dosage of PSL was 5.6 mg/day in the P group and 12.1 mg/day in the C group ( $P < 0.01$ ). There was one case of relapse in the P group and two cases in the C group. There were two deaths in the P group and zero in the C group. [Conclusions] In the P group, the PSL dosage after 6 months was lower than that in the C group, and the number of days of hospital stay tended to be lower.

#### W45-1

##### **Risk of adrenal insufficiency in patients with polymyalgia rheumatica**

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Conflict of interest: None

[Objective] To determine whether patients with polymyalgia rheumatica (PMR) are more susceptible to glucocorticoid-induced adrenal insufficiency compared to patients with rheumatoid arthritis (RA). [Methods] This cross-sectional study included PMR and RA patients who underwent adrenocorticotrophic hormone (ACTH) tests to assess adrenal function. The eligibility criteria were as follows: previous use of prednisolone (PSL)  $\geq 5$  mg/day, use of PSL for 6 consecutive months before ACTH test, and current use of PSL at 5 mg/day or less. The association between disease type (PMR vs. RA) and insufficient adrenal response was assessed using logistic regression models. [Results] Twenty-six of 34 (76.5%) patients with PMR and 13 of 37 (35.1%) patients with RA had insufficient adrenal response. Compared to patients with RA, patients with PMR were more likely to have insufficient adrenal response, even after adjusting for age, sex, and PSL dose (adjusted odds ratio, 6.75; 95% confidence interval, 1.78-25.60). [Conclusions] Patients with PMR have a higher risk of glucocorticoid-induced adrenal insufficiency than patients with RA. Assessing the adrenal function in patients with PMR will contribute to establishing a more appropriate glucocorticoid reduction strategy.

## W45-2

### Association of pathological findings and EB virus in the development and spontaneous regression of methotrexate-associated lymphoproliferative disorder in patients with rheumatoid arthritis

Noboru Kitamura, Yosuke Nagasawa, Kaita Sugiyama, Masako Tsukamoto, Hiroshi Tsuzuki, Shoji Yoshizawa, Marina Hamaguchi, Yutaka Tanikawa, Masahiro Nishihara, Shinya Asatani, Kumiko Akiya, Hitomi Haraoka, Masami Takei, Hideki Nakamura  
Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine

Conflict of interest: Yes

[Objective] Although the involvement of EBV and pathological difference in the development and spontaneous regression of MTX-LPD has been suggested, the underlying mechanism remains unknown. In this study, we analysed patients who had developed MTX-LPD to evaluate the association between the spontaneous regression of MTX-LPD with pathological difference and EBV. [Methods] We analysed the age, stage, disease activity, MTX doses, lymphocyte counts, EBV RNA, EBER and pathological findings in patients with MTX-LPD at our hospital. Moreover, we investigated the factors related to spontaneous regression, which is a characteristic of MTX-LPD. [Results] Thirty-four patients were enrolled in the study. Histologically, DLBCL was the most common in 16 cases. The MTX dose at onset was 8.3 mg/week, and the total dose was 1530.3 mg. The EBV load in peripheral blood was 270.4 copy/ $\mu$ L, and 50% patients were EBER-positive in pathological tissues. Twenty-one patients had spontaneous regression after MTX discontinuation. EBV RNA in the peripheral blood, EBER in pathological tissues, improvement rate of lymphocyte count and Hodgkin lymphoma were considered significant factors related to spontaneous regression. [Conclusion] EBV may be involved in the development of MTX-LPD and its spontaneous regression.

## W45-3

### Pathology and clinical background of rheumatoid arthritis-related lymphoproliferative diseases

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Conflict of interest: None

[Objective] The pathogenesis of rheumatoid arthritis (RA)-related lymphoproliferative disease (LPD) is suggested to involve RA immunological abnormalities in addition to methotrexate (MTX) use. We investigated clinical features of RA according to pathological classification. [Methods] We retrospectively researched 56 patients who were treated in our hospital between 2016 and 2021 for pathologically diagnosed RA-LPD. The evaluation factors covered the history of MTX use, diagnosis date of RA and LPD, rheumatoid factor (RF), and histopathological type. [Results] The pathological diagnosis of the 56 patients were; 35 malignant lymphoma (ML), 13 lymphoid dysplasia, and 8 lymphoid hyperplasia. MTX non-users were included in 2 cases (5.7%) of ML and 1 case (7.6%) of dysplasia. The RF positivity rate was significantly higher in the ML group than the dysplasia or the hyperplasia group (80% vs 38% vs 42%;  $p=0.01$ ). RF titer was also higher in ML than other groups (mean 304 IU/mL [SD 774] vs 122 [94] vs 25 [23];  $p=0.01$ ). These findings suggested the association between RA immunological abnormalities and pathological patterns. [Conclusions] Among RA-LPD, malignant lymphoma has higher RF positivity and titer, suggesting a relationship between ML and RA immunological abnormalities.

## W45-4

### Risk factors for idiopathic femoral head necrosis in systemic lupus erythematosus

Takeshi Kuroda<sup>1,4</sup>, Mihoko Yamazaki<sup>2</sup>, Yukiko Nozawa<sup>3</sup>, Yoichi Kurosawa<sup>4</sup>, Eriko Hasegawa<sup>4</sup>, Ayako Wakamatsu<sup>4</sup>, Hiroe Sato<sup>1,4</sup>, Daisuke Kobayashi<sup>4</sup>, Takeshi Nakatsue<sup>4</sup>, Yoko Wada<sup>5</sup>, Masaaki Nakano<sup>6</sup>, Ichiei Narita<sup>4</sup>

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Conflict of interest: None

[Objective] The purpose of this study was to clarify the factors related to idiopathic osteonecrosis of the femoral head (ION) in patients with SLE. [Methods] 132 patients with SLE were selected on the basis of having been newly diagnosed and requiring high-dose prednisolone, including pulse therapy, as the initial treatment. All the patients initially underwent MRI at 3 months after the start of corticosteroid treatment to detect any early changes in the femoral head. These examinations were then performed again 3 months later. Laboratory parameters were evaluated at the start of steroid treatment and at 1 month thereafter. [Results] By 3 months after the start of corticosteroid treatment, ION was diagnosed by MRI in 33 patients (25.0%). Ten patients were diagnosed as unilateral and 23 patients were bilateral. SLEDAI was not related to the frequency of ION. Patients with a higher triglyceride (TG) level showed a significantly higher frequency of ION both before ( $p=0.004$ ) and 4 weeks after ( $p=0.003$ ) steroid initiation. In addition, patients with a higher total cholesterol (TC) level before steroid treatment showed a significantly higher frequency of ION ( $p=0.03$ ). [Conclusions] Both of high TG and high TC levels are important risk factors for ION in patients with SLE.

## W45-5

### Study of the risk of steroid-Induced osteonecrosis in patients with systemic lupus erythematosus

Toshiaki Kobayashi, Hiroyuki Yamashita, Shintaro Aozaki, Ryo Kuwata, Takuya Harada, Satsuki Yasui, Misa Yamaji, Atsubumi Ogawa, Hidenori Sakai, Kyoko Motomura, Yuko Takahashi, Hiroshi Kaneko  
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Conflict of interest: None

[Object] We define the risk factors of steroid-induced osteonecrosis (aseptic necrosis; AN) for patients with systemic lupus erythematosus (SLE) in terms of steroid dosage. [Methods] SLE patients who received steroid pulse therapy or prednisolone  $\geq 50$  mg (or 1 mg/kg/day from October 2006 to September 2021) were retrospectively evaluated. [Results] AN developed in 17 of 78 SLE patients. The total observation period was 332.8 years, thus, 5.11/100 person-years. Eleven (64.7%) cases occurred within 2 years and 15 (88.2%) cases occurred within 5 years. Significantly more AN occurred in patients who received pulse therapy with a total methylprednisolone dose of 1500 mg or more ( $p<0.01$ ). The cumulative steroid dose, excluding pulse therapy, was higher in the AN group at 30 days ( $p=0.028$ ), 60 days (the following four are all  $p<0.01$ ), 90 days, 180 days, and 360 days. The cumulative amount per body weight at the onset was significantly higher at 30 days ( $p<0.01$ ). After 1 year, the steroid dose was  $9.78\pm 2.77$  mg vs  $7.63\pm 2.44$  mg, which was higher in the AN group ( $p=0.01$ ), though the initial dose was  $55.3\pm 12.8$  mg vs  $51.8\pm 10.1$  mg, which was not significantly different ( $p=0.44$ ). [Conclusion] Osteonecrosis in SLE may be a risk factor not only for pulse therapy but also for high steroid doses early in treatment.

## W45-6

### One-month hospitalization for induction therapy is highly associated with sarcopenia in patients with connective tissue disease

Hironari Hanaoka, Jun Kikuchi, Sho Ishigaki, Kazuoto Hiramoto, Yasushi Kondo, Shuntaro Saito, Yuko Kaneko  
Keio University School of Medicine

Conflict of interest: None

[Objective] To investigate the clinical characteristics of patients with connective tissue disease who developed sarcopenia during 1-month hospitalization for induction therapy. [Methods] We examined patients who were hospitalized for induction therapy from 2020 to 2021 and selected those available for skeletal mass indexes (SMI) by using dual energy X-ray absorptiometry at before and after increasing dose of glucocorticoid (GC). We divided them into 2 groups according to diagnosis of sarcopenia



after increasing dose of GC and compared baseline clinical characteristics. Multivariate analysis conducted to identify the independent factor associated with sarcopenia. [Results] Forty-five patients were enrolled. Mean observational period was 29.4±12.7 days and 40 (88.9%) patients were diagnosed with sarcopenia. At baseline, patients with sarcopenia had a lower body mass index ( $p=0.001$ ) and SMI ( $p<0.001$ ). A significant lower number of lymphocytes ( $p=0.015$ ) and higher incidence of infection were observed in patients with sarcopenia ( $p=0.049$ ). Multivariate analysis revealed SMI at baseline ( $p=0.021$ ) was associated with sarcopenia. [Conclusions] One-month hospitalization with induction therapy was highly associated with sarcopenia in patients with connective tissue disease

## W46-1

### Treatment of knee arthritis in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Background] Knee arthritis is one of the most common RA joint disorders and has a strong effect on ADL. The knee joint, which is a large joint, has a large amount of target synovial tissue and cytokines and is exposed to load, but there is no report that any treatment is effective. [Method] From October 2010 to August 2020, patients who were enrolled in the KURAMA cohort and exhibited knee joint symptoms, were included. The subjects were 1612 cases for whom clinical data were available one year later. [Results] The mean DAS28 (ESR), CDAI, SDAI, ESR, CRP, and MMP3 at baseline were 4.24, 15.0, 16.6, 34.3 mm/h, 1.47 mg/dl, 204.9 ng/ml. The usage rates of MTX, glucocorticoids and b/tsDMARDs at baseline were 65.6%, 41.4% and 42.1%, respectively. One year later, knee symptom disappeared in 1131 patients (70.1%). Multivariate analysis showed a predominant correlation between the disappearance of symptoms after 1 year and following treatment; new introduction of b/tsDMARDs, changes in b/tsDMARDs and the use of IL6 inhibitors at 1 year. Glucocorticoid use was correlated with residual knee joint symptoms. [Conclusion] Introduction and change of b/tsDMARDs was effective for improving knee joint symptoms, and the use of IL6 inhibitors was particularly effective.

## W46-2

### Short-spacing or increase dosage of Biologics for rheumatoid arthritis patients with subclinical synovitis suppress joint destruction - STARBOARD study-

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Conflict of interest: None

[Objective] The residual synovitis even after bDMARDs treatment for rheumatoid arthritis (RA) may induce joint destruction. The enhanced treatment (ET) such as short-spacing or dosage increase of bDMARDs are recommended to such patients, if applicable. We investigated the course of ET. [Methods] We examined hand and foot joints of 40 RA patients treated with standard dose of infliximab, tocilizumab, or golimumab by ultrasound (US). Patients with residual synovitis, Power Doppler score (PD)  $>2$ , were asked to enhance treatment (PD+/ET+). Patients without ET even with residual synovitis (PD+/ET-) or those without synovitis (PD-) continued current treatment. We investigated PD, SDAI, CRP, MMP-3 and mTSS at ET (baseline) and 1 year after that. Their changes were investigated between each group. [Results] Nine PD+/ET+ patients had significantly higher SDAI, MMP-3, and PD than 31 PD- patients at baseline, but their MMP-3 ( $p=0.019$ ) and PD ( $p=0.042$ ) were significantly decreased during 1 year. PD+/ET+ patients had joint destruction before ET ( $p=0.022$ ), but it was suppressed after ET ( $p>0.99$ ), similarly to PD- patients. [Con-

clusion] Enhanced treatment for the residual synovitis even after bDMARDs decrease the synovitis and suppress the joint destruction in RA patients.

## W46-3

### Comparison of efficacy between Sarilumab and TNF inhibitors in rheumatoid arthritis patients with large joint symptoms

Kazuya Kishimoto<sup>1</sup>, Hirotaka Yamazawa<sup>1</sup>, Kaori Ishimura<sup>1</sup>, Chisato Ashida<sup>1</sup>, Hiroki Akazawa<sup>1</sup>, Atsuhiko Yamamoto<sup>3</sup>, Fusayo Ikeda<sup>2</sup>, Akinori Okada<sup>1</sup>, Daisuke Tomita<sup>1</sup>, Tetsu Itami<sup>1</sup>, Toshihiko Shiga<sup>1</sup>, Yuji Nozaki<sup>1</sup>, Koji Kinoshita<sup>1</sup>, Itaru Matsumura<sup>1</sup>

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Conflict of interest: None

[Objective] Knee joint symptoms have been reported to be associated with the severity of RA. In this study, we investigated the efficacy of IL-6 inhibitors and TNF inhibitors (TNFi) in treating large joint symptoms using joint echocardiography. [Methods] We compared the efficacy of 24 patients who received sarilumab (SAR) and 86 patients who received TNFi on large joint symptoms using the EULAR-OMERACT Combined Score. [Results] There were no significant differences in age, disease duration, or disease activity between the TNFi and SAR groups. The rate of concomitant MTX use was 79.1% in the TNFi group and 58.3% in the SAR group, and there were no significant differences in dosage. The change from baseline in CDAI was -14.0 and -20.4 ( $p=0.038$ ) at 24 weeks and -13.6 and -18.9 ( $p=0.114$ ) at 52 weeks in TNF and SAR groups, respectively. The change from baseline in Combined Score in the right knee was -0.15 and -0.28 ( $p=0.029$ ) at 24 weeks, -0.20 and -0.45 ( $p<0.001$ ) at 52 weeks, the change in the left knee was -0.13 and -0.18 ( $p=0.125$ ) at 24 weeks, and -0.21 and -0.35 ( $p=0.016$ ) at 52 weeks in the TNF and SAR groups, respectively. [Conclusion] The SAR group is expected to be more effective than the TNFi group, especially for cases with knee joint symptoms.

## W46-4

### Status of use of bDMARDs for rheumatoid arthritis in our hospital: From the NOSRAD registry

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Conflict of interest: None

[Objective] To examine the status of use of bDMARDs for rheumatoid arthritis in our hospital with using the NOSRAD registry. [Methods] 1008 patients of rheumatoid arthritis who introduced bDMARDs before August 2019 were included in this study. The examination items consist of Cumulative survival rate of Kaplan-Meier method. [Results] The average age at the start of administration were 70.1±10.7 years old (Abatacept), 55.4±14.3 years old (Adalimumab), 57.9±13.4 years old (Certolizumab pegol), 56.1±15.2 years old (Etanercept), 66.4±13.0 years old (Golimumab), 53.1±15.2 years old (Infliximab), 64.7±15.3 years old (Sarilumab) and 57.4±15.9 (Tocilizumab). Survival rate of whole cases in Tocilizumab was significantly higher than these cases in other bDMARDs without Sarilumab. [Conclusions] Survival rate of whole cases in Tocilizumab was significantly higher than these cases in other bDMARDs without Sarilumab.

## W46-5

### Effect of Sarilumab on inhibiting joint destruction in clinical practice for rheumatoid arthritis

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Conflict of interest: None

[Objective] With the advent of biologics, disease activity in patients with rheumatoid arthritis (RA) can be controlled. In this study, we investigated the effect of Sarilumab (SAR) on inhibiting joint destruction (JD) in clinical practice. [Methods] Of the 66 patients who were introduced to SAR, 19 patients who continued treatment for over 52 weeks and had evaluable radiographs were included in this study. JD was performed using modified total sharp score (mTSS), and the radiographic non-progression rate (mTSS  $\leq$  0.5) was determined. RA patients were also divided into with or without methotrexate (MTX) groups. [Results] At the beginning of treatment, Erosion score (ES) was 8.0, Joint space narrowing score (JSNS) was 22.0, median Total score (TS) was 27.0. The mean changes at 52 weeks were -0.03 for ES, -0.08 for JSNS, and -0.1 for TS, indicating no progression of JD. The radiographic non-progression rate was 89.4%. There was no significant difference in mTSS between with and without MTX. [Conclusions] The mTSS change was less than 0 and the radiographic non-progression rate was 89.4%. The effect of SAR on inhibiting JD was observed in clinical practice. SAR was also shown to inhibit JD in patients without MTX. This effect of SAR was indicated in both with and without MTX.

## W46-6

### The significance of decreasing cfDNA levels with tocilizumab therapy in rheumatoid arthritis

Tepei Hashimoto<sup>1</sup>, Yuichi Yokoyama<sup>2</sup>, Kohsuke Yoshida<sup>3</sup>, Takahiro Yoshikawa<sup>1</sup>, Tetsuya Furukawa<sup>1</sup>, Naoto Azuma<sup>1</sup>, Akira Hashiramoto<sup>3</sup>, Kiyoshi Matsui<sup>1</sup>

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Conflict of interest: None

[Objective] Endogenous DNA is released into the blood circulation as cell-free DNA (cfDNA) following cell death. We have previously reported that cfDNA in plasma and synovial fluid are increased in RA, and cfDNA released from synovial cells are suppressed with tocilizumab (TCZ) treatment *in vitro*. In addition, cfDNA induces joint inflammation via TLR9 pathways *in vivo*. This study aimed to evaluate the significance of cfDNA in RA treated with TCZ and TNF-I. [Methods] We enrolled 126 patients with RA who initiated treatment with bDMARDs, including 72 with TCZ and 54 with TNF-I. Plasma cfDNA levels were measured at baseline, week 4, and week 12 using qPCR assays. Disease activity was also evaluated at the same timepoint, using DAS28ESR. [Results] DAS28ESR at baseline was not different between those who received TCZ and TNF-I, and it was significantly improved in both biological groups at week 12. However, cfDNA levels in plasma were significantly decreased with TCZ at week 12, but not with TNF-I. In particular, in the biological treatment-naïve patients with TCZ at week 12, cfDNA levels were significantly lower in patients with DAS28ESR remission than those in others and correlated with the DAS28ESR. [Conclusions] TCZ may suppress inflammation via the TLR9 pathway by decreasing cfDNA.

## W47-1

### Differences in clinical features associated with vitamin D deficiency between patients with systemic lupus erythematosus and rheumatoid arthritis

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Conflict of interest: None

[Objective] This study was aimed to clarify the differences in factors related with the vitamin D levels between patients with SLE and RA. [Methods] Patients who were diagnosed as having SLE or RA and measured serum 25 (OH)D levels during October 2020 and September 2021 were reviewed. Spearman's rank correlation coefficient was used to analyze the correlation between the 25 (OH)D and the other variables. [Results] A total of 37 patients (18 SLE and 19 RA) were registered. The median age and disease duration were 50.0 (interquartile range (IQR) 35.5 - 70.0) yrs and 5.0 (IQR 2.0 -13.5) yrs, respectively. Thirty out of the pa-

tients (81.1%) met the definition of vitamin D deficiency (<20 ng/mL). The median 25 (OH)D levels were comparable between the two groups (SLE vs. RA: 13.9 ng/mL vs. 14.6 ng/mL,  $p=0.76$ ). 25 (OH)D levels showed an inverse correlation with age ( $r_s=-0.27$ ), disease duration ( $r_s=-0.41$ ), prednisolone dose ( $r_s=-0.10$ ) in patients with SLE, whereas a positive correlation with them ( $r_s=0.42, 0.38, 0.09$ ) in those with RA. [Conclusions] Our results revealed patients with SLE tend to develop vitamin D deficiency in association with younger age and short disease duration regardless of dosage of glucocorticoids unlike RA.

## W47-2

### Clinical features of patients with anti-SS-A antibody-positive systemic lupus erythematosus patients

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Division of Rheumatic Diseases, National Center for Global Health and Medicine, Tokyo, Japan

Conflict of interest: None

[Objective] We investigated the clinical features of patients with systemic lupus erythematosus (SLE) with and without anti-SS-A antibody (aSS-A Ab). [Methods] We compared 118 patients who newly developed SLE in our department between 1999 and 2019 retrospectively. First, we compared patients with and without aSS-A Ab. Patients were then divided into 4 groups according to the positivity of aSS-A Ab (termed SS-A+ and SS-A-) and the positivity of at least one of anti-dsDNA, anti-Sm, or anti-RNP antibodies (termed other Ab+ and other Ab-); 1) SS-A+/other Ab- (N=12), 2) SS-A+/other Ab+ (N=55), 3) SS-A-/other Ab+ (N=44), and 4) SS-A-/other Ab- (N=7). [Results] The patients with aSS-A Ab tended more likely to be female ( $p=0.17$ ) and have arthralgia ( $p=0.12$ ), while the rate of hematuria and pleural effusion tended to be lower ( $p=0.08$  and  $p=0.13$  respectively). The rate of hematuria in 2) tended to be lower than in 3) ( $p=0.24$ ). [Conclusions] SLE patients with aSS-A Ab tended to be female and have arthralgia more likely, and have hematuria and pleural effusion less frequently than those without aSS-A Ab. In the group of patients positive for one or more of anti-dsDNA, anti-Sm, and anti-RNP antibodies, hematuria tended to be less frequent in the aSS-A Ab-positive group than in negative.

## W47-3

### Association between anti-RNP antibodies and history of preterm birth in patients with systemic lupus erythematosus (SLE): a cross-sectional study using the LUNA registry

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Conflict of interest: None

[Objective] We hypothesized that the presence or absence of anti-RNP antibodies would affect the history of preterm birth in SLE patients. [Methods] This was a cross-sectional study using patient data from the multicenter SLE registry (LUNA registry) and included women with a history of childbirth and no history of miscarriage. The primary outcome was the presence or absence of preterm birth. [Results] Of the total population of 1541 patients, 254 patients were included in the analysis. Anti-RNP antibodies were positive in 123 patients (48.43%), lupus anticoagulant positive in 54 patients (21.25%), anticardiolipin  $\beta$ 2GPI antibodies positive in 33 patients (12.99%), and anti-SS-A antibodies positive in 158 patients (62.21%). The median first gestational age was 27 (IQR 24-30), 69 patients (27.17%) had a history of preterm labor, and 85 patients (34.56%) had a history of nephritis. In multivariate analysis adjusted for antiphospholipid antibodies, anti-SS-A antibodies, first gestational age, and history of nephritis, anti-RNP antibodies was not associated with the presence or absence of a history of preterm birth. [Conclusions] In the LUNA cohort, anti-RNP antibodies was not associated with a history of preterm birth in SLE patients.

#### W47-4

##### Clinical Features of Systemic Lupus Erythematosus with Persisted Hypocomplementemia

Takuya Harada<sup>1</sup>, Hiroyuki Yamashita<sup>1</sup>, Sotaro Nakajima<sup>2</sup>, Shintaro Aozaki<sup>1</sup>, Ryo Kuwata<sup>1</sup>, Satsuki Yasui<sup>1</sup>, Misa Yamaji<sup>1</sup>, Atsubumi Ogawa<sup>1</sup>, Hidenori Sakai<sup>1</sup>, Toshiaki Kobayashi<sup>1</sup>, Kyoko Motomura<sup>1</sup>, Yuko Takahashi<sup>1</sup>, Hiroshi Kaneko<sup>1</sup>

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Conflict of interest: None

[Objective] We investigated the clinical and immunological differences between patients with normalization of hypocomplementemia after treatment and those with persistent hypocomplementemia in systemic lupus erythematosus (SLE). [Methods] We collected data on patients with low C3 ( $<73$  mg/dL) or low C4 ( $<11$  mg/dL) at the time of diagnosis of SLE between 2010 and 2019, and compared those whose hypocomplementemia normalized after treatment with those whose hypocomplementemia persisted. [Results] Hypocomplementemia normalized in 49 patients and persisted in 18 patients. Consistently, there were no significant differences in organ damage, therapeutic agents, anti-dsDNA antibody titers, or disease activity. In the persisted group, significantly more patients were positive for either anti-SS-A or anti-phospholipid antibodies than in the normalized group ( $p=0.039$ ). In anti-SS-A antibody positive patients, the count of lymphocytes after treatment was significantly lower in the persisted group. More antiphospholipid antibody-positive patients in the persisted group required antithrombotic therapy. [Conclusions] Patients with persisted hypocomplementemia in SLE may have anti-SS-A or antiphospholipid antibodies and ongoing immune abnormalities caused by these antibodies.

#### W47-5

##### The association of hypocomplementemia and infectious disease complication in systemic lupus erythematosus: a retrospective observational study of the LUNA registry

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Conflict of interest: None

[Objective] To analyze the association between hypocomplementemia and infectious disease complications in SLE. [Methods] The patients registered in the multicenter SLE registry "LUNA" were divided into two groups by the lower limit of standard CH50 value. We compared the incidence of infection requiring hospitalization during the one year. [Results] Of the 628 registered patients, 60 (9.6%) belonged to the low CH50 group. The low CH50 group showed significantly lower age ( $39.3 \pm 12.1$  vs  $46.1 \pm 14.5$ ,  $p < 0.01$ ), higher disease activity (SLEDAI score; 6 (IQR 4-10) vs 4 (1-6),  $p < 0.01$ ), higher dosage of glucocorticoid ( $7.1 \pm 5.8$  mg vs  $5.2 \pm 3.6$  mg,  $p = 0.01$ ) and higher usage rate of tacrolimus (53.1% vs 50.0%,  $p = 0.03$ ) as compared to the non-low CH50 group. There were no significant differences in the usage of other immunosuppressants between the two groups. However there was no significant difference between the two groups, the rate of incidence of infection requiring hospitalization in the past year in the low CH50 group was tend to be higher than the non-low CH50 group (8.8% vs 2.7%,  $p = 0.09$ ). [Conclusions] We could not find an association between complement and infectious disease complications in SLE. We plan to analyze with larger sample size and longer observation in the future.

#### W47-6

##### Characteristics and pathological analysis of patients with SLE who underwent cardiac surgery in our hospital

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Conflict of interest: None

[Objective] The purpose of this study was to know the pathological tissue and clinical features of heart disease associated with SLE. [Methods] Thirty patients who underwent cardiac surgery among inpatients diagnosed with SLE from 2012 to 2018 at our hospital were included. Paraffin sections were prepared for patients who had undergone left atrial appendage resection during surgery, and immunohistochemical staining was performed using anti-human IgG, IgM, C3 and anti-neutrophil elastase antibodies, compared with histology of non-collagenous disease group investigated. [Results] Antiphospholipid antibodies were positive in 12 cases, SS-A antibodies were positive in 12 cases, and RNP antibodies were positive in 8 cases, suggesting that these autoantibodies are associated with heart disease. The left atrial appendage is stained in the myocardial tissue, and in the pathological tissue, the SLE is more dominant in the group with SLE than in the control group, and the immune complex deposition in the muscle tissue is related to the onset mechanism. We also validate another mechanism which are related to NET formation in dramatic onset. [Conclusions] The possibility of the onset of immune complex deposition in muscle tissue may be the cause of heart disease in SLE patients.

#### W48-1

##### Significance of Hydroxychloroquine for SLE achieved LLDAS

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Conflict of interest: None

[Objective] The purpose of this study was to determine the value of additional HCQ administration in SLE patients with sustained LLDAS. [Methods] The effect of HCQ was assessed before and 3 months after HCQ administration. Disease activity was measured by SLEDAI. Serum cytokines, adipokines, and S100A8 and S100A9, which are known to reflect disease activity, were measured. [Results] SLEDAI and serum anti-dsDNA antibodies were further significantly reduced. Among cytokines, TNF- $\alpha$ , IL-6, MCP-1, IL-1ra, VEGF-A, S100A8, S100A9, leptin, and resistin were significantly decreased, and serum adiponectin was significantly increased. (TNF- $\alpha$ , IL-6, MCP-1, VEGF-A, leptin:  $p < 0.05$ . IL-1ra, S100A8, S100A9, adiponectin, resistin:  $p < 0.0001$ ). Decreases in S100A8 S100A9, VEGF-A and MIP-1a were greater in cases with positive or elevated anti-dsDNA antibodies (S100A8, S100A9, VEGF-A, MIP-1a:  $p < 0.05$ ). [Conclusions] In SLE patients who maintained LLDAS achievement, additional HCQ administration further improved disease activity and activity-related cytokines. In addition, beneficial effects on atherosclerosis-related adipokines was observed, suggesting that additional HCQ should be considered even in SLE patients with sustained LLDAS.

## W48-2

### Association of hydroxychloroquine treatment and 3-year renal function change in patients with SLE: a longitudinal observational cohort study

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Conflict of interest: None

[Objective] To confirm the renoprotective effects of hydroxychloroquine (HCQ) in Japanese SLE patients using the LUNA registry. [Methods] Longitudinal observational cohort study. 162 SLE patients, who and whose serum creatinine levels (Cr) were registered annually from 2016 until 2019, and whose eGFR in 2016 was 60 and more and less than 120, were analyzed. HCQ (+) was defined as patients treated with HCQ at least 3 out of 4 years, and the others were defined as HCQ (-). [Results] HCQ (+) 24 patients (biopsy-proven LN 4 patients)/HCQ (-) 138 patients (biopsy-proven LN 33 patients). No difference was seen between HCQ (+) and HCQ (-) in 2016 background: age  $39.8 \pm 10.0/43.9 \pm 13.2$  y.o., female rate  $95.8/89.9\%$ , disease duration  $10.3 \pm 7.2/12.2 \pm 8.8$  years, SLEDAI  $5.3 \pm 3.5/5.0 \pm 5.5$  and anti-ds DNA  $15.5 \pm 19.5$  EU/mL/ $19.1 \pm 38.0$  EU/mL. In 2016 registration, HCQ (+) was treated more prednisolone than HCQ (-), but no difference in percent of patients treated with tacrolimus. eGFR in 2016 were not significantly different ( $83.5 \pm 12.7/85.4 \pm 15.2$ ). The patient number with eGFR  $< 60$  in 2019 were HCQ (+) 2 patients and HCQ (-) 10 pa-

tients ( $p = 0.69$ ), and delta eGFR generated by subtraction of 2019 eGFR from 2016 eGFR were  $4.5 \pm 14.1/5.1 \pm 11.2$  ( $p = 0.79$ ) [Conclusions] Renoprotective effects of HCQ were not confirmed in this study.

## W48-3

### Efficacy and Safety of Calcineurin Inhibitors for Active Lupus Nephritis

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Conflict of interest: None

[Objective] The efficacy of calcineurin inhibitors (CNIs) as induction therapy for lupus nephritis (LN) of ISN/RPS Class III, IV, or V has been clarified. On the other hand, thrombotic microangiopathy (TMA) and nephrotoxicity due to CNI have been reported, and the appropriate administration method of CNI in patients with LN is not clear. [Methods] From August 2012 to July 2021, renal biopsies were evaluated in 48 patients and diagnosed as having lupus nephritis in ISN/RPS classes III, IV, or V. We analyzed them retrospectively, dividing them into 21 patients who received CNI and 27 who did not. [Results] There were no significant differences in remission achievement rate, steroid dose, or incidence of adverse events at 6 and 24 months. There was no case which contracted TMA. In 10 patients, CNI was replaced with other immunosuppressants, but nephritis did not recur. There were 11 cases of single agent use and 10 cases of use in combination with MMF, and there was a significant pathological poor prognosis factor in the use group in combination with MMF, but there was no significant difference in complete remission achievement rate and adverse event rate. [Conclusions] CNI may be considered to be administered without MMF to patients with LN without pathological poor prognosis factors.

## W48-4

### Long-term outcomes and risk factors for relapse in lupus nephritis patients treated with combination therapy of tacrolimus and mycophenolate mofetil

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Conflict of interest: Yes

[Objective] We retrospectively analyzed the long-term outcomes and risk factors for relapse in lupus nephritis (LN) patients treated with combination therapy (Multi) of tacrolimus and MMF. [Methods] All 27 active LN patients treated with Multi between Oct. 2009 and Nov. 2018 in our department were examined. Data are expressed as median (IQR). [Results] The age was 38 (30-45) years. Nine patients were treated for new-onset LN, whereas 18 patients were treated for LN relapse. The urinary protein/creatinine ratio and eGFR before treatment were  $4.2$  ( $2.2-6.0$ ) g/gCr and eGFR  $62.6$  ( $45.1-89.0$ ) mL/min/ $1.73$  m<sup>2</sup>, respectively. The observation duration was 94 (63-111.5) months. Histological classes were III in 1, III+V in 4, IV in 12, IV+V in 9, and V in 1, according to the ISN/RPS 2003 classification. After 3 (2-6) months of treatment, 26 patients (96%) achieved complete remission (CR), but 16 patients (62%) relapsed at 32 (13.8-64.5) months after CR achievement. The Kaplan-Meier analysis showed early relapse was associated with chronic lesions in renal biopsy and normal or higher C4 levels at treatment initiation (Log-rank,  $P = 0.006$ ,  $P < 0.001$ , respectively). [Conclusions] Multi was effective in inducing CR for LN. Chronic lesions and normal or higher C4 levels were associated with early relapse.

## W48-5

### Efficacy and Safety of Cyclophosphamide-Tacrolimus Combination Therapy for Lupus Nephritis

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Conflict of interest: None

[Objective] To evaluate the efficacy and safety of pulsed cyclophosphamide (pCYC) and tacrolimus (TAC) for lupus nephritis (LN). [Methods] We retrospectively studied patients treated with pCYC or mycophenolate mofetil (MMF) in addition to prednisolone (PSL) escalation as remission induction following for at least 6 months (M). Complete remission (CR) was defined as a urine protein/creatinine (Cr) ratio of less than 0.5 g/gCr, normalization of serum Cr (sCr), or an increase in sCr within 10% of the pretreatment value, and no further PSL escalation. [Results] 100 cases were in the following groups: 1) pCYC (41), 2) pCYC+TAC (29), and 3) MMF (30, including with TAC). Age, 40 (30-49) years; male: female, 15:85; disease duration, 4.4 (0.5-126.4) M; sCr, 0.77 (0.63-1.07) mg/dl; proteinuria, 2.68 (1.2-5.5) g/gCr. Histology, III 24 (mixed 7); IV, 66 (mixed 22); V, 3; unknown, 7; chronic lesion, 42; the initial PSL, 0.98 (0.87-1.05) mg/kg. At 6 and 12 M, CR were 1) 48.8%, 51.2%, 2) 72.4%, 86.2%, and 3) 56.7%, 60.0%, respectively ( $p=0.006$  at 12 M). One death in 2), but there was no significant difference in serious adverse events. [Conclusions] pCYC+TAC for LN showed high CR rate and tolerability, suggesting the advantage of early TAC use and can be effective in refractory/relapse cases of MMF.

## W48-6

### Efficacy and safety of switching immunosuppressive drugs in patients with systemic lupus erythematosus

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Conflict of interest: None

[Object] This study aimed to clarify the outcomes after switching immunosuppressive drugs in systemic lupus erythematosus (SLE) and to evaluate the usefulness of changing the mode of action. [Methods] The subjects of this study were 39 SLE patients (age  $41.5 \pm 12.6$  years, 35 females) who underwent an immunosuppressive drug switch from January 2016 to September 2020. We assessed reasons for the change, drug continuation rate, treatment failure-free survival, disease flare requiring an increased prednisolone dose or addition of immunosuppressive drugs, and adverse events. We compared the outcomes between the cycling group and the switching group. [Results] The immunosuppressive drugs before the switching were 22 antimetabolites and 17 calcineurin inhibitors. 27 and 12 patients received drugs with similar and another mode of action, respectively. The reasons for the change were inadequate efficacy in 20 cases, adverse events in 14, and others in 5. The treatment failure-free survival tended to be higher in the cycling group than the switching group, although the other outcomes showed no clear differences between the two groups. [Conclusions] Continuation of the drugs with similar and another mode of action may be effective in changing immunosuppressive drugs in SLE.

## W49-1

### Diagnosis of Depression Complicated by Rheumatoid Arthritis: A Study of the Validity of a Psychiatrist's Diagnosis and Questionnaire Method

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Conflict of interest: Yes

[Objective] About 15% of patients with RA have depression, and most of these studies have used questionnaire methods. Most of the studies have used questionnaires for depression, and because the questionnaire includes questions about physical symptoms. We examined the validity of depression diagnosis by questionnaire method. [Methods] 49 outpatients with RA who consented to the study. Age, gender, type of DMARDs, PSL use, CRP and SDAI were investigated. The PHQ-9 and CES-D were used as questionnaires; a score of 10 or more on the PHQ-9 and 16 or more on the CES-D was considered a cutoff. The psychiatrist was blinded to the results of the questionnaire and conducted a structured interview. The diagnosis made by the psychiatrist was defined as the Gold Standard and was compared with the PHQ-9 and CES-D. [Results] Psychiatrist's diagnosis was abnormal in 9 patients. The PHQ-9 had a specificity of 3%, a sensitivity of 43%, a PPV of 7%, and a NPV of 20%; the CES-D had a specificity of 18%, a sensitivity of 100%, a PPV of 18%, and a NPV of 100%. [Conclusions] The specificity and sensitivity of the PHQ-9 were low, and the sensitivity of the CES-D was relatively high, but the specificity and PPV were not high, which was considered to be a limitation of the questionnaire method.

## W49-2

### Cytokine-profile in Hemophagocytic lymphohistiocytosis in adult-onset Still's disease and SLE

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Conflict of interest: None

[Objective] To determine whether the cytokine profile differs between hemophagocytic lymphohistiocytosis (HLH) in adult-onset Still's disease (AOSD) patients and HLH in SLE patients. [Methods] Pre-treatment sera were collected from 12 AOSD-HLH patients, 10 SLE-HLH patients, 16 AOSD patients without HLH, and 22 SLE patients without HLH. Cytokine levels in the serum were measured using a multiplex assay (Luminex). [Results] The serum levels of IL-1, IL-6, IL-8, IL-18, TNF- $\alpha$ , and IP-10 were increased in AOSD compared with the control group, and the levels of IL-6, IL-8, IL-10, IL-18, TNF- $\alpha$ , and IP-10 were increased in SLE. Comparing the cytokine levels of AOSD-HLH and SLE-HLH, the levels of IL-6 (AOSD: 55, SLE: 11 ng/ml) and IL-18 (AOSD: 10722, SLE: 1155 ng/ml) were increased in AOSD, and IFN- $\alpha$  (AOSD: 0.0, SLE: 4.6 ng/ml) and TNF- $\alpha$  (AOSD: 23, SLE: 37 ng/ml) levels were elevated. Furthermore, in AOSD, the levels of IP-10 and TNF- $\alpha$  were higher in HLH than in non-HLH; in SLE, serum IFN- $\alpha$  and IP-10 were elevated in HLH patients. [Conclusions] Cytokine profiles differed between AOSD-HLH and SLE-HLH, with IL-6 and IL-18 being important cytokines in AOSD-HLH, and IFN- $\alpha$  playing an important role in SLE-HLH.

## W49-3

### Clinical features and efficacy of Upfront Combination Therapy in pulmonary arterial hypertension associated with connective tissue disease

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Conflict of interest: None

[Objective] To clarify the efficacy of Upfront Combination Therapy (Up-therapy) on patients with pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH). [Methods] Twenty-four cases

with therapeutic intervention for CTD-PAH in University of Tsukuba hospital from 2015 to 2021 were included in this study. 1) We retrospectively evaluated their clinical features. 2) We divided the cases into 2 groups whether treated with Up-therapy or Sequential Combination Therapy (Seq-therapy), and compared the clinical course between them. [Results] 1) Cases were comprised of 11 with SLE, one with SLE + SSs, seven with SSs, and five with other CTDs. Cases were also classified based on their cause of PH as 13 with Group 1, 10 with Group1 + 3, and one with Group 1 + 5. Fourteen cases received immunosuppressive therapy concurrently with pulmonary vasodilator. 2) Up-therapy or Seq-therapy were initiated in 11 and 15 cases, respectively. eRVSP was reduced from 62.6±12.5 to 29.5±10.5 mmHg in Up-therapy and from 59.3±15.5 to 41.1±17.8 mmHg in Seq-therapy 1 year after the therapeutic intervention. The number of deaths were one with Up-therapy and five with Seq-therapy. [Conclusions] These results suggested that Up-therapy may reduce eRVSP and mortality in cases with CTD-PAH.

#### W49-4

##### Study of clinical practice in connective tissue disease associated pulmonary arterial hypertension using the MDV database

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Conflict of interest: None

[Objective] Pulmonary Arterial Hypertension (PAH) is associated with CTD including SSs, SLE, and MCTD, and is one of the complications of CTD with a poor prognosis. However, epidemiological information is limited in Japan and the association of CTD activity and appropriate therapeutic strategy including immunosuppressants have not been determined. We aimed to elucidate patient background, diagnosis, and treatment status etc for CTD patients and CTD-PAH patients in the clinical setting in Japan using the Medical Data Vision (MDV) data. [Methods] Patient background for CTD patients, and patient background and treatment patterns for CTD-PAH patients were examined using the MDV data collected from 2008 to 2020. [Results] From the MDV data, 39,043 CTD patients (SSs: 9.6%, SLE: 36.7%, MCTD: 2.6%, others: 51.1%) and 234 CTD-PAH patients (SSs: 42.7%, SLE: 17.1%, MCTD: 10.3%, others: 29.9%) were confirmed. Amongst CTD-PAH patients, the average steroid dose of 58 patients for whom immunosuppressive therapy just before the PAH onset was 12.5 mg/day of prednisolone (Q1: 5.0 mg/day, Q3: 15.0 mg/day). [Conclusions] This study showed the clinical practice of CTD-PAH patients in Japan using the MDV data, and PAH may develop without organ involvements requiring high-dose steroid administration.

#### W49-5

##### Clinical features of venous thromboembolism in patients with connective tissue disease

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Conflict of interest: None

(Objective) We aimed to clarify clinical features of venous thromboembolism (VTE) in patients with connective tissue diseases (CTDs). (Methods) Our study included patients with CTDs who was admitted to our hospital between September 1<sup>st</sup> in 2011 and August 31<sup>st</sup> in 2021. Among them, we selected patients who had diagnosed with VTE. Clinical information of those patients was collected from medical charts. (Result) A total of 753 patients with CTDs were admitted to our hospital and 25 patients was diagnosed with VTE. Thirteen patients developed VTE within 6 months before and after the first remission induction therapy ("early group", median 1.0 months, mean age 64.3), while 12 patients developed VTE at any time other than this period ("late group", median 208.7 months, mean age 72.7). Twelve patients had rheumatoid arthritis (4 patients in early group), 4 patients had vasculitis (3 patients in early group) and 3 patients had inflammatory myopathy (2 patients in early group).

Serum mean D-dimer value was 13.6 µg/ml (9.8 µg/ml in early group) and mean CRP value was 4.3 mg/dl (6.2 mg/dl in early group). (Conclusion) VTE was often developed in patients with CTDs before and after the first remission induction therapy and differed from the cases in late group in terms of clinical features.

#### W49-6

##### Tight control is effective for maintaining renal function in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To clarify risk factors for decreased renal function in RA. [Methods] Using 7-year data from a cohort (TOMORROW) consisting of 208 RA patients and 205 age- and sex-matched volunteers (Vo), risk factors for worsening renal function were identified. Renal function was also estimated with macGFR adjusted for muscle mass. [Results] At baseline, normal eGFR was 86.1 in RA and 96.1% in Vo, and the risk factors for renal dysfunction were RA, age, and hypertension. The number of subjects with worsening renal function was 26 in RA and 44 in Vo. The risk factor was just age (HR 2.97, 95% CI 1.61-5.47, p < 0.001). In the macGFR-based analysis, age (HR 1.72, 1.16-2.56, p = 0.003) and NSAIDs use (HR 1.72, 0.33-0.76, p = 0.007) were risk factors. In a multiple regression analysis of the change in eGFR over 7 years, oral NSAIDs (p = 0.010) and hypertension (p = 0.007) were risk factors for reduction, but RA was not identified as a risk factor (p = 0.387). In fact, the NSAIDs usage rate in RA decreased from 43.8 to 7.0% in 7 years. [Conclusions] In the TOMORROW study, it is considered that the good control of disease activity and the decrease in NSAIDs usage led to the maintenance of renal function. Renal function could be maintained by performing tight control.

#### W50-1

##### Change of physical function in rheumatoid arthritis patients during the COVID-19 pandemic -focused on locomotive syndrome-

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Conflict of interest: None

[Objective] There is a concern that physical function of rheumatoid arthritis (RA) patients may decline due to the effects of refraining from going out during the COVID-19 pandemic. [Methods] The 25-question Geriatric Locomotive Function Scale (GLFS-25) defined 16 points or more as Locomotive syndrome (LS). Of the 538 RA patients (T-FLAG Study) who visited our clinics in 2020, 325 patients were non-LS. Among them, 286 patients visited the clinics in 2021. The patient background factors (2020) to become LS one year later (2021) were determined by multi-variable logistic regression analysis. [Results] Of the 286 patients, 38 patients became LS one year later. The age at baseline was 63.6±16.0/64.3±12.7 years (mean±standard deviation, LS/non-LS group), the disease duration was 8.6±9.1/10.8±9.0 years, and CDAI was 5.7±5.1/3.3±4.9, and GLFS-25 was 9.6±3.4/6.3±4.4 points, which were significantly higher in LS group for CDAI and GLFS-25 (p < 0.05). CDAI (OR 1.10, 95%CI 1.02-1.19) and GLFS-25 (OR 1.15, 95%CI 1.03-1.29) were significant related factors to LS. [Conclusions] It was considered important not only to suppress the disease activity of RA but also to suppress GLFS-25 to a lower score in order to prevent the onset of LS in RA patients during the COVID-19 pandemic.



## W50-2

### Annual trends of spinal surgery in RA patients

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Conflict of interest: Yes

**Objective:** To investigate the annual trend, patients' characteristics, and surgery-related complications following spine surgery in patients with rheumatoid arthritis (RA). **Methods:** We interrogated the Diagnosis Procedure Combination database in Japan, including patients who underwent spine surgery with or without RA from April 2012 to March 2017. **Results:** A total of 9991 patients with RA underwent spine surgery, which corresponded to 5.3% of all cases. The number of spine surgery in RA patients rose from 1321 cases in 2012 to 1671 cases in 2017, although the proportion to all spine surgery cases was consistent. RA patients showed a higher prevalence of cases requiring revision surgery or perioperative death, as compared with non-RA patients. **Conclusions:** The number of spine surgery in RA patients gradually rose during the observation period. RA patients showed a higher prevalence of perioperative complications.

## W50-3

### Predictive validity of frailty regarding subjective RA symptom deterioration

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Conflict of interest: None

**[Objective]** To examine whether frailty can predict symptom exacerbation of rheumatoid arthritis (RA). **[Methods]** In February-May 2019 and one year later, we conducted a survey of RA patients aged 40-79 years attending two university hospitals. **[Results]** Of the 293 patients (85.7% female, mean age 65.3±9.8 years), 23.2% (68 patients) were classified as frailty at baseline, and 72.0% of them were still frail one and a half years later when frailty was defined as a score of 8 or more on the Kihon Check-list (KCL). Only 7.2% (n=21) of the non-frail respondents answered that they were "in worse than a year ago", but the percentage was higher among those who were frail at baseline, 20.6% (14) ( $p < 0.05$ ). Frailty was significantly associated with worsening of subjective rheumatic symptoms at 1 year (OR=2.28, 95% CI=1.04-4.98), even after adjusting for sex, age, education, and marital status (OR=1.91, 95% CI=0.91, 95% CI=0.91), and there was also a significant trend for a decline in physical function (HAQ change  $< -0.125$ ) (OR=1.91, 95% CI = 0.97-3.74). **[Conclusions]** The frailty assessed by KCL may be useful as a prognostic indicator for RA patients.

## W50-4

### Transition of diagnosis in 69 cases of "seronegative RA": an analysis of a 10-year follow-up

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Conflict of interest: None

**[Objective]** To elucidate transition of diagnosis in cases with "seronegative rheumatoid arthritis (RA)". **[Methods]** Among 1192 cases with clinical diagnosis of RA on 1 Apr 2011 in our hospital, cases whose rheumatoid factor and anti-CCP antibody were both negative were extracted. Clinical diagnoses were tracked for 10 years. As for cases whose care in our hospital ended within 10 years, the survey was done until the last visit. **[Results]** Of the 1192 cases, 69 cases were seronegative, 53 of whom (77%) has only RA diagnosis. Of the 53, 42 (61%) has been treated under the same diagnosis. On the other hand, the diagnosis of "seronegative RA" had been withdrawn in 11 (16%). The latest diagnoses of the 11 were osteoarthritis in 3, polymyalgia rheumatica, remitting symmetrical seronegative synovitis with pitting edema syndrome, calcium pyrophosphate deposition disease, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, suspected psoriatic arthritis, adult T cell leukemia/lymphoma, fibromyalgia in 1 each, respectively. As for the 16 "seronegative RA" cases with other rheumatic or musculoskeletal-related diagnoses in 2011, the diagnosis "seronegative RA" had been withdrawn in 9 (18%). **[Conclusions]** The diagnosis "seronegative RA" had been withdrawn in 29% in 10 years.

## W50-5

### Current status of patient referral between local clinics and center for rheumatic diseases under the pandemic of coronavirus disease 2019

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Conflict of interest: None

**[Objective]** The aim of this study was to investigate the influence of coronavirus disease 2019 (COVID-19) for the patient referral to our hospital. **[Methods]** The clinical data of the patients who were introduced to our hospital between January 2018 and July 2021 were retrospectively collected and compared before the pandemic (from January 2018 to February 2020) with after the pandemic (after March 2020). **[Results]** The number of referred patient significantly decreased from 0.98/day (before the pandemic) to 0.56/day (after the pandemic). The rate of the referral purpose for surgery did not change between before and after the pandemic, however, the patients for surgery of the large joint in lower limb significantly increased from 34.6% to 50.0%. On the other hand, the rate of the patients for surgery of the upper limb significantly decreased from 38.4% to 22.6%. The drug treatment newly introduced in our hospital did not change between before and after the pandemic. **[Conclusions]** The number of the referred patients decreased after the epidemic, suggesting that the patients who were afraid of spreading of COVID-19 refrained from visiting local clinics.

## W50-6

### Investigation into the clinical features of polymyalgia rheumatica in Japan: using real-world data from 2015 to 2020

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Conflict of interest: Yes

[Objective] To investigate the clinical features of polymyalgia rheumatica (PMR) in Japan. [Methods] This feasibility study (FS) used data from a real-world database. We aggregated the number of the patients who was recorded with the ICD-10 code for PMR (PMR patients). In addition, we aggregated the number of PMR patients by age or by gender, the prescription rate of glucocorticoids (GC) within 30 days from when PMR was recorded, and the prevalence of comorbidities. [Results] 6,325 PMR patients were recorded in the database in 2020. Prevalence was seen slightly higher in females with a male-to-female ratio of 1:1.3. The mean age was 74.3 years, and the rate of patients over 50 years was 96.5% (50s; 6.9%, 60s; 17.8%, 70s; 34.7%, 80s; 31.5%, 90s; 5.6%). 53.6% of the patients were prescribed GC. The prevalence of rheumatoid arthritis (RA), giant cell arteritis, osteoporosis (OP), diabetes mellitus (DM), and malignancies (MAL) was 30.5%, 1.0%, 26.2%, 31.5%, and 16.2%, respectively. [Conclusions] In this FS, our dataset showed that PMR was common among the elderly in their 70s and 80s, and more than half of the PMR patients were prescribed GC. Our investigation into the clinical features of PMR demonstrated a trend for comorbidities (RA, OP, DM, MAL etc.) to be recorded together with PMR.

## W51-1

### The role of C10orf10/decidual protein induced by progesterone in chondrocytes and its involvement in osteoarthritis pathogenesis

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Conflict of interest: None

[Objective] Autophagic dysfunction in chondrocytes is a hallmark of osteoarthritis (OA) pathogenesis. Recent studies have reported that C10orf10/decidual protein induced by progesterone (DEPP) is located in mitochondria, and is involved in autophagy. Here, we evaluated the functions of DEPP in chondrocytes and the involvement of DEPP in OA pathogenesis. [Methods] DEPP expression analyses and gain- or loss-of-function experiments were performed using human chondrocytes. OA was induced in DEPP knockout (KO) mice by destabilization of the medial meniscus, followed by histological analyses. [Results] DEPP expression was lower in OA chondrocytes, and induced by oxidative stress. Autophagic flux was decreased by DEPP knockdown, whereas increased by DEPP overexpression. DEPP-overexpressing cells maintained cell viability following oxidative stress by promoting mitochondrial autophagy. In an OA model, DEPP KO exacerbated the progression of cartilage degradation, and increased the number of TUNEL-positive cells. [Conclusions] DEPP maintained cell viability against oxidative stress via enhancing mitochondrial autophagy. We suggest that autophagic dysfunction related to DEPP deficiency in OA chondrocytes could be a novel mechanism of OA progression.

## W51-2

### Involvement of Inflammasome Synovitis in the Pathology of Rapidly Destructive Coxopathy Compared with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] RDC is characterized by pathological bone resorption of hip joint similar with RA. The etiology is still unclear. Synovitis related with NLRP3 inflammasome is involved in the pathology of RA. The aim of this study is to verify the involvement of NLRP3 inflammasome synovitis in RDC. [Methods] The clinical data of 64 patients with RDC, osteoarthritis (OA), and osteonecrosis of the femoral head (ONFH) were extracted from the medical records, and synovium collected during surgery was immunohistochemically stained. In vitro, FLS were co-cultured with macrophages activated by the inflammasome pathway, and after co-culture, FLS were co-cultured with osteoclast precursor cells to verify the expression of inflammatory markers and osteoclasts by qPCR and TRAP staining. [Results] there was no increase in systemic inflammation-related factors in the blood. TRAP-positive cells and NLRP3-related markers were expressed in immunohistology and qPCR. RDC consisted with vitro study. Osteoclast differentiation was significantly increased by stimulated FLS. [Conclusions] RDC is related with local inflammation not with systemic inflammation different from RA. The pathology of RDC would be involved in synovitis activated by NLRP3 inflammasome consistent with RA.

## W51-3

### The function of microRNA in articular cartilage and its application to the treatment of osteoarthritis

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Conflict of interest: None

[Objective] MicroRNA (miRNA) is important for chondrocyte differentiation and homeostasis. The miRNA-455 has been identified as a miRNA whose expression is down-regulated in chondrocytes. In this study, we investigated its function in chondrocytes and potential for therapeutic application. [Methods] We generated and evaluated miRNA-455 knockout mice. The miRNA-455 target genes were screened using a reporter library carrying the full-length cDNA of 4891 genes. The identified target genes were knocked down with siRNA in the knockout mice, and gene expressions in articular cartilage were examined. Furthermore, we administered miRNA-455-5p and -3p into the knee joint of mouse osteoarthritis model. [Results] The miRNA-455 knockout mice showed progressive cartilage degeneration at the 6 months. The miRNA-455-5p and -3p strand both repressed HIF-2. The knockdown of HIF-2 $\alpha$  in miRNA-455 knockout mice suppressed the expression of genes associated with cartilage degeneration in articular cartilage. Intra-articular administration of miRNA-455-5p and -3p suppressed the articular cartilage degeneration. [Conclusions] We found that both miRNA-455-5p and -3p contribute to the homeostasis of articular cartilage, and demonstrated possibility of miRNA nucleic acid therapy for osteoarthritis.

## W51-4

### Does the stem design affect the degree of freedom in the stem anteversion and position? - a computer simulation study

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Conflict of interest: None

[Objective] The present study aimed to examine whether the stem design affected the degree of freedom of the stem anteversion (DFS) and position according to the change in the stem anteversion. [Methods] Thirty-seven hips before total hip arthroplasty were examined using computed tomography. Three-dimensional templating (3D template, Kyocera) was performed using the taper wedge stem (TW) and the fit and fill stem (FF). The difference between the maximum and minimum stem anteversions was defined as DFS, and the stem alignment changes in the coronal/sagittal planes, stem depth change according to, the change in the stem anteversion were also examined. [Results] The means DFSs in TW and FF were significantly different (22° vs. 9°, respectively). The stem alignment changes of TW in the coronal/sagittal plane were significantly larger

than those of FF whereas no significant difference was found in the stem depth change. DFSA was significantly correlated with the stem alignment changes in the coronal/sagittal planes. [Conclusions] The stem design affected DFSA. The stem anteversion in TW may be more adjustable but a risk for deviation from the target anteversion remains. The appropriate preoperative planning and surgical procedures to achieve the targeted alignments are important.

## W51-5

### Plasmin may be involved in cartilage degeneration in osteoarthritic knee joints

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Conflict of interest: None

[Objective] To investigate the mechanisms underlying cartilage degeneration in OA, focusing on the activity of plasmin. [Methods] Cartilages were obtained from 17 end-stage OA knees at macroscopically intact areas (Pres) and degenerated areas (Deg) at prosthetic surgery. After weighing, proteins were extracted, and the concentrations of tPA, uPA, uPAR, PAI-1, fibronectin and D-dimer + FDP were determined by Luminex. The activities of tPA and plasmin were measured respectively by specific assay kits. Chondrocytes obtained from OA cartilage were cultured either in monolayers or in alginate beads. After 48 hours, RNA was obtained, and the expression of tPA and uPA were compared between the two methods of culture by qPCR analysis. [Results] The concentrations of tPA, uPA, uPAR, PAI-1, fibronectin and D-dimer + FDP were significantly greater in the Deg compared to the Pres. The activities of tPA and plasmin were significantly elevated in the Deg. In the cell culture analysis, the expression levels of tPA and uPA were significantly higher in the chondrocytes cultured in monolayers than those in the alginate beads. [Conclusions] The expression of tPA and uPA was more enhanced in the Deg, which could cause cartilage degeneration in the areas through the induction of plasmin activity.

## W51-6

### Relationship between bone mineral density and skeletal muscle mass, BMI, and locomotor degree in patients with end-stage knee joint disorder scheduled for total knee arthroplasty

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Conflict of interest: None

Purpose: End-stage knee osteoarthritis is considered to be a cause of locomotive syndrome. In this study, we investigated the correlation between bone mineral density and skeletal muscle mass in patients who are scheduled total knee arthroplasty (TKA), and examined the relationship with locomotive syndrome. Method: Among the patients who underwent the first TKA from July 2020 to May 2021, TKA patients who underwent preoperative osteoporosis screening were included. Preoperative end-points were basic patient information such as sex age and BMI, bone mineral density and limb skeletal muscle index (SMI) by DXA, and locomotive degree 0-3. Result: The patients were 82 (male: 18) with an average age of 75 years. In the univariate analysis, the items that correlate with bone mineral density were SMI ( $p < 0.01$ ) and BMI ( $p < 0.01$ ). In addition, when multiple regression analysis was performed using bone density, gender ( $P < 0.01$ ) and BMI ( $P = 0.03$ ) were influential factors. Locomotive degree was not extracted as a factor affecting bone mineral density. Conclusion: Gender and BMI were independently involved in bone mineral density. The relationship between skeletal muscle mass and bone mineral density was not independent, and the degree of locomotive syndrome did not associate with decreased bone mineral density.

## W52-1

### Comparison of Abatacept and Janus Kinase (JAK) inhibitors in Rheumatoid Arthritis-associated Interstitial Lung Disease

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Conflict of interest: None

[Objective] We aimed to compare the relative efficacy and safety of abatacept (ABT) and Janus Kinase inhibitors (JAKi) in RA-associated interstitial lung disease (ILD). [Methods] Single-center, retrospective study of 71 RA patients with ILD (ABT:  $n = 45$ , JAKi:  $n = 26$ ) [Results] At baseline, the ABT group had a longer disease duration, shorter past bDMARDs or JAKi use, and more usual interstitial pneumonia (UIP) cases. There was no significant difference of the treatment continuation rate for the first two years (ABT: 46%, JAKi: 47%,  $p = 0.54$ ). ABT was discontinued due to inefficacy ( $n = 12$ ), infection ( $n = 2$ ), lung disease ( $n = 2$ ) and others ( $n = 8$ ), while JAKi was withdrawn due to inefficacy ( $n = 6$ ), infection ( $n = 2$ ) and others ( $n = 4$ ). The incidence rate of lung complications wasn't significantly different (ABT: 21.5%, JAKi: 22.9%,  $p = 0.57$ ). The change of DAS28-CRP and PSL usage after one-year treatment was not significantly different (the ratio of DAS28-CRP; ABT: 0.64, JAK: 0.59,  $p = 0.26$ , and the ratio of PSL usage; ABT: 0.40, JAKi: 0.49,  $p = 0.61$ ). [Conclusions] Between ABT and JAKi, there was no significant difference in the efficacy and safety for RA-ILD patients although the patients' characteristics at baseline were different. ABT and JAKi can be used for RA-ILD likewise.

## W52-2

### The efficiency and safety of abatacept in rheumatoid arthritis-related interstitial lung disease

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Conflict of interest: None

[Objective] The purpose of this study was to evaluate the efficacy and safety of abatacept (ABT) in RA patients with interstitial lung disease (ILD). [Methods] We retrospectively evaluated pulmonary function, DAS28-CRP, steroid dose, and safety before and after treatment with ABT in patients with RA-ILD from 2017.1 to 2021.4. Active ILD was defined as  $>10\%$  worsening of %FVC and  $>15\%$  worsening of %Dlco in addition to 5-10% worsening of %FVC. [Results] There were 20 patients with a median age of 75 years (IQR 13) and 75% males. Comparison before and after the introduction of ABT showed that %FVC 82.7% (25%) to 81.3% (21%),  $p = 0.5$ , DAS28-CRP 3.6 (1.3) to 2.1 (0.9),  $p = 0.002$ , steroid dose 5 mg (2.8 mg) to 5 mg (2 mg),  $p = 0.07$ , respectively. After one year of treatment, FVC was maintained in 15 patients (83%) and worsened in 3 patients (17%), and all worsened cases were patients with ILD activity ( $p = 0.04$ ). The 1-year continuation rate of ABT was 94%, and there was one case of infection requiring hospitalization and no acute lung injury during the observation period of 16.5 months. [Conclusions] Patients with active ILD should be carefully monitored for changes in respiratory function. ABT can be safely continued and may reduce the progression of respiratory function.

## W52-3

### Effect of intravenous cyclophosphamide in patients with acute exacerbation of rheumatoid arthritis-related interstitial lung disease

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Conflict of interest: None



[Objective] We aimed to investigate the effect of intravenous cyclophosphamide (CYC) as the initial therapy in patients with acute exacerbation (AE) of rheumatoid arthritis-related interstitial lung disease (RA-ILD) using the Japanese Diagnosis Procedure Combination inpatient database. [Methods] We identified patients with AE of RA-ILD who received high-dose methylprednisolone within 3 days after admission. Patients were divided into two groups: those receiving intravenous CYC within 3 days after admission (CYC group) and those who did not (control group). One-to-four propensity-score matching analyses were performed. [Results] After propensity score matching, 129 patients in the CYC group and 516 patients in the control group were analyzed. 90-day in-hospital mortality was not significantly different between the groups (50.4% vs 42.2%, hazard ratio 1.20, 95% CI 0.91-1.58). Hospital cost was higher in the CYC group (\$19,800 vs \$16,100,  $p = 0.012$ ). A larger proportion of patients in the CYC group received platelet transfusion (7.0% vs 2.3%, odds ratio 3.05, 95% CI 1.20-7.73). [Conclusions] The initial therapy with CYC did not show a survival benefit in patients with AE of RA-ILD. CYC was associated with higher hospital cost and a larger proportion of platelet transfusion.

## W52-4

### Clinical features of rheumatoid arthritis (RA) with pulmonary lesions whose respiratory symptoms precede the diagnosis of RA

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Conflict of interest: None

[Objective] We investigated the clinical characteristics of patients with rheumatoid arthritis (RA) with pulmonary lesions who have pulmonary symptoms prior to RA diagnosis. [Methods] From July 1st to October 15th, 2021, RA patients with a history of outpatient visits to our division were enrolled, and among them, we extracted those who had chronic airway lesions. Then we analyzed each case retrospectively. [Results] Of all 115 RA patients, 47 had coexisting lung lesions. Furthermore, 14/47 (30%) cases were extracted that the pulmonary condition preceded the RA diagnosis. The median age of RA onset in the preceding group was 66 years, significantly older than the non-preceding group (51 years,  $P = 0.02$ ). CT findings showed pulmonary emphysema lesions significantly more in the preceding group than the non-preceding group (50% vs. 22%,  $P = 0.04$ ), and early upper lobe-dominant lesions was significantly higher in the preceding group than the non-preceding group (50% vs. 18%,  $P = 0.04$ ). [Conclusions] We suggested that the cases in which the pulmonary symptoms preceded the RA diagnosis showed more emphysematous lesions, and the upper lobe lesions in the early stage.

## W52-5

### Examination about a merger and the progress of ILD according to the age group in the chest CT reading shadow result of antiCCP antibody-positive 568 RA patients in Keiyo Orthopedic Hospital

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Keiyo Orthopedic Hospital

Conflict of interest: None

[Objective] Merger of ILD was an important factor related to mortality directly, but increase of the prevalence was shown in the RA patients recently. It is reported that mortality of RA-ILD is upward trend. As I checked a merger, progress of ILD by the chest CT reading shadow result according to age groups, I report 568 antiCCP antibody-positive examples of patients with our hospital going to hospital rheumatoid arthritis. [Methods] 568 patients with the reading shadow result that also photographed the chest CT more than twice recently in three years in RA patients visited a hospital for treatment as for the object from January through December in 2020 by our hospital with positive antiCCP antibody. I investigated a patient background including merger, progress and KL-6 of ILD by the chest CT reading shadow result according to age groups. [Results] About the merger rate of ILD, the A, B group did not have the ILD merger exam-

ple. As an age group rose in the G group from the, C group, the merger rate of ILD became high and was 47.4% in the G group. [Conclusions] The ILD merger rate by the chest CT reading shadow result was high in elderly people. Because a potential progress example existed even if KL-6 was normal level, it was thought that attention was necessary for medication.

## W52-6

### The use of biologic agents for Rheumatoid arthritis with pulmonary non-tuberculous mycobacterial infection in our hospital

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Conflict of interest: None

Background: The central and peripheral airway lesions as pulmonary complications of Rheumatoid arthritis (RA) cause the colonization of pathogens, including non-tuberculous mycobacteria (NTM). In particular, the standard treatment for pulmonary NTM disease has not been established. There is little evidence whether biologic agents (bDMARDs) can be safely used for RA patients with pulmonary NTM infection. Objective: To evaluate the clinical course of RA patients with pulmonary NTM infection treated with bDMARDs. Methods: RA patients with pulmonary NTM infection at our hospital were retrospectively analyzed. Results: Among 1318 of RA patients enrolled, 56 of them were positive for NTM more than once from sputum, and 9 of them were treated with bDMARDs. 5 of these cases had clinical overt pulmonary NTM infection. All cases were nodular and bronchiectasis types of NTM, and treated with Abatacept. On the other hand, in one case, NTM was newly detected in sputum while using bDMARDs, so the treatment with bDMARDs has been discontinued. Conclusion: bDMARDs were used in RA patients with nodular and bronchiectasis pulmonary NTM disease without worsening of NTM infection. In addition, the patient treated with bDMARDs improved RA disease activity and reduced the dose of steroids.

## W53-1

### Cases suggesting the effectiveness of glucocorticoid pulse therapy for exacerbation of bronchiectasis with rheumatoid arthritis

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Conflict of interest: None

[Objective] We investigated the effectiveness of glucocorticoid pulse therapy for exacerbation of bronchiectasis (BE) with rheumatoid arthritis (RA). [Methods] From January 2016 to September 2021, we registered the patients whose medical records included "RA" and "BE" as diagnosis and treated methylprednisolone (mPSL) pulse therapy for the exacerbation of BE. We analyzed each episodes retrospectively. [Results] 11 patients (10 females) were enrolled, and four patients (36%) had history of several (2-4) times of admission by BE exacerbation. Duration of RA was 16 years (median) and BE was 12 years (median). Anti-CCP antibody was positive in 91%. CT showed centrilobular lesion (73%) and bronchial wall thickening (55%). Cough or sputum were 15/18 cases (83%). The median mPSL doses was 250 mg/day for 3 days, and the same dose in the second course was added in 6/18 patients (33%). The erythrocyte sedimentation rate decreased significantly from 68.2 to 42.9 mm/hr ( $P < 0.001$ ), and minimum of SpO<sub>2</sub> in the 6-minute walking test increased from 89.4 to 93.3% ( $P = 0.09$ ). There was no adverse event caused by glucocorticoid pulse therapy. [Conclusions] Glucocorticoid pulse therapy in RA-BE exacerbation may reduce inflammation and improve some markers of respiratory status.

## W53-2

### Elevation of serum B7H3 levels in the patients with RA and RA-ILD

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Conflict of interest: None

[Background] B7H3 (also known as CD276) is a newly found molecule of B7 family that regulates immune response. Elevated levels of B7H3 in the bronchoalveolar lavage fluid have been reported to predict the progression of UIP. The role of B7H3 in the development of RA and RA-ILD remains unknown. To answer the question, we measured serum B7H3 levels in RA patients and examined the association between B7H3 levels and clinical features. [Methods] The subjects were 32 RA patients who were outpatients of our department and whose sera were available. B7H3 levels were measured by ELISA. [Results] Serum B7H3 was elevated in the serum from RA compared to controls (RA:  $25.3 \pm 7.7$  vs controls:  $18.1 \pm 6.6$  ng/mL,  $p=0.037$ ). Serum B7H3 levels were correlated with the age of RA patients. No association of B7H3 levels was found with gender, seropositivity, and CRP levels. Moreover, B7H3 levels were increased in patients with ILD compared to those without ILD (IP (+):  $29.0 \pm 6.5$  vs (-):  $23.3 \pm 7.7$  ng/mL,  $p=0.026$ ). B7H3 levels, however, failed to predict the future progression of ILD. [Conclusion] Serum B7H3 levels are elevated in RA, in RA-ILD, suggesting the involvement of B7H3 in the development of RA and RA-ILD.

## W53-3

### Renal dysfunction with rheumatoid arthritis

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Conflict of interest: None

[Objective] MTX is an anchor drug for Rheumatic diseases that is contraindicated for chronic hepatic dysfunction and renal dysfunction. With the aging of RA patients, we must pay attention to both liver and renal function. And, we decided to examine the actual hepatic situation including DMARD-naïve patients. [Methods] The study data was obtained from RA patients ( $n=739$ ) who visited to our hospital for the 1<sup>st</sup> time from 2012 to 2019. We investigated lifestyle-related diseases (LRDs), used drugs, and disease activity at their 1<sup>st</sup> visit, and examined risk factors related to CKD. [Results] eGFR reduction was also associated with age, urinary protein, LRDs, and Fib4i. Regarding the drug, DMARD and steroid users had lower eGFR. In the disease activity, the CR group had less renal damage than the other groups. And more, we performed Logistic regression analysis by adding influencing factors associated with RA such as duration along with the obtained previous results. Statistically significant differences were showed in age, hypertension, dyslipidemia, dysuricemia, Fib4i, urinary protein, and disease activity \* disease duration. [Conclusion] We could suggest that management of LRDs, and sustained good control of disease activity of RA are important for the prevention of renal dysfunction.

## W53-4

### Patient with rheumatoid arthritis (RA) who developed Felty's syndrome during treatment with upadacitinib: a case report

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Conflict of interest: None

A 52-year-old woman with multi-drug resistant RA was treated with upadacitinib. After 6 months, her blood tests showed a decreased number of white blood cells (1900 / $\mu$ L). Therefore, upadacitinib was discontinued. However, four weeks later, she presented with fever and a white blood cell count of 900 / $\mu$ L. The patient was admitted to our hospital. Broad-spectrum antibiotics and granulocyte colony-stimulating factor (G-CSF) administration were initiated. However, the increase in white blood cell count was modest. Bone marrow aspiration showed an increased proportion of hematopoietic cells. Abdominal computed tomography revealed splenomegaly. Her rheumatoid factor (RF) level was elevated to 9880 U/mL. Based on

the patient's clinical course, physical findings, and various laboratory results, she was finally diagnosed with Felty's syndrome. Treatment was initiated with methotrexate and abatacept; subsequently, the number of white blood cells gradually returned to normal.

## W53-5

### Does the development of iatrogenic immunodeficiency-related lymphoproliferative disorder (OIIA-LPD) affect subsequent disease activity of rheumatoid arthritis? ~ From ANSWER cohort data ~

Tadashi Okano<sup>1</sup>, Motomu Hashimoto<sup>2</sup>, Kenji Mamoto<sup>1</sup>, Yutaro Yamada<sup>1</sup>, Shohei Anno<sup>1</sup>, Shinsuke Yamada<sup>2</sup>, Ryu Watanabe<sup>2</sup>, Kazuo Fukumoto<sup>2</sup>, Wataru Yamamoto<sup>3</sup>, Takayuki Fujii<sup>4</sup>, Akira Onishi<sup>5</sup>, Takuya Kotani<sup>6</sup>, Ayaka Yoshikawa<sup>6</sup>, Yuichi Maeda<sup>7</sup>, Yasutaka Okita<sup>7</sup>, Yonsu Son<sup>8</sup>, Hideki Amuro<sup>8</sup>, Hirotaka Yamada<sup>9</sup>, Yuzuru Yamamoto<sup>9</sup>, Ryota Hara<sup>10</sup>, Masaki Katayama<sup>11</sup>, Hiroaki Nakamura<sup>1</sup>

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Conflict of interest: None

[Objective] The frequency of iatrogenic immunodeficiency-related lymphoproliferative disorder (OIIA-LPD) is increasing in patients with RA, but the course of disease activity after the onset is unknown. [Methods] 71 RA patients who were histologically and clinically diagnosed with OIIA-LPD during RA treatment in the ANSWER cohort. [Results] The average age at the onset of LPD was 66.3 years, 67.6% of women, and the duration of RA was 13.2 years. Methotrexate (MTX) was used at 96.6%, the average dose was 9.2 mg/w, and the cumulative years of MTX use was 10.0 years. Tacrolimus use was 18.3%, steroid use was 35.2%, and bDMARDs and JAK inhibitor use was 33.8%. DAS28-CRP was 2.8, 2.9, 3.4, 3.3, 3.0, 3.0 in the order of 6 months before onset, 3 months before onset, at the time of onset, 3 months after onset, 6 months after, and 12 months after onset. There were 20 cases in which chemotherapy was administered for LPD treatment, and the cumulative number of years of MTX use was significantly longer in the chemotherapy group, but the disease activity after the onset of LPD was kept low. [Conclusions] Disease activity after the onset of OIIA-LPD increased at the time of onset and 3 months after the onset, but improved thereafter.

## W53-6

### A Investigation of bone microstructure of proximal femur in rheumatoid arthritis patients using 3D-SHAPER

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Conflict of interest: None

[Objective] DXA-Based 3D Analysis is a software that incorporates a model-based algorithm to analyze three-dimensional architecture from a standard dual energy X-ray absorptiometry (DXA) scan. [Methods] We analyzed femur microstructure with RA patients using 3D-SHAPER and examined the relationship between serum ACPA/RF, disease activity and HAQ. [Results] Number of patients was 159 (M/F=29/130), age was 67.5y, glucocorticoid dose was 3.8 mg/d and MTX dose is 8.5 mg/w. BMD at the femoral neck was correlated with age and mHAQ. The high ACPA group had significantly lower in femoral neck BMD and neck trabecular

vBMD than the low ACPA group. The high RF group had significantly lower in neck trabecular vBMD. The high SDAI group had significantly lower in all portion of trabecular vBMD. The high mHAQ group had significantly lower in femoral neck BMD, neck, trochanter and shaft trabecular vBMD, in proximal cortical vBMD and cortical bone surface density. [Conclusions] RA patients with autoantibody positive develop significant bone loss in trabecular bone, and worsening HAQ causes bone loss in both trabecular and cortical bone. Therefore, RA patients with autoantibody positive are more likely to develop osteoporosis and control of disease activity and HAQ is important for prevention of fracture.

## W54-1

### Study on the classification of polymyalgia rheumatica using cluster analysis

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Conflict of interest: None

[Objective] Polymyalgia rheumatica (PMR) is a heterogeneous disease group that is sometimes difficult to distinguish from old-onset rheumatoid arthritis (EORA) and is sometimes associated with giant cell arteritis (GCA). In this study, we used cluster analysis to examine the classification of PMR. [Methods] We conducted a hierarchical clustering analysis of 110 cases of PMR, using clinical symptoms such as fever, arthralgia, and myalgia, and serological findings such as CRP, erythrocyte sedimentation rate (ESR), MMP-3 and rheumatoid factor (RF) as parameters. [Results] The results of the hierarchical clustering analysis showed that there were three clusters (A-C). Cluster A was characterized by a small proportion of males (17.4%), a young mean age of onset (70.9 years), and high MMP-3 levels. Cluster B was 35% male, mean age at onset was 73.1 years, and RF positivity was lower at 6.5%. Cluster C consisted of 30% males, with a mean age at onset of 76.6 years, and had a higher incidence of fever and arthralgia, with higher levels of inflammatory markers such as CRP and ESR. Also, the RF positivity rate and GCA complication rate tended to be relatively high at 21.7% and 13.3%, respectively. [Conclusions] The cluster analysis showed that PMR could be divided into three disease types.

## W54-2

### The utility of the screening malignancy before the treatment of biologics and JAK inhibitors

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Conflict of interest: None

[Objective] Malignancy under the treatment of biologics (Bio) and JAK inhibitor (JAKi) has been reported. Hence it leads us to conduct screening-examinations of malignancy before those therapy. The aim of this study is to clarify the utility of screening-examination. [Methods] From April 2016 to September 2021, we examined 336 cases as screening (upper gastrointestinal endoscopy, twice fecal occult blood, ultrasound of thyroid gland and abdomen, thoracoabdominal plane CT, serum PSA examination for men, breast and gynecology cancer screening for women). [Results] In those 336 cases (median 68 years old), malignant tumor is 3.9% (13 cases, median 77.5 years old). The details of malignancy were as follows: prostate cancer (n=6), gastric cancer (n=2), colon cancer (n=1), lung cancer (n=1), breast cancer (n=1) and uterus and ovarian cancer (n=2). Successful cases administered-biologics after curative treatment for malignancy were 64.3% (9 cases). [Conclusions] Screening-examination before the treatment of Bio/JAKi has a significant meaning, especially serum PSA examination for male patients more than 70 years old. Furthermore, early detection and curative treatment could result in improvement of disease activity through initiation of biologics.

## W54-3

### Five year change of eGFR in patients with rheumatoid arthritis treated with biological DMARDs

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Conflict of interest: None

[Objective] To investigate the estimated glomerular filtration rate (eGFR) change in patients with rheumatoid arthritis (RA). [Methods] We retrospectively examined 5 year change of eGFR among patients with RA who took biological disease modifying anti-rheumatic drugs (bDMARDs) firstly between 2011 April to 2015 March. [Results] Three-hundred and forty-one RA patients (Male 66, Female 275, mean age of 60.0 years old) took bDMARDs, and 289 were followed up over 5 years. Proportion of chronic kidney disease (CKD) classification changed from 44.1 to 17.9% in CKD-G1, 43.8 to 54.4% in CKD-G2, 8.9→26.4% in CKD-G3, 2.90 to 1.37% in CKD-G4 and 0.29 to 0.00% in CKD-G5. eGFR (ml/min/1.73 m<sup>2</sup>) decline in each CKD group was, 22.2±17.1 in CKD-G1, 11.5±17.6 in CKD-G2, 6.31±8.58 in CKD-G3, 7.67±0.19 in CKD-G4, respectively. Although, we could not demonstrate statistical relationship between the change of eGFR and the DMARDs, proteinuria is associated with greater decline of eGFR (30.0±18.0 vs 15.0±17.5 ml/min/1.73 m<sup>2</sup>, p<0.01) [Conclusions] Rheumatologists should set up a treatment plan, considering eGFR decline. Proteinuria can stratify patients at risk for eGFR decline in RA patients.

## W54-4

### The association between grit and burnout in academic rheumatologists: the TRUMP2-SLE study

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Conflict of interest: None

[Objectives] Grit, captured as perseverance and passion for long-term goals, is predictive of success in many professions. However, it remains unclear whether grit is associated with burnout among rheumatologists, who face emotional exhaustion to maintain a long-term physician-patient relationship. [Methods] This was a cross-sectional study involving 51 rheumatologists from five university hospitals. The exposure was grit, measured as the mean score of the 8-item Short Grit Scale (range: 1 to 5 [extremely gritty]). The outcomes were mean scores of 3 burnout domains measured via the 16-item MBI-GS (i.e., exhaustion, professional efficacy, and cynicism, ranges: 1 to 6). General linear models were fit with covariates (age, sex, job title [assoc. prof. or higher vs. lower], marital status and having children). [Results] Higher grit was associated with higher professional efficacy (per 1-pt increase, 0.51 pt. [95%CI 0.18 to 0.84 pt.]), while we found insufficient evidence that grit was associated with exhaustion and cynicism. Lower job title was associated with lower professional efficacy. Female sex and not having children were associated with higher ex-



haustion. Younger age was associated with higher cynicism. [Conclusions] Grit was associated with some manifestations of burnout.

## W54-5

### A case of acute renal failure due to bilateral ureteral stones during the course of eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

[Case] 58-year-old woman [Onset] The patient was referred to our hospital because of a sudden abdominal pain. A blood test revealed a marked increase in eosinophil count 5,578 / $\mu$ L. Based on a history of bronchial asthma, purpura on lower legs, and mononeuritis multiplex, she was diagnosed as eosinophilic granulomatosis with polyangiitis. Intravenous methylprednisolone 0.5 g 3 days was given for remission induction and started prednisolone (PSL) 50 mg/day follow. Clinical response was well, PSL was tapered to 35 mg/day at the latest. Next month, she suddenly became anuric. A CT scan showed stones in the bilateral ureteropelvic junction, and emergency left-sided nephrostomy was performed. [Discussion] Glucocorticoid (GC) decrease urinary calcium reabsorption and promote the formation of ureteral stones. In this case, CT was performed before GC treatment and 11 days later, ring-shaped calcium stones were deposited in the bilateral ureteropelvic junction. We could not find any similar reports in the literature, but we think it strongly suggesting the involvement of GC. Prevention of recurrence is an important issue for the future. [Clinical significance] We experienced a case of bilateral ureteral stones caused by GC use, so we report it here for paying attention.

## W55-1

### Mid-term results of unconstrained total elbow arthroplasty for rheumatoid elbow

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Conflict of interest: None

[Objective] Total elbow arthroplasty (TEA) for rheumatoid (RA) elbow is widely considered to be useful. There are two types of TEA: semi-constrained and unconstrained type. Objective of this study was to clarify the mid-term results of unconstrained TEA for RA elbow. [Methods] Patients who underwent TEA for RA elbow from August 2009 to January 2017 and had a follow up of at least 2 years were included in this study. Range of motion of elbow, clinical score, valgus instability, and complications were evaluated. Furthermore, radiolucent line, fracture, and dislocation or subluxation were evaluated at the last follow up. [Results] 28 elbows in 26 cases were included in this study. Implant was unconstrained type, NRE in all cases. The mean follow up period was 95 months. Range of motion was significantly improved postoperatively, and JOA score, MEPS were also significantly improved. At the last follow up, 7 elbows had valgus instability, 4 of which were in braces, and 1 was revised after a fall at 9 years after surgery due to loosening of humeral implant. [Conclusions] In this study, we evaluated the mid-term results of unconstrained TEA for RA elbow. Unconstrained TEA had a good clinical result for RA elbow. However, we should take care of valgus instability.

## W55-2

### The indication of the TKA lateral approach to the genu valgum is limited

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Conflict of interest: None

[Objective] To reassess the indication of the lateral parapatellar ap-

proach (LPP) to the genu valgum. [Subjects and methods] 39 knees that underwent TKA for Krakow type I genu valgum, 20 knees with lateral approach (LPP), and 19 knees with medial approach (MPP). [Results] MPP was more common in the cases suffered from RA and with successful reduction. Additional lateral dissection was performed in 5% of LPPs and 36.8% of MPPs, and 90% of LPPs used CR implants. In LPPs, there were many cases of excessive external rotation of the tibial component, and 2 knees of the tibial component were placed laterally and 1 knee of each group was subsided. Although LPPs were attempted for two patients with genu valgum and patellar dislocation, they were given up on the way because of the difficulty to complete. [Discussion] When LPP is used for the genu valgum with lateral contracture, it is easy to achieve soft tissue balance. However, troubles are likely to increase because of the difficulty to secure surgical field. On the other hand, for mild genu valgum, MPP was sufficiently operable without using highly constrained implants. [Conclusion] For genu valgum with patellar dislocation and less contracture, the advantage of using the lateral approach is small, and its indication is limited.

## W55-3

### Stiff knee in haemophilia: surgical timing and procedure for total knee arthroplasty

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Conflict of interest: None

[Introduction] Total knee arthroplasty (TKA) for a stiff knee of patients with hemophilia (PWH) represents a challenge for orthopaedic surgeon, due to the difficulties of exposing the knee and high complication rate compared to a flexible knee. [Objective] To optimize the surgical exposure, and to propose a threshold angle of stiff knee in treating haemophilic knee joints, retrospectively. [Methods] 67 primary TKAs for PWH (mean age, 48 years) were performed, and incisional approaches to joint were standard (58 cases) and V-Y quadricepsplasty (VY) (9 cases). Pre-post knee angles were evaluated in each group. [Results] Stiff knee was seen preoperatively in 25%. Postoperative range of motion (ROM) and flexion were significantly increased compared with preoperatively in both groups. Postoperative flexion did not reach 90° needed for daily life in V-Y group. Univariate logistic regression analysis demonstrated that preoperative ROM and flexion were significantly associated with V-Y. [Conclusions] TKA for PWH should not be further postponed when TKA can be performed using a standard approach rather than VY to gain sufficient flexion for activity of daily living. TKA should be performed before the stage to avoid preoperative flexion <45° and ROM <35° in terms of surgical indications.

## W55-4

### The change in the position femoral nerve during the anterior approach to the hip

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Conflict of interest: None

[Objective] The aim of this study is to identify the change in position of the femoral nerve during DAA to the hip. [Methods] The distance between the femoral nerve and anterior acetabulum was measured in clock face method. [Results] At 90°, the distance was closer in the extended position and the external rotation position compared to the supine position and the middle position. [Conclusions] This study demonstrates that the femoral nerve become closer to the hip during hip arthroplasty with extension position of the hip.

## W55-5

### **Proliferation of tibial nerve in muscle graft after amputation using Regenerative Peripheral Nerve Interface: a case report of polyarteritis nodosa**

Songho Chang<sup>1,2</sup>, Takumi Matsumoto<sup>2</sup>, Yuji Maenohara<sup>2</sup>, Yasunori Omata<sup>2</sup>, Sakae Tanaka<sup>2</sup>

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Conflict of interest: None

[Objective] In recent years, as a new method for preventing neuroma and phantom pain after amputation, the regenerative peripheral nerve interface (RPNI) in which a severed nerve stump is embedded into a free muscle graft collected from an amputated limb has attracted attention. In this study, embedded nerve into a free graft muscle was evaluated histologically in amputated limbs with RPNI. [Case] A 61-year-old woman underwent amputation of both lower legs using RPNI for gangrene of both feet due to polyarteritis nodosa. She underwent additional left leg amputation 1 year and 7 months after the initial surgery due to poor healing of the left leg wound. At the time of re-amputation, free muscle graft and embedded tibial nerves ending with RPNI in the initial surgery were collected and histologically evaluated. [Results] Proliferation of nerve fiber bundles and sprouting of nerve ending of severed tibial nerve into free graft muscle was confirmed with HE and NF staining. [Discussion / Conclusion] To date, this is the first report showing sprouting of severed nerve in free muscle graft in amputation using the RPNI with a human sample. [Clinical significance] The results of this study will contribute to further understanding of pathophysiology of RPNI.

## W55-6

### **A case report: Septic arthritis of the knee joint which was difficult to judge as elderly-onset RA**

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Conflict of interest: None

[Objective] We reported that Septic arthritis of the knee joint which was difficult to judge as elderly-onset RA. [Case Report] The case was a 72-year-old woman. Although she had been treated at clinic her pain worsened and she became difficult to walk. and Consult our hospital. Severe right Knee pain complained and swelling was observed in the entire right lower limb. Blood sampling showed hyper-CRP and mild increase in blood sinking, but RF was negative. A huge bone cyst was found in the upper tibial bone, and EORA was suspected. Since it cannot be denied, joint puncture was performed, but the joint fluid leukocyte count was 700  $\mu$ L, the crystal was negative, and the culture was negative. In consultation with the patient, the surgical method was decided based on the  $\alpha$ -defensin value at the time of surgery. Intraoperative  $\alpha$ -defensin measurement showed a strong positive result, and it was judged to be septic arthritis. Washing and debridement were performed, and the bone cyst was supplemented with vancomycin in HOYA's Biopex®-R, which is a calcium phosphate paste. The patient's pain improved with the postoperative course, and CRP became negative. Six months after the operation, no abnormal findings were found in blood sampling, and the patient was able to T-cane walk.

## W56-1

### **JCR Member Questionnaire Study: Effect of Immunoserological Indicators on Pregnancy Tolerance in Patients with SLE**

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Conflict of interest: None

[Objective] This study was conducted to understand how physicians decide whether or not to accept a pregnancy in SLE patients with only abnormalities in serological markers remaining. [Methods] From December 2020 to January 2021, JCR society members (physicians) were asked a web-based questionnaire on pregnancy tolerance using a clinical scenario. The scenarios were as follows: (1) Age: 28/35 years old; (2) Serological data: negative anti-ds-DNA antibody, CH50 normal/anti-ds-DNA 30 IU/ml, CH50 24 IU/ml (mildly abnormal)/anti-ds-DNA antibody 120 IU/ml, CH50 14 IU/ml (highly abnormal); (3) Duration of stable clinical symptoms: 3/6 months. A total of 12 patterns were created by combining the three items, and the responses were randomly distributed. The analysis method was descriptive statistics, and generalized estimating equations were used to examine the effect on pregnancy tolerance. [Results] We received responses from 463 physicians; 84.9% were rheumatologists. Serological abnormalities, both mild and severe, associated with pregnancy non-tolerance (coefficients: -0.25,  $p < 0.001$  and -0.65,  $p < 0.001$ ). [Conclusions] Serological abnormalities, both mild and severe, were significantly correlated with physician's non-acceptance of pregnancy.

## W56-2

### **Analysis of the risk for pregnancy outcomes in patients with connective tissue disease who have not performed preconception care**

Rina Mino, Hiromi Shimada, Risa Wakiya, Shusaku Nakashima, Mikiya Kato, Taichi Miyagi, Yusuke Ushio, Koichi Sugihara, Mao Mizusaki, Kanako Chujo, Tomohiro Kameda, Hiroaki Dobashi

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Conflict of interest: None

[Objective] We clarify the effects of non-preconception care (PC) on pregnancy outcomes with connective tissue diseases (CTD). [Methods] We used the data from 131 cases which were treated from the time of pregnancy planning and gave birth from the pregnancy registry of rheumatic diseases in our institution. We retrospectively analyzed the association between the presence of PC and clinical course such as disease activity and treatment agents, or pregnancy outcomes. [Results] Of all 131 cases, PC was performed in 115 (87.7%) cases. In the non-PC group, all cases were unplanned pregnancies before pregnancy permission. Non-PC group, the dose of glucocorticoid was significantly higher ( $P < 0.01$ ), and the rate of increased dose of glucocorticoid due to elevated disease activity of underlying disease was also high ( $p < 0.01$ ). There was no significant difference in the live birth rate ( $P = 0.44$ ), however, the rates of preterm birth, low birth weight significantly increased in non-PC group (both of  $P < 0.01$ ). Along with this, the rate of neonatal intensive care unit management in postnatal newborns was significantly higher ( $P < 0.01$ ). [Conclusions] PC is an extremely important treatment strategy for patients with CTD who want to become mothers.

## W56-3

### **Serum C3 and titer of anti-dsDNA antibody are risk factors for preterm birth and low birth weight in patients with systemic lupus erythematosus**

Hiromi Shimada, Risa Wakiya, Shusaku Nakashima, Mikiya Kato, Taichi Miyagi, Yusuke Ushio, Koichi Sugihara, Rina Mino, Mao Mizusaki, Kanako Chujo, Tomohiro Kameda, Hiroaki Dobashi

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Conflict of interest: None

[Objective] We clarify which disease activity parameters at conception could be risk factors for preterm birth (PB) and low birth weight (LBW) in SLE patients. [Methods] We used the data of SLE patients who

had been treated at the planning for pregnancy and gave birth from rheumatic disease pregnancy registry. We collected SLEDAI score and the rate of LLDAS achievement, complement levels (C3, C4, CH50) and the titer of anti-dsDNA antibody, and retrospectively analyzed the association with PB, LBW. [Results] The subjects were 60 pregnancies of 45 patients. Of all cases, PB occurred in 14 cases (23.3%), and LBW occurred in 23 cases (38.3%). SLEDAI score and the rate of LLDAS achievement became risk factors for PB (both of  $p < 0.01$ ), and SLEDAI score was also a risk factor for LBW ( $P = 0.04$ ). Low level of C3 and the high titer of anti-dsDNA antibody was risk factors for PB ( $P = 0.03, 0.01$ ). Cases with low C3 and high anti-dsDNA antibody titers had an increased risk of PB ( $P = 0.02$ ). Low C3 and CH50 were risk factors for LBW ( $P = 0.02, 0.03$ ). Cases with low C3 and no decrease in CH50 were at higher risk ( $P = 0.03$ ). [Conclusions] We revealed that PB and LBW are strongly associated with disease activity at conception, and high serum C3 levels and high anti-dsDNA antibody titers became risk factors.

## W56-4

### A case of preeclampsia with SLE that was attempted to be differentiated from lupus nephritis by measuring the sFlt-1/PIGF ratio

Yuki Terashima<sup>1</sup>, Yuji Miyoshi<sup>1</sup>, Shuko Mishima<sup>1,2</sup>, Eisuke Kanematsu<sup>1</sup>, Tomoko Sano<sup>1</sup>, Daisuke Asatori<sup>1</sup>, Kazusa Saegusa<sup>1</sup>, Naoki Tanomogi<sup>1</sup>, Masahiro Iida<sup>1</sup>, Yoshitaka Ueda<sup>1</sup>, Eisuke Takamasu<sup>1</sup>, Kae Onishi<sup>1</sup>, Takayasu Kise<sup>1</sup>, Masako Utsunomiya<sup>1</sup>, Yoshiki Nagai<sup>1,3</sup>, Naoto Yokogawa<sup>1</sup>, Kota Shimada<sup>1</sup>

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Conflict of interest: None

[Case] A 31-year-old woman with G3P1 was diagnosed with SLE 6 years ago, and was treated with PSL 2 mg, azathioprine, and hydroxychloroquine with a SLEDAI-2K score of 0. Although she started taking low-dose aspirin from the 12<sup>th</sup> week of pregnancy, on week 32 she complained of elevated diastolic blood pressure and epigastric pain, with acute kidney injury, proteinuria, and elevated hepatic enzyme levels. She was admitted to the hospital for an emergency. On the 2nd day of hospitalization, renal function was poorly improved and proteinuria increased. Though no findings suggestive of extrarenal lesions of SLE existed, lupus nephritis was among differential diagnosis. Emergency cesarean section was performed as preeclampsia (PE). After surgery, renal function improved promptly, and she was discharged on POD7. The sFlt-1/PIGF ratio, which is known to be high in predicted PE, was high (120). [Clinical significance] Pregnancy with SLE has a high risk of PE, and differentiation from lupus nephritis is also important. The sFlt-1/PIGF ratio is a useful test for prediction of PE. In this case, it was clinically treated as PE, and the condition was clearly improved only by emergency cesarean section, suggesting that the sFlt-1/PIGF ratio is useful in the above differentiation.

## W56-5

### Pregnancy outcomes in female patients with rheumatoid arthritis who discontinue methotrexate treatment for hope a baby

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Division of Rheumatology, Department of Internal Medicine, St. Marianna University School of Medicine

Conflict of interest: None

[Objective] The purpose of this study was to investigate the effect of MTX withdrawal on pregnancy outcomes in patients with rheumatoid arthritis (RA) of reproductive age. [Methods] In this study, we investigated the pregnancy outcome, RA treatment, and infertility factors in RA patients who discontinued MTX for conceive. [Results] The mean age at onset of RA was 28.5 years, and the mean age at MTX withdrawal was 34.5 years. Of the 52 patients enrolled, 33 gave birth after discontinuing MTX and 19 did not. The age at the time of MTX discontinuation was significantly different between the childbirth and non-childbirth groups ( $p = 0.0258$ ). There was a significant difference in the use of NSAIDs and salazosulfapyridine between the two groups ( $p = 0.0079$  and  $p = 0.0438$ , respectively). Among the present cases, 4 out of 6 patients with RA who

were younger than 20 years of age became pregnant and gave birth after MTX discontinuation. [Conclusions] MTX may affect only mature follicles, and the effect has been reported to be reversible. The results of this study suggest that for successful delivery in women with RA, the decision to become pregnant should be made at the youngest possible age, NSAIDs should not be used, and the duration of MTX administration before pregnancy should be shortened.

## W56-6

### Smooth Transition Care for Patients with Childhood-Onset Rheumatic Diseases: Using Analysis of the Experience Process

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Conflict of interest: None

[Objective] The purpose of this study was to examine the process of living with the disease and the transitional support required by patients. [Methods] Consenting pediatric rheumatic disease patients aged 16 years or older who visited the outpatient clinic of the Department of Pediatrics at our hospital were evaluated using a semi-structured interview that included questions about basic attributes, school life with the disease, daily life, relationships with family and others, how they deal with the disease, and worries and anxieties about the disease. Analysis was conducted using the M-GTA method of continuous comparative analysis. [Results] Thirteen subjects aged 16-27 years were included in the study. Analysis using the verbal transcripts generated 2 categories were extracted based on the relationships among the 18 concepts. Eventually, they came to accept the transition to adulthood. In the course of the survey, it became clear that the patients were dealing with their illness through independence in disease management. [Conclusions] In order to facilitate smooth transitions, it will be necessary to open outpatient clinics that support the transition period, provide nursing services to support independence, and create places for patients outside of pediatric departments.

## W57-1

### Correlations between anti-DNA antibody and SLE disease activities using Kyoto Lupus Cohort (KLC)

Yuto Nakakubo<sup>1</sup>, Hideaki Tsuji<sup>1</sup>, Takeshi Iwasaki<sup>1</sup>, Mirei Shirakashi<sup>1</sup>, Ryosuke Hiwa<sup>1</sup>, Koji Kitagori<sup>1</sup>, Shuji Akizuki<sup>1</sup>, Ran Nakashima<sup>1</sup>, Hajime Yoshifuji<sup>1</sup>, Hideo Onizawa<sup>2</sup>, Akira Onishi<sup>2</sup>, Masao Tanaka<sup>2</sup>, Akio Morinobu<sup>1,2</sup>

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Conflict of interest: None

[Objective] To reveal the association between disease activities of systemic lupus erythematosus (SLE) and anti-DNA antibody (Ab). [Methods] Data were collected from Kyoto Lupus Cohort (KLC) from 2019 to 2021. First, we analyzed the correlation between SLE disease activities and anti-DNA Ab at one point. Next, correlations in the changes between the disease activities and anti-DNA Ab were analyzed. [Results] SLEDAI ( $n = 310$ ) was higher in patients positive for anti-DNA Ab ( $7.94 \pm 5.20$ ) than those negative for it ( $4.56 \pm 4.65$ ) ( $p < 0.0001$ ). SLEDAI had a weak correlation with anti-DNA Ab (RIA) ( $R = 0.239$ ,  $p < 0.0001$ ) and with anti-ds-DNA IgG (ELISA) ( $R = 0.240$ ,  $p < 0.0001$ ). Next, the changes in anti-DNA Ab and SLEDAI were analyzed in 100 patients. The observation period was  $419.9 \pm 180.6$  days, and the duration of the two visits was  $70.4 \pm 50.4$  days. The correlations were  $R = 0.043 \pm 0.15$  in random intervals,  $R = -0.30$  in the shortest interval, ( $61.6 \pm 40.6$  days), and  $R = -0.08$  in the longest interval ( $419.9 \pm 180.6$  days). [Conclusions] Anti-DNA Ab has a weak correlation with disease activity of SLE. It is useful for SLE management.

## W57-2

### The relationship between results of sonography and biomarkers in RA patients

Kimiko Hori<sup>1</sup>, Tsuyoshi Watanabe<sup>2</sup>, Takaya Sugiura<sup>2</sup>



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Conflict of interest: None

[Objective] We investigated the correlation between the results of joint sonography and CRP, ESR and MMP-3. [Subjects and methods] 60 joint sonography reports were applied. We investigated the correlation between biomarkers such as CRP, ESR, MMP-3 and joint sonography score (Total GS, PD, combined score, swollen joint count). The number of swollen joints of PD and GS were the sum of the numbers of Grade 2 or 3. The Combined score is based on the OMERACT score. For the statistical analysis, we use Spearman's rank correlation coefficient. [Results] 16 males and 44 females. Age  $72.7 \pm 11.9$  years. CRP  $2.58 \pm 2.87$  mg / dl. ESR  $67.7 \pm 34.4$  mm/h. MMP-3  $226.3 \pm 245.7$  (ng/mL). CRP and ESR values did not correlate with various echo parameters. MMP-3 showed a significant positive correlation with all parameters. The total GS score, and the number of swollen PD joint were highly correlated. [Discussion] Joint sonography is a useful index for the evaluation of rheumatoid arthritis. MMP-3 reflects joint destruction. Joint sonography also reflects early damage of joint. Elevation of joint sonography score and MMP-3 joint sonography score may predict a predictor of joint destruction. [Conclusion] Joint sonography did not correlate with CRP and ESR, but showed a positive correlation with MMP-3.

## W57-3

### The Examination of MBDA score in ACPA-negative rheumatoid arthritis

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<sup>2</sup>Department of Internal Medicine, Hokkaido Spinal Cord Injury Center

Conflict of interest: Yes

[Objective] ACPA has high sensitivity and specificity of RA, so it is used for diagnosis. However, even if ACPA is negative, RA may be diagnosed. Therefore, we investigated serum biomarkers useful for differential diagnosis between ACPA-negative RA and other joint diseases. [Methods] We measured ACPA, RF, and MBDA (multi-biomarker disease activity) scores for undifferentiated Arthritis cases (n = 167) within 1 year of onset. MBDA score is calculated from 12 serum biomarkers (MMP-1, MMP-3, IL-6, TNFR-1, VCAM-1, EGF, VEGF-1, YKL-40, leptin, Resistin, CRP, SAA). [Results] It was 79 of 167 cases that had a diagnosis of RA. There were 51 ACPA-positive cases, and 49 were diagnosed with RA. The sensitivity (62.0%), specificity (97.7%), and accuracy (80.8%) of ACPA in RA (n=79) were higher than those of other markers. 116 were ACPA negative, including 30 RA cases. Of the 30 cases, the MBDA score (cut off: 25) was positive (specificity: 81.4%, accuracy: 81.0%). [Conclusions] If a patient with joint pain is ACPA positive, early RA can be diagnosed. In addition, even if ACPA is negative, RA is suspected, and if MBDA score is positive, it is highly possible that RA can be diagnosed in the future.

## W57-4

### Examination of IL-33 production and cd57 (hnk-1)-expressing NK cell inpatients with ACPA-negative RA

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Conflict of interest: None

[Objective] The trend of IL-33 as an alarm in danger has been investigated for its relationship with various immune diseases. In this study, we investigated the relationship between IL-33 and innate immune NK cell differentiation marker (CD57)-expressing cells in patients with rheumatoid arthritis. [Methods] The subjects were 174 patients who visited the rheumatology department, and the breakdown was unknown (UA: 67) and rheumatoid arthritis (RA: 107) patients. RA patients were divided into two

groups: the ACPA antibody negative group (47) and the positive groups (60). The study measured IL-33, CRP, RF, Ig (GAM), IL-6, LBP and NK cells. [Results] The IL-33 concentration (mean SE pg/ml) of RA patients was  $13.4 \pm 4.2$  in the ACPA negative group and  $74.4 \pm 3.4$  in the positive group, which were significantly higher in the positive group ( $p < 0.02$ ). CD57 (HNK-1) was weakly correlated with IL-33 in the ACPA-positive group ( $r = 0.283$ ). In other studies no significant changes were observed between the ACPA negative group and the positive group. [Conclusions] IL-33 flows out of the cell during cell injury. From this study, a correlation between IL33 and CD57 (HNK-1) was observed in ACPA-positive patients, so the trend of NK cells is also important locally in the joints.

## W57-5

### Comparative study of both RF-anti-CCP antibody-negative RA and RF-anti-CCP antibody-positive RA

Takeshi Kaneko<sup>1</sup>, Kahori Ishida<sup>1</sup>, Taro Akira<sup>1</sup>, Makiko Ikoma<sup>1</sup>, Takehiro Suzuki<sup>1</sup>, Takashi Hosokawa<sup>1</sup>, Koji Nomura<sup>2</sup>, Hiroshi Fujiwara<sup>1</sup>

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<sup>2</sup>Department of Orthopedic Surgery, Osaka General Medical Center

Conflict of interest: None

[Objective] Clinical characteristics of patients with rheumatoid arthritis (RA) have been reported to change over time. We compared clinical features of rheumatoid factor (RF) / anti-CCP antibody (ACPA) in patients who were RA negative and those who were RA positive. [Methods] We retrospectively compared clinical features of patients with negative RA (negative group) and those with positive RA (positive group) between April 2017 and March 2020. [Results] Of 359 cases, there were 118 cases (32.9%) in the negative group and 190 cases (52.9%) in the positive group. The average age of onset was higher in the negative group (66.3 years vs. 58.0 years [ $P < 0.001$ ]). The amount of MTX administered in March 2021 was lower in the negative group (8.21 mg / week, vs 9.52 mg / week [ $P = 0.0068$ ]). The negative group used fewer bDMARDs or JAK inhibitors than the positive group (27.1% vs. 41.6%). The mean value of DAS28-ESR at 1 year after diagnosis was lower in the negative group (2.57 vs. 2.96 [ $P = 0.0060$ ]). The rate of interstitial pneumonia complications was also lower in the negative group (6.78% vs. 17.4%). [Conclusions] The average age of onset was higher in the negative group. The negative group had a lower incidence of interstitial pneumonia and a lower mean DAS28-ESR after treatment.

## W57-6

### Analysis of the clinical features of elderly onset rheumatoid arthritis (EORA)-in case definition of elderly is 75-years and over

Masayuki Miyata

Center for Rheumatology and Collagen Disease, Fukushima Red-Cross Hospital

Conflict of interest: None

[Objective] To clarify clinical features of EORA [Methods] We enrolled 100 EORA patients in our department. These patients were divided into two groups; 45 seropositive and 55 seronegative EORA. We investigated the differences between the groups. [Results] Female/male was 82/18 and 56/44 in seropositive and seronegative EORA, respectively. CRP values at the first visit of seropositive and seronegative were  $3.4 \pm 4.0$  and  $8.1 \pm 5.7$  mg/dl, respectively. We calculated scores by using ACR/EULAR classification criteria in seropositive and seronegative RA. The scores in seropositive and seronegative were  $7.0 \pm 1.8$  and  $4.0 \pm 1.7$ , respectively. There was significant difference. The scores in seronegative EORA were low, because affected joints size tend to be larger and affected joints number was smaller. In this regard, it is necessary to apply US to evaluate exact number of affected joints. The prevalence of interstitial pneumonia was 38% and 7% in seropositive and seronegative, respectively. [Conclusions] The differences were seen in female/male ratio, CRP value, scores of point, affected joints size and number, and prevalence of interstitial pneumonia between seropositive and seronegative. Seropositive has features of traditional RA, in contrast, seronegative has features of EORA.

## W58-1

### A clinical Study of SLE treated by Belimumab

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Nephrology and Rheumatology, Kyorin University

Conflict of interest: None

[Background] According to the EULAR recommendations, glucocorticoid (GC) should be administered as low as possible in the treatment of SLE. Belimumab (BLM), a humanized monoclonal antibody against soluble B lymphocyte stimulating factor, was launched in Japan in 2017, and is expected to be effective in suppressing disease activity and reducing GC use. [Objective] The aim of this study was to estimate the effect of BLM added to conventional therapy retrospectively. [Methods] This study was a single-center case-control study. The observation period was from January 2018 to March 2021, and we compared the clinical outcomes of patients who were administered BLM with those who did not in our hospital. [Results] BLM was mostly administered to patients in the maintenance phase of treatment (95%). The median age was 39 years, and the continuation rate was 91%. In the evaluation of disease activity, a decreasing in anti-ds-DNA antibodies and a reduction in the GC dose were found. As for the effect on lupus nephritis, there was no significant difference in proteinuria and eGFR after induction, but the relapse rate after GC reduction was low. [Conclusions] BLM could reduce the disease activity of SLE and may have the saving effect of GC dose, thereby improving the long-term outcome of SLE patients.

## W58-2

### Effects of belimumab (BE) in patients with systemic lupus erythematosus (SLE)

Tatsuo Ishizuka, Kei Fujioka, Hideki Tani, Akari Miwa, Mariko Tangiku  
Gifu Municipal Hospital

Conflict of interest: None

[Objective] We have examined the clinical effects in patients with SLE. [Methods] We selected 25 cases (F/M 21/24) from 2018 to 2021 in patients with SLE treated with BE (iv or sc) to clarify the effect of BE on immunological data, disease activities (SLEDAI), activities of daily living score (AS) (Lupus 26: 849, 2017), and dose of prednisolone (PSL) after treatment for 6 months (M) and 12 M. [Results] Mean BMI and duration of disease were  $20.7 \pm 4.3$  kg/m<sup>2</sup> and  $12.8 \pm 13.5$  years. After treatment with BE for 6 M and 12 M, anti-dsDNA antibodies (AU/ml) were significantly decreased ( $p < 0.025-0.05$ , before: vor  $25.7 \pm 22.6$ , 6 M  $16.3 \pm 12.5$ , 12 M  $13.4 \pm 7.8$ ), C3 and C4 were not significantly decreased, and CH50 (U/ml) were only significantly increased for 12 M ( $p < 0.05$ , vor  $28.6 \pm 10.4$ , 12 M  $35.2 \pm 9.8$ ). Levels of SLEDAI score were significantly decreased ( $p < 0.01$ , vor  $9.7 \pm 4.2$ , 6 M  $5.1 \pm 2.9$ , 12 M  $4.0 \pm 3.1$  and AS were also significantly improved ( $p < 0.01-0.05$ , vor  $28.4 \pm 14.8$ , 12 M  $14.7 \pm 16.6$ , 24 M  $16.8 \pm 11.8$ ). Doses of PSL (mg) were significantly decreased ( $p < 0.001-0.002$ , vor  $10.8 \pm 7.5$ , 6 M  $6.1 \pm 3.6$ , 12 M  $4.9 \pm 3.3$ ). [Conclusions] Effects of BE on immunological data, disease activities, AS and dose reduction of PSL were excellent in patients with SLE. BE might be available for clinical remission.

## W58-3

### Current status of belimumab treatment for systemic lupus erythematosus at our hospital

Mao Mizusaki, Risa Wakiya, Shusaku Nakashima, Hiromi Shimada, Koichi Sugihara, Mikiya Kato, Taichi Miyagi, Yusuke Ushio, Rina Mino, Kanako Chujo, Tomohiro Kameda, Hiroaki Dobashi  
Rheumatology, Kagawa University Hospital

Conflict of interest: None

[Objective] The purpose of this study was to determine the current status of belimumab (BEL) administration to patients with systemic lupus erythematosus (SLE) in our hospital. [Methods] We retrospectively analyzed the reasons for additional BEL administration, adverse events, and

disease activity indicators in SLE patients who received BEL in our hospital after 2018. [Results] Five cases of SLE were included in this study. Four of the five patients were female, with a mean age of  $51.4 \pm 9.6$  years and a mean duration of illness of  $17.4 \pm 10.0$  years. The reasons for additional BEL administration were decreased PSL in five patients, refractory pericarditis in one patient, skin rash and arthritis in two patients, and immunological activity in two patients. The mean disease activity before the introduction of BEL was SLEDAI 4±4, and LLDAS was achieved in 3 patients. After 12 weeks of BEL induction, SLEDAI improved in 2 patients and 1 patient achieved new LLDAS. [Conclusions] At our institution, BEL was additionally administered to SLE patients with refractory disease and was effective; with the exception of one case, there were no problematic adverse events. Serum cytokine analysis before and after BEL treatment will be included in the discussion.

## W58-4

### The impact of belimumab on SLE after negative anti-ds-DNA antibody

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Conflict of interest: None

[Objective] Belimumab (BEL) has been reported to be effective in controlling disease activity in systemic lupus erythematosus (SLE) patients with anti-ds-DNA antibody positive and low complement. Can we expect BEL to be effective in patients who are positive for anti-ds-DNA antibodies at diagnosis and subsequently negative for anti-ds-DNA antibodies, but who still have active SLE? [Methods] We retrospectively observed the effects of BEL on corticosteroid (CS) dose reduction and disease activity in patients who met the criteria. The endpoints were CS dose and SLEDAI at induction and 24 weeks after induction of BEL. [Results] Six eligible SLE patients attending our hospital (six females, age  $44.7 \pm 15.8$  years) were enrolled in the study. The duration of disease was  $13.3 \pm 15.2$  years. There was a trend of improvement in SLEDAI from  $9.0 \pm 4.9$  to  $1.7 \pm 1.5$  before and after 24 weeks of BEL ( $p = 0.029$ ). Prednisolone use showed a decreasing trend from  $7.5 \pm 4.2$  mg to  $4.0 \pm 0.9$  mg before and after 24 weeks of BEL ( $p = 0.036$ ). [Conclusions] We observed a reduction in CS and improvement in SLEDAI after 24 weeks of BEL treatment in SLE patients who had become negative for anti-ds-DNA antibodies. It is possible that BEL may have an add-on effect even after negative anti-ds-DNA antibodies.

## W58-5

### Comparison of multi-target therapy and addition of belimumab as an intensified treatment for SLE

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Conflict of interest: None

[Objective] Belimumab (BLM) has been marketed and used in Japan since 2017 as a novel treatment for systemic lupus erythematosus (SLE). BLM is usually added for treatment intensification and glucocorticoid (GC) reduction, but it is not clear how much difference it makes compared to existing treatment intensification methods. In the present study, we compared the efficacy and safety of multi-target therapy and BLM for the treatment of SLE. [Methods] we collected and analyzed the data from the electronic medical records of SLE patients who were already using immunosuppressive drugs (TAC/CYA or MMF/MZR) and who added immunosuppressive drugs (MT group) or BLM (BLM group). [Results] Patients were 11/10 in MT/BLM group. There were no differences in baseline characteristics, disease activity, or GC use. There was no significant difference between the two groups in the course of treatment after intensification. However, the continuation rate was slightly higher in the BLM group, and

adverse events tended to be slightly higher in the MT group. [Conclusions] Multi-targeted therapy and the addition of BLM were equally effective in enhancing treatment of SLE, but the addition of BLM may be superior in terms of persistence and safety.

## W58-6

### Postmarketing surveillance of safety of belimumab (BEL) in Japanese adult patients (pts) with systemic lupus erythematosus (SLE): interim report

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Conflict of interest: Yes

[Objective] Evaluate the safety of BEL in pts with SLE. [Methods] Adverse events (AEs) were collected from December 2017 through a drug-use survey (GSK Study 207735). The maximum observation period from BEL initiation was 156 weeks. [Results] Of 1229 pts evaluated at Week 52, 763 were available for safety analysis in September 2021; 90.3% were female; average age: 41.7 years; average SLE duration: 11.9 years. The combination of immunosuppressants (excluding steroids) was 83.2%, use of antimalarials was 47.6%, and median observation period was 365 days. Overall, 259 AEs occurred; 117 were serious. Most common AEs: infections and parasites (n=44), musculoskeletal and connective tissue disorders (n=21), and renal and urinary tract disorders (n=17). There were cases of 'depression/suicide contemplation/suicide attempt' (an "important identified risk" of BEL; n=3 severe), herpes zoster ("serious infectious disease"; n=3), and malignant tumor ("significant potential risk"; n=5). The mean (SD) daily steroid dose (prednisone-equivalent) reduced from baseline 11.6 (9.3) mg to 7.1 (4.8) mg at Week 52. [Conclusions] Safety data reported in this interim analysis were similar to reports in clinical trials and overseas follow-up observations. Pharmacovigilance analyses are ongoing. **Funding:** GSK.

## W59-1

### Analysis of factors involved in relapse in systemic lupus erythematosus and examination of steroid tapering discontinuation

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Conflict of interest: None

[Objective] The goal of the treatment of systemic lupus erythematosus (SLE) is to reduce the dose of steroids. The purpose of this study is to extract the factors related to relapse and steroid discontinuation. [Method] The medical records of 123 patients with SLE were retrospectively examined, and a situation that requires enhanced treatment is defined as relapse. 17 patients who had one or more relapses and 106 patients who did not have relapses (22 patients: more than PSL 5 mg, 58 patients: PSL 5 mg or less, 26 subjects: no PSL) were analyzed. [Results] There were significantly more relapses in males, lupus nephritis and Class IV histological type. There were significantly fewer relapses in patients taking hydroxychloroquine. Age tended to be younger in cases of relapse. In patients with PSL discontinuation, there was less neuropsychiatric lupus and the rate of tacrolimus concomitant use was low. [Conclusion] In the treatment of sys-

temic lupus erythematosus, lupus nephritis (especially Class IV), being young, and neuropsychiatric lupus interfere with steroid tapering, and it is speculated that steroids play an important part in controlling these phenotypes. In addition, the steroid tapering effect of the combined use of hydroxychloroquine was clear.

## W59-2

### A study of possible discontinuation of prednisolone (PSL) in 19 cases of SLE under the use of immunosuppressive agents and regulators

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Conflict of interest: None

[Objective] The purpose of this study was to retrospectively examine the clinical findings in patients with SLE on maintenance therapy who were able to discontinue PSL and those who continued to take PSL, and to examine the clinical differences between the two groups. [Methods]: We analyzed the relationship between the following items and PSL discontinuation in patients with SLE. We analyzed the relationship between the following items and PSL discontinuation in patients with SLE: (1) patient background (years of disease and presence of complications), (2) treatment (concomitant use of immunosuppressants and immunomodulators), (3) laboratory findings (presence of anti-dsDNA antibody, anti-sm antibody, complement and IgG). [Results] Of the 10 patients who discontinued PSL, concomitant medications included hydroxychloroquine (HCQ) in 8, tacrolimus (Tac) in 4, mycophenolate mofetil (MMF) in 5, and belimumab (BLM) in 3. PSL was more likely to be discontinued in patients using HCQ. (Odds ratio 5.54, P value 0.092) [Conclusions] HCQ was found to be associated with PSL discontinuation regardless of other treatments, reaffirming its usefulness in PSL discontinuation.

## W59-3

### Relationship between rapid glucocorticoid tapering regimen and clinical outcomes in patients with proliferative lupus nephritis

Hayato Shimizu<sup>1,2</sup>, Hideki Oka<sup>1,2</sup>, Shuji Sumitomo<sup>2</sup>, Maki Kanamori<sup>1</sup>, Hiroaki Nishioka<sup>1</sup>, Koichiro Ohmura<sup>2</sup>

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Conflict of interest: None

[Objective] Rapid glucocorticoid (GC) tapering has been recommended for lupus nephritis (LN) recently. The aim of this study is to investigate the relationship between GC tapering regimen and clinical outcomes in patient with LN. [Methods] Patients with proliferative LN (class III or IV) were included and divided into two groups according to GC dosage at month 6. We retrospectively compared primary efficacy renal response (PERR) and complete renal response (CRR) at month 24 between the two groups. [Results] Twenty-seven patients were included. The mean eGFR and urine protein-to-creatinine ratio (UPCR) at baseline were 66.7 mL/min/1.73 m<sup>2</sup> and 3.125 g/gCr, respectively. Rapid GC tapering group (PSL ≤ 10 mg/day at month 6) and conventional GC tapering group (PSL > 10 mg/day at month 6) were 11 and 16 patients, respectively. Baseline characteristics were balanced between the two groups except for use of cyclophosphamide (CY) or mycophenolate mofetil (MMF). Achievements of PERR and CRR at month 24 were similar between the two groups (adjusted OR 1.52 (p=0.743) and 2.99 (p=0.341), respectively, after adjustment of CY/MMF usage and UPCR at baseline). [Conclusions] Our results suggest rapid GC tapering regimen is as effective as conventional GC tapering for patients with proliferative LN.

## W59-4

### Retrospective analysis on the efficacy and safety of belimumab in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objective] To evaluate the efficacy and safety of belimumab (BEL) in patients with systemic lupus erythematosus (SLE) in our institute. [Methods] Medical records of 33 SLE patients who had received BEL were retrospectively analyzed. [Results] The average age was  $45 \pm 12.6$  years. The average disease duration of SLE was  $14.0 \pm 8.6$  years. Average anti-ds-DNA antibody titer was  $59.7 \pm 89.6$  U/ml, and average SLEDAI-2K was  $4.6 \pm 3.2$ . ALL patients received prednisolone (PSL) and the average dose of PSL was  $12.0 \pm 13.6$  mg/day. Three months after BEL administration, SLEDAI-2K decreased significantly to  $2.5 \pm 2.1$  and anti-ds-DNA antibody titer decreased significantly to  $17.8 \pm 25.2$  U/ml. In addition, the average dose of PSL could be lowered to  $6.1 \pm 3.5$  mg/day significantly. Eight cases discontinued BEL; ineffectiveness in 2 cases, hope to get pregnant in 2 cases, and adverse events in 4 cases. [Conclusions] BEL could improve SLE disease activity and reduce the dose of steroids. There were no serious adverse events during 3 months of BEL therapy in our institute. BEL could improve SLE disease activity and reduce the dose of steroids. There were no serious adverse events during 3 months of BEL therapy in our institute.

## W59-5

### Therapeutic efficacy of belimumab and steroid reduction for systemic lupus erythematosus in our hospital

Daisuke Tomita, Yuji Nozaki, Hirotaka Yamazawa, Kaori Ishimura, Chisato Ashida, Akinori Okada, Tetsu Itami, Kenji Sakai, Toshihiko Shiga, Kazuya Kishimoto, Koji Kinoshita, Masanori Funauchi, Itaru Matsumura  
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Conflict of interest: None

In SLE, it is important to achieve low disease activity to reduce organ damage and maintenance dose steroids to reduce side effects. Belimumab (BEL) is a biologic agent that can be used for SLE and has been reported to improve disease activity and reduce steroid dose. It has also been reported to be effective in the treatment of active lupus nephritis. In this study, we investigated the clinical course of SLE patients who were treated with BEL in our department. We analyzed the patient background of 34 patients who were introduced with BEL after 2018, SLEDAI-2K, LLDAS achievement rate, and PSL weight loss effect 24 weeks after the introduction. The mean age of the patients was 45.5 years, and the mean age of the patients was 45.5 years. The mean age was  $45.1 \pm 13.4$ , the mean disease duration was  $14.3 \pm 11.5$ , and the female ratio was 83.9%. The mean PSL dose was  $11.8 \pm 3.5$  mg. The PSL dose after 24 weeks of BEL was  $7.9 \pm 3.5$  mg, which was 18.0% lower. In terms of disease activity, the SLEDAI-2K improved to  $3.8 \pm 3.5$ , and the LLDAS achievement rate significantly increased from 23.3% to 50%. The results suggest that BEL can improve SLE disease activity and reduce PSL. In addition, it may increase the LLDAS achievement rate and reduce the risk of organ damage.

## W59-6

### Glucocorticoid discontinuation in pediatric-onset systemic lupus erythematosus: a single-center experience

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Conflict of interest: None

**Objective:** Glucocorticoid (GC) discontinuation in systemic lupus erythematosus (SLE) might be achievable with the advent of new therapeutic options. **Methods:** This study included 31 children with diagnosed pediatric SLE between 2002 and 2021, after the exclusion of patients who were followed for less than one year and those lost to follow-up. **Results:** GC could be discontinued in 19 (61%) patients during a median observation period of 105.5 (17-221) months. Of them, 5 (26%), 12 (63%), and 18 (95%) patients could discontinue GC in 3, 5, and 10 years from treatment initiation, respectively. Additionally, 18 patients did not experience flares

after GC discontinuation during a median duration of 37.2 (7.2-106.8) months. Three patients achieved drug-free remission. At last follow-up, all patients achieved low disease activity and, 19 and 9 patients were receiving mycophenolate mofetil (MMF), MMF plus calcineurin inhibitor, respectively. Flares were observed in 15 patients. MMF for initial immunosuppressants ( $P = 0.01$ ) and shorter interval between therapy initiation and achieving maintenance GC dose ( $P = 0.001$ ) were associated with significantly reduced flare risk. Femoral head necrosis was observed in two patients. **Conclusion:** These results support GC discontinuation in pediatric SLE.

## W60-1

### Clues to mortality trends and their related factors in IgG4-related disease: A Japanese single-center study

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Conflict of interest: None

**Objectives:** This study aimed to clarify mortality trends and its related factors in patients with immunoglobulin G4-related disease (IgG4-RD). **Methods:** We retrospectively reviewed the medical records of patients with IgG4-RD at a single center in Japan. We calculated the crude mortality rate and the standardized mortality ratio (SMR) using national Japan mortality statistics. Cox regression analyses were performed to assess mortality-related factors. **Results:** A total of 179 patients with IgG4-RD were included and the median follow-up from diagnosis was 47 months (IQR 19-96). The crude mortality rate was 11.1 per 1,000 person-years, and SMR was 0.86 (95% confidence interval [CI] 0.41-1.59) in our cohort. Univariate Cox regression analyses indicated that the number of affected organs at diagnosis (hazard ratio [HR] 1.45, 95% CI 1.02-2.05), eGFR  $< 45$  mL/min/1.73 m<sup>2</sup> at diagnosis (vs.  $\geq 45$ , HR 8.48, 95% CI 2.42-29.79), and the presence of malignancy during the clinical course (HR 3.93, 95% CI 1.10-14.02) had a significant impact on the time to death.

## W60-2

### Identification and pathway analysis of T/B cells specific differentially expressed genes by RNA-Seq in affected salivary glands of patients with IgG4-related disease

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Conflict of interest: None

[Objective] To clarify T/B cells specific differentially expressed genes (DEGs) by RNA-Seq in affected organs of patients with IgG4-related disease (IgG4-RD). [Methods] Pathologically confirmed submandibular glands (SMGs) and PBMC were collected from treatment naïve definite IgG4-RD patients (N=3), subsequently CD3<sup>+</sup>T cells and CD19<sup>+</sup>B cells were sorted by MACS. We compared the gene expression of 1) CD3<sup>+</sup>T cells and 2) CD19<sup>+</sup>B cells by RNA-Seq between SMGs and PBMC, and performed principal component analysis (PCA), and pathway analysis using Ingenuity Pathway Analysis (IPA). [Results] 1) In PCA, gene expression patterns of CD3<sup>+</sup>T cells of SMGs differed from those of PBMC. 214 up-regulated and 50 down-regulated DEGs were identified in SMGs compared with PBMC. In IPA, Th2, Th1, Toll-like receptor (TLR), SLE in T cell pathway, and IL-17 signaling were up-regulated in SMGs. 2) In PCA, gene expression patterns of CD19<sup>+</sup>B cells of SMGs differed from those of PBMC. 630 up-regulated and 109 down-regulated DEGs were identified in SMGs compared with PBMC. In IPA, SLE in B cell pathway, complement system, IL-15 production, and IL-8 signaling were up-regulated in SMGs. [Conclusions] Using RNA-Seq, we identified DEGs and possible pathogenic pathways in T/B cells derived from affected organs of IgG4-RD.

## W60-3

### Validation of performance of the 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-related disease (IgG4-RD)

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Conflict of interest: None

**Objective** To verify performance of 2020 RCD criteria for IgG4-RD (2020 criteria). **Methods** We retrospectively analyzed 1) final critical diagnosis, performance of 2) 2011 and 3) 2020 criteria, and 4) concordance of two sets of criteria, in patients with suspected IgG4-RD or mimickers who hospitalized between Jan 2020 and Aug 2021, and underwent biopsy of masses and measurement of serum IgG4. **Results** 1) Among 122 cases, 58 cases were diagnosed as IgG4-RD, and 64 cases were as others (Sjögren's syndrome: 43, malignant lymphoma: 7, Castleman's disease: 2, Kikuchi's disease: 1, sarcoidosis: 1, and undefined: 10). 2) For 2011 criteria, IgG4-RD cases were regarded as definite in 24, probable in 0, possible in 32, unsatisfied in 2 cases. Other cases were 0, 0, 11, and 53 cases, respectively. Sensitivity and specificity of definite were 41.4% (95%CI: 36.2-41.4%) and 100% (95.3-100%). 3) For 2020 criteria, IgG4-RD cases were regarded as definite in 26, probable in 1, possible in 30, unsatisfied in 1 cases. Other cases were same as in 2011 criteria. Sensitivity and specificity of definite were 44.8% (36.9-44.8%) and 100% (95.3-100%). 4) Kappa coefficient between two sets was 0.9. **Conclusions** The concordance between two sets was high. The sensitivity of 2020 criteria was higher than 2011 criteria.

## W60-4

### Comparison of clinicopathological features of patients with and without hypocomplementemia in IgG4-related kidney disease (IgG4-RKD): multi-center study of IgG4-RKD working group in Japanese Society of Nephrology

Takako Saeki<sup>1</sup>, Yoshifumi Ubara<sup>2</sup>, Yoshinori Taniguchi<sup>3</sup>, Takao Saito<sup>4</sup>, Hitoshi Nakashima<sup>5</sup>, Mitsuhiro Kawano<sup>6</sup>

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Conflict of interest: None

[Objective] To compare the clinicopathological features of Japanese patients with IgG4-related kidney disease (IgG4-RKD), with and without hypocomplementemia. [Methods] We retrospectively examined the clinicopathological features of 55 patients with definitely diagnosed IgG4-RKD, collected from the institutions associated with IgG4-RKD working group between April 2012 and May 2019, with reference to the presence of hypocomplementemia. [Results] Among 55 patients with IgG4-RKD, 39 (64%) had hypocomplementemia. In the hypocomplementemia group, serum IgG levels and non-IgG4 IgG levels (the total IgG minus IgG4), were significantly higher and eGFR before treatment was significantly lower. There was no significant inter-group difference in the levels of serum IgG4, IgE and the number of extra-renal involved organs. Renal specimens were obtained in 49 patients (hypocomplementemia 59%). In the hypocomplementemia group, the degree of interstitial inflammatory cell expansion and the frequency of deposition of IgG or complement on the tubular basement membrane in immunofluorescence study were significantly higher. [Conclusions] Hypocomplementemia in IgG4-RKD is associated with elevated serum levels of IgG subclasses other than IgG4 and might be related to renal interstitial inflammation.

## W60-5

### Clusters according to organ involvements and their serological features in IgG4-related disease

Yusuke Sakaue, Kazuhiro Kurasawa, Azusa Kikuchi, Sara Komatsu, Yoriko Tasaka, Yui Yoshida, Yuta Takamura, Tomoyuki Miyao, Ayae

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Rheumatology, Dokkyo Medical University

Conflict of interest: None

[Objective] To determine whether there exist subgroups in IgG4-related disease (IgG4RD), we performed cluster analysis according to organ involvement and clarified the serological characteristics of each cluster. [Methods] Patients with IgG4RD diagnosed from 2009 to 2021 at our hospital were enrolled. Cluster analysis was performed according to the presence or absence of organ involvement, and the clinical and serological characteristics of each cluster were analyzed. [Results] The subjects were 110 patients with IgG4RD (79 males, 31 females, average age 65.2 years). Seven clusters were identified: 1) Systemic type with involvement of lacrimal gland, salivary gland, lymph node, retroperitoneal fibrosis (RPF), kidney (n = 15); 2) Lacrimal gland type (n = 22); 3) Salivary gland type (n = 15); 4) Lymph node type (n = 11); 5) RPF type (n = 11); 6) Lung type (n = 15); 7) Autoimmune pancreatitis type (n = 21). No differences were found in gender or age and levels of IgG, IgG4, and IgE. However, IgG4 / IgG (%) were elevated in clusters with Mikulicz disease-like features (systemic, lacrimal, and salivary gland types) compared to lymph node type and RPF type (p < 0.01). [Conclusions] In IgG4RD, there were subgroups characterized by organ involvement and serological findings.

## W60-6

### Clinical features of immunoglobulin G4-related disease with high peripheral blood eosinophil

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Conflict of interest: None

[Objective] Immunoglobulin G4-related disease (IgG4)-related disease (IgG4RD) is a fibroinflammatory condition and IgG4-positive lymphoplasmacytic infiltration can occur in almost all organs. In some patients, IgG4RD is complicated with hypereosinophilia. This study aimed to investigate eosinophilia in IgG4RD. [Methods] We enrolled patients with IgG4RD who were diagnosed from April 2008 to December 2020 in Tottori university hospital. Patients were divided into high eosinophil group (HG: >500/ $\mu$ L) and low eosinophil group (LG:  $\leq$ 500/ $\mu$ L) according to the eosinophil blood count at diagnosis. We retrospectively reviewed the clinical features of the two groups. [Results] A total of 32 patients were enrolled for this study. Eosinophilia was identified in five cases (15.6%) at diagnosis. The median number of organ involvement was 5 in HG and 3 in LG. Median erythrocyte sedimentation rate was 105 mm/h and 44 mm/h (p = 0.056), median serum albumin was 3.1 g/dL and 3.9 g/dL (p = 0.045), and complication of malignancy was 80% and 25.9% (p = 0.037) for HG and LG, respectively. Serum IgG4 (HG: 1160 mg/dL vs. LG: 548 mg/dL) was tended to higher in the high eosinophil group. [Conclusions] Proper care must be taken for malignancies in patients with IgG4RD who are complicated with hypereosinophilia.

## W61-1

### Effect of sarilumab on unacceptable pain and inflammation control in Japanese patients with moderately-to-severely active rheumatoid arthritis (RA): post-hoc analysis of a phase 3 study (KAKEHASI)

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Conflict of interest: Yes

[Objective] To investigate the effect of sarilumab (SAR) on unacceptable pain (UP) and inflammation control in patients (pts) with moderately-to-severely active RA. [Methods] In this post-hoc analysis of the KAKEHASI study, 243 pts received SAR 150 mg, SAR 200 mg or placebo

(PBO) every 2 weeks, all in combination with methotrexate, over 52 weeks. Change from baseline (BL) in percentage of pts with UP (visual analogue scale [VAS] >40 mm; Svensson B, et al. Scand J Rheumatol, 2020) was assessed. [Results] Mean pain VAS at BL ranged from 54.9-67.1 mm; 191/242 (78.9%) pts presented with UP. At Week (Wk) 16, the proportion of pts with UP decreased to 64.0% (48/75) with PBO and 28.5% (43/151) with SAR ( $P<.001$  vs BL). SAR showed fast onset of action with a sustained reduction in the proportion of pts with UP vs PBO ( $P<.05$ ) from Wk 2. At BL, 50.6-57.1% of patients presented with both UP and CRP  $\geq 1$  mg/dL; at Wk 2 and Wk 16, this was reduced to 6.3% (10/160) and 2.0% (3/150), respectively, with SAR and 48.1% (39/81) and 39.2% (29/74), respectively, with PBO. A higher proportion of patients achieved inflammation control without UP with SAR 200 mg than with SAR 150 mg as early as Wk 2. [Conclusions] SAR administration reduced UP and inflammation in Japanese RA patients.

## W61-2

### Efficacy of Sarilumab to Failure of Biological Therapy in Patients with Rheumatoid Arthritis in Our Cases

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Conflict of interest: None

**Background/Objectives:** Eight biologics (excluding biosimilars) and five Janus kinase (JAK) inhibitors are available for rheumatoid arthritis (RA) in Japan. To clarify the position of sarilumab, the second anti-IL-6 receptor antibody, this study retrospectively examined our patients. **Subjects:** Thirty-three RA patients observable for 24 weeks, with sarilumab treatment at Saitama Medical University Hospital and Japanese Red Cross Ogawa Hospital by October 2021. **Results:** Of the 33 patients, 23 had a history of biologics or JAK inhibitors use, and 11 had a history of two or more drugs use. Five of 33 cases dropped off within the 24-week observation period but had no severe adverse events. The mean CDAI after 24 weeks was significantly improved at 5.71, also in the group with history of other biologics/JAK inhibitors use, from 15.52 to 6.66. The group with history of two or three biologics/JAK inhibitors use other than tocilizumab also showed a significant improvement (the mean CDAI from 20.26 to 8.40), whereas five patients with history of tocilizumab use showed a trend toward improvement but did not reach significant difference (from 15.48 to 9.12). **Conclusion:** Sarilumab was effective also in patients switching from other biologics excluding Tocilizumab and JAK inhibitors.

## W61-3

### Comparisons of clinical outcomes between sarilumab and tocilizumab in rheumatoid arthritis in clinical practice: Results from the TBCR study group

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Conflict of interest: Yes

[Objective] Following tocilizumab (TCZ), a new anti-IL-6R agent for rheumatoid arthritis (RA), sarilumab (SAR) has been available since 2018.

We analyzed the short-term outcomes of SAR, including comparisons with TCZ, using data from a multicenter study. [Methods] From the multicenter registry (TBCR), we retrospectively analyzed RA patients who started SAR 200 mg (N=90) or TCZ (N=98) after the launch of SAR and were followed-up for at least 24 weeks. Missing values were imputed by LOCF. [Results] TCZ was subcutaneous in 41.7%. The SAR group had a longer disease duration (16.5 vs 9.1 years), a higher Stage 3/4 (58.5 vs 43.8%), and a higher proportion of prior biologics (72.7 vs 51.0%). DAS28-CRP improved from 4.34/4.57 (SAR/TCZ) at week 0 to 2.29/2.37 at week 24, with no difference between groups. The 24-week retention rate was 94.6% for SAR and 93.6% for TCZ. Analysis within the SAR group showed that the remission rate at 4 weeks in Bio-naïve was higher than that in Bio-switch (57.9 vs 28.6%), but no significant difference at 24 weeks. [Conclusions] Under the different patient background, SAR was as effective as TCZ. The initial response of SAR was better in the Bio-naïve but there was no difference at 24 weeks, suggesting that a clinical response to Bio-switch may be expected.

## W61-4

### RAPID-3 at 1 month after sarilumab may be a predictor of treatment continuation

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Conflict of interest: None

[Objective] We investigate predictors of treatment continuation of sarilumab in daily clinical practice. [Methods] We conducted a retrospective survey of the medical records of 21 patients with rheumatoid arthritis who started sarilumab from August 2019 to June 2021, and examined treatment continuation predictors. [Results] 21 patients (20 female) were evaluated, mean age was  $55.0 \pm 3.3$  years, mean disease duration was  $12.6 \pm 1.8$  years, MTX was treated with 71.4% ( $8.8 \pm 0.8$  mg/week), PSL was treated with 28.5%, Bio-naïve was 42.9%, baseline DAS28-ESR was  $4.54 \pm 0.32$ , SDAI was  $18.3 \pm 2.8$ , RAPID-3 was  $11.7 \pm 1.6$ , mean treatment period was  $0.9 \pm 0.2$  years. At Week 12, DAS28-ESR was  $2.50 \pm 0.28$ , SDAI was  $7.8 \pm 1.4$ , and RAPID-3 was  $6.6 \pm 1.2$ , the remission rates were 66.7%, 11.1 and 26.3%, respectively. There were 3 patients of discontinuation due to inadequate response, and 2 patients of discontinuation due to adverse events. RAPID-3 at 1 month after sarilumab was extracted as a factor strongly associated with the discontinuation of sarilumab (Mann-Whitney U test;  $P=0.028$ , Spearman's rank correlation coefficient;  $\rho=0.533$ ,  $P=0.019$ ). [Conclusions] RAPID-3 at 1 month after sarilumab may be a predictor of subsequent treatment continuation.

## W61-5

### Efficacy of Sarilumab Treatment in Patients with Rheumatoid Arthritis in Daily Clinical Practice

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Conflict of interest: Yes

[Objective] Treatment outcomes of sarilumab (SAR) in RA patients were retrospectively investigated using the data from the Toyohashi RA Database. [Methods] A total of 16 patients with RA treated with SAR from July 2019 to March 2021 were included. Baseline (BL) patients' characteristics, disease activity time-course, MTX and PSL concomitant rates, continuation rates of SAR, and reasons for SAR discontinuation were investigated. [Results] BL characteristics: Mean age was 63.2 years old, females were 68.8%, and RA duration was 9.6 years. Nine patients (56.3%) were biologics or JAK-inhibitor naïve. Mean SDAI was significantly decreased as follows: 18.0 at BL, 8.3 at 1 month (m), 4.4 at 3 m, and 4.8 at 6 m. SDAI remission rate at 6 months was 50.0%. Mean dose and concomitant rates of PSL were decreased from 2.6 mg/day (27.0%) at BL to 0.8 mg/day (13.3%) at 6 m, whereas the MTX were decreased from 5.1 mg/week (60.0%) at BL to 2.8 mg/day (40.0%) at 6 m. Continuation rates of SAR were 81.5% at 6 m, 67.7% at 9 m, and 67.7% at 12 m. SAR was discontinued in 5 cases due to the lack of efficacy in 3 cases and adverse injection site reaction in 2 cases. [Conclusions] SAR was initially effective. SAR



was initially discontinued in 5 cases; however, the continuation rate was stable after 6 months.

## W61-6

### Results of multicenter use of salilumab for RA (FRAB-registry) one year after the start of administration

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<sup>1</sup>Rheumatic Center, Yagi Hospital, <sup>2</sup>The Fukuoka RA Biologics Therapeutics Study Group

Conflict of interest: None

[Objective] Study on the efficacy and safety of SARI at facilities participating in the Fukuoka RA Biologics Therapeutics Study Group [Methods] In 90 cases that have passed 52 weeks after SARI administration, the continuation rate, CRP, CDAI, HAQ-DI, PSL doses were observed. The 90 cases were divided into various two groups, and, stratified analysis was carried out. [Results] 52-week continuation rate were 65.2%. All of CDAI, HAQ, and PSL dose showed significant improvement. The continuation rate by the Kaplan-Meier method of each layered analysis was not significantly different in the Log-rank test. There was no significant difference in the group-to-group comparison divided into two groups by weight, BMI, presence or absence of MTX combination, number and type of pre-BIO/JAK, presence or absence of TCZ use history, and presence or absence of complications. Adverse event incidence was 65.6%, mainly administration part reaction, stomatitis, neutropenia, liver dysfunction, etc. [Conclusions] SARI showed an improvement in clinical indices regardless of body weight, BMI, MTX use, pre-BIO/JAK, and complications.

## W62-1

### Prediction of first biological DMARDs treatment failure using peripheral blood flow cytometry: From FIRST registry and FLOW study

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Conflict of interest: None

[Objective] Inadequate response (IR) to the first-line b/ts DMARDs is an issue gathering attention. In this study, we will develop a model which predicts IR to the first-line b/ts DMARDs. [Methods] Data of RA patients at the initiation of the first-line b/ts DMARDs was collected from FIRST registry. IR, which was defined as the failure-to-achieve LDA in 6 months, was investigated. Clinical features and peripheral blood immunological phenotype measured by flow cytometry (FCM) was collected from FLOW study and used in prediction models of IR. [Results] Among 2,009 patients (60 years old, 80% female, CDAI 27), 461 patients (23%) experienced treatment IR to the first-line b/ts DMARDs. There were various IR rates for the following product classes: TNFi 26%; IL6Ri 14%; CTLA4Ig 22%; JAKi 4%; ( $p<0.01$ ). Among 32 models tested, a model that included clinical features and FCM data estimated that 27% of the patients were at risk of IR. 45% of the at-risk-patients treated by TNFi resulted in IR, whereas IL6Ri or CTLA4Ig treated at-risk-patients showed 15% IR each. [Conclusions] In the real world, TNFi is the most used product class for the first-line. This study supports the product selection in the first-line b/ts DMARDs therapy, therefore providing early disease-control of RA.

## W62-2

### Relationship between tartrate-resistant acidic phosphatase 5b and joint destruction in treated rheumatoid arthritis

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Conflict of interest: None

[Object] To clarify the relationship between serum tartrate-resistant acidic phosphatase 5b (sTRACP-5b) and joint destruction in treated rheumatoid arthritis (RA). [Methods] Male ( $\leq 55$  yo) and female (before menopause RA patients in the treatment with DMARDs were enrolled in this study. All subjects underwent both sTRACP-5b measurements and radiographic examinations at enrollment and one year later. Reduction  $>12.4\%$  (minimal significant change; MSC) in sTRACP-5b levels was defined as significant decrease. Radiographic remission (RR) was defined as yearly progression  $>0.5$  by modified total sharp score. Medical data was collected retrospectively in all subjects. [Results] 31 of 37 subjects were female and 27 had seropositivity. 9 patients showed significant decreases in sTRACP-5b and had higher rates of RR than non-sTRACP-5b-decrease patients (88.9 vs. 42.9%,  $p=0.02$ ). Univariate analysis for RR revealed changes in sTRACP-5b levels and RA disease activity as possible association factor, and only sTRACP-5b decreases were related to RR in multivariate analysis ( $p<0.01$ ). [Conclusions] Changes in sTRACP-5b levels were related to joint destruction in RA during treatment. Especially, decreases of more than MSC in sTRACP-5b were associated with higher rates of radiographic remission.

## W62-3

### Synovitis score is a predictor of prognosis for increased postoperative drug treatment

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Conflict of interest: None

[Objective] The purpose of this study was to examine whether the synovitis score is a predictor of postoperative drug treatment intensification. [Methods] Thirty RA patients who were able to obtain synovial samples at TKA were included in this study. The patients were divided into maintenance group (MG) and enhanced group (EG: drug treatment was strengthened within 1 year), and compared the patients background and the synovitis score. We also performed multiple logistic regression analysis with postoperative drug treatment intensification as the objective variable. [Results] Preoperative disease activity was significantly higher in EG than in MG (DAS28-CRP: EG 3.79, MG 2.77, CDAI: EG 16.5, MG 9.7,  $p<0.01$ ). Rooney score (RS) was significantly higher in EG, 29.3 than the MG, 15.1 ( $p<0.001$ ). In univariate analysis of drug treatment enhancement, Total RS (TRS) and DAS28 were extracted, and TRS was listed as a factor in multivariate ( $p<0.05$ ). [Conclusions] It has been reported that TKA improves DAS28 one year after surgery. 67% patients of this study maintained drug treatment due to the effects of TKA. In addition, our results indicate that evaluating the synovitis score may be useful as a guide for further drug treatment enhancement when performing TKA under inadequate disease activity.

## W62-4

### Relationship between the RF titer and disease activity in patients undergoing rheumatoid arthritis treatment

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Conflict of interest: None

[Objective] We examined the relationship between the rheumatoid factor (RF) titer and disease activity in patients undergoing RA treatment. [Methods] We analyzed Simplified Disease Activity Index (SDAI) in 1241 RA patients treated at our hospital, which were divided into 5 groups by the RF (IgM class) titer. [Results] Age:  $63.4\pm 12.7$  years, disease duration:  $14.0\pm 11.4$  years, stage (1/2/3/4, %): 17.7/20.0/26.6/35.7, class (1/2/3/4,

%) 17.6/46.4/33.8/2.2, RF: 135.0±261.3 IU/ml, RF positive: 78.4%, Biologics or JAK inhibitors use: 43.5%, PSL use: 32.4%, PSL dosage: 3.8±2.7 mg/day, MTX use: 57.4%, MTX dosage: 7.5±2.6 mg/week, CRP: 0.7±1.6 mg/dl, and SDAI: 10.0±9.2. SDAI were 5.3 (2.4~10.6) [Median (interquartile range)] in the [RF≤10 IU/ml] group, 6.3 (3.3~11.5) in the [10<RF<30 IU/ml] group, 6.9 (3.7~13.5) in the [30≤RF<100 IU/ml] group, 8.9 (4.4~16.6) in the [100≤RF<300 IU/ml] group, and 11.4 (5.6~18.8) in the [300 IU/ml≤RF] group. There was a significant difference between these groups. The correlation coefficient between the RF titer and SDAI was significant ( $r=0.18$ ,  $p<0.01$ ). [Conclusions] Disease activity was high in patients undergoing RA treatment with high RF titers. It was suggested that the RF titer could be an auxiliary index of disease activity in RA treatment.

## W62-5

### Fluctuations in anti-CCP antibody titers affect fluctuations in disease activity in patients with rheumatoid arthritis: TOMORROW study

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Conflict of interest: None

[Purpose] We investigated whether there is a relationship between aging of anti-CCP antibody titers and disease activity in RA patients. [Methods] We used RA patient data from 2010 (at enrollment: BL) to 2019 in the TOMORROW study (a prospective cohort study of 208 RA patients and 202 volunteers matched by age and gender). Comparison of anti-CCP antibody titer elevated and non-elevated groups, changes in anti-CCP antibody titer after 9 years ( $\Delta$  anti-CCP antibody) and each BL factor (age, BMI, disease duration, presence or smoking, RF, MMP-3, mHAQ, DAS) and its fluctuation was examined using univariate analysis and multivariate analysis. [Results] The anti-CCP antibody titer tended to increase over the years. BL-RF and smoking were significantly higher in the anti-CCP antibody titer elevated group ( $p<0.05$ ), but there was no significant difference in  $\Delta$ DAS ( $p=0.19$ ). A weak correlation was found in BL-RF ( $r=0.26$ ,  $p<0.01$ ) and  $\Delta$ RF ( $r=0.21$ ,  $p<0.01$ ) in the correlation with  $\Delta$  anti-CCP antibody, but BL-DAS ( $r=0.01$ ,  $p=0.88$ ) and  $\Delta$ DAS ( $r=0.15$ ,  $p=0.07$ ) did not show a significant correlation. For each variation, smoking ( $p<0.01$ ) and  $\Delta$ DAS ( $p<0.05$ ) were extracted as independent factors. [Conclusion] Fluctuations in DAS as well as smoking were cited as variables in anti-CCP antibody titers in RA patients.

## W62-6

### Neutrophil count reduction 1 month after initiating sarimumab can predict clinical remission within 3 month in rheumatoid arthritis patients

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Conflict of interest: None

Neutropenia is a common adverse event of sarimumab (SAR) in rheumatoid arthritis (RA) patients; however, the association between it and the SAR clinical efficacy remains inconclusive. We analyze SAR-induced neutrophil decrease at 1 month predicts clinical remission within 3 month. We reviewed medical records of RA patients initiating SAR between Aug 2018 and Aug 2021 in our hospital. The Clinical Disease Activity Index (CDAI) was evaluated at baseline (before initiating SAR) and 1, 2, and 3 months after administration. Clinical remission was defined when CDAI decreased < 2.8. The ratio of neutrophil counts 1 month after initiating SAR to those at baseline (neutrophil ratio) was also calculated. Among 66 SAR-treated patients, 42 with valid CDAI and neutrophil counts were enrolled (with median age of 69 years and 35% females). Multivariate logistic regression analysis suggested baseline CDAI (odds ratio (OR) 0.96,  $p = 0.236$ ), the neutrophil ratio (OR 1.00,  $p = 0.245$ ) as predictors of CDAI

remission. Neutrophil ratio < 0.8 was associated with achieving remission (Fisher's exact test,  $p = 0.02$ ) with no apparent increase of severe infection. More than 20% reduction of neutrophil count 1 month after initiating SAR predicts clinical remission within 3 month at an early treatment phase.

## W63-1

### Cost-effectiveness of molecular targeted drugs in rheumatoid arthritis: three different approaches using a cohort model and real-world data

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Conflict of interest: Yes

[Objective] To assess cost-effectiveness of molecular targeted drugs in rheumatoid arthritis (RA). [Methods] A lifetime estimation using a cohort model (study A) and 2 short-term estimations (study B and C) were performed. In study A and B, effectiveness was defined by ACR response at 24- and 52-weeks, respectively, derived from indirect comparisons of clinical trials. In study C, previously defined effectiveness (equivalent to DAS≤3.2) at 54-weeks was assessed using Medical Data Vision (MDV) database. Costs of standard therapies in study A and resources used in MDV database in study B and C after removing drugs with inadequate information were considered. [Results] In study A, incremental costs per quality adjusted life years gained were lower in etanercept BS (25 mg) (lower costs) and infliximab (IFX) BS (¥0.4 million, M) compared with csDMARDs. In study B, yearly costs per person with ACR50 response were lower in tocilizumab (TCZ)-SC (¥1.9 M) and abatacept (ABT)-SC (¥2.3 M). In study C, after adjusting backgrounds, costs per person in 54-weeks were lower in TCZ-SC (¥1.3 M) and TCZ-IV (¥1.6 M) and achieving rates of effectiveness were higher in TCZ-IV (45.3%) and IFX (43.0%). [Conclusions] Molecular targeted drugs with lower prices showed higher cost-effectiveness.

## W63-2

### Baseline characteristics and outcomes of initiators of tocilizumab (TCZ) and other b/tsDMARDs in CorEvitas' RA Japan Registry

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Conflict of interest: Yes

[Objective] On behalf of CorEvitas' (formerly Corrona-J) Japan Investigators, we describe patient (pts) characteristics and socioeconomic impact of Japanese rheumatoid arthritis (RA) pts initiating a b/ts DMARD and changes from baseline (BL) to 12 months (mo). [Methods] Pts (n=301) were b/ts DMARD-naïve initiators of TCZ (n=60), Tumor necrosis factor inhibitors (TNFi; n=162), abatacept (ABT; n=53), and Janus kinase inhibitors (JAKi; n=26) from CorEvitas' RA Japan Registry. Adjusted estimates of change in disease activity, work productivity, and health care resource utilization from BL to 12 mo were reported. [Results] At BL, mean age ranged from 52-65 years and RA duration from 5-10 years. Mean BL CDAI was 20.5-TCZ, 22.5-TNFi, 19.8-ABT, and 20.5-JAKi. In wage workers (n=187; TCZ=33; TNFi=111; ABT=25; JAKi=18), mean overall work impairment (OWI) at BL was 15.9%-TCZ, 7.9-TNFi, 10.2-ABT, and

9.6-JAKi. In adjusted models, mean CDAI decreased 15.6 units-TCZ, 15.3-TNFi, 12.7-ABT, and 15.1-JAKi and OWI decreased 4.6%-TCZ, 4.6-TNFi, 7.2-ABT, and 7.4-JAKi from BL to 12 mo; 83-90% of initiators remained on therapy. [Conclusions] Improvement in outcomes from BL to 12 mo occurred in real-world pts and demonstrated the effectiveness of b/ts DMARDs, informing future socioeconomic impact studies.

### W63-3

#### Drug retention rate of the 2nd b/ts-DMARD in refractory rheumatoid arthritis patient and prognostic factors of the negative reasons for discontinuation

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Conflict of interest: None

[Objective] We investigate the effectiveness of the second b/ts DMARD after failing the primary treatment to grasp characters of pre-difficult-to-treat (pre-D2TRA) patient. [Methods] Using clinical data from the SUNSET registry, drug retention rates of the second b/ts-DMARD were examined by Kaplan-Meier's method. Predictors of the negative reason of discontinuation were investigated using multivariate analysis. [Results] Three hundred and seventy-eight treatments of the second b/ts-DMARD were analyzed. The drug retention rate for 2 years was TNF inhibitors (n=157) 47.8%, IL-6 inhibitors (n=136) 56.0%, abatacept (n=54) 47.1% and JAK inhibitors (n=31) 55.2% respectively. Change of mode of drug action and prior TNF treatment did not affect to the persistency rate. Otherwise, the achievement of CDAI50 or CDAI low disease activity (LDA) at 3 months correlated to that. Body mass index, RA duration, joint distraction, tender joint count, oral steroid concomitant, patient's global assessment and mHAQ were associated to the non-achievement of CDAI50 and CDAI LDA at 3 months. [Conclusions] The achievement of CDAI50 or CDAI LDA at 3 months correlated to drug retention rate of the second b/ts-DMARD and The change of mode of drug action and prior TNF treatment did not affect to that.

### W63-4

#### Relapse risk factors after discontinuation of b/ts-DMARDs in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] We investigated the factors involved in the clinical course after discontinuation of biological/targeted synthetic disease-modifying antirheumatic drugs (b/ts-DMARDs). [Methods] From September 2003 to June 2020, 111 RA patients in remission or low disease activity (LDA) of CDAI at the time of discontinuation and were confirmed the clinical course until 24 months after discontinuation were enrolled. Cases remained in remission or LDA until 24 months were referred to as "remission group", and those resumed b/ts-DMARDs or worsened to moderate disease activity of CDAI were classified as "relapse group". [Results]: Sixty-seven patients were in the relapse group, and the time to relapse was 8 months (median). All patients treated with JAK inhibitor (Tofacitinib only, n=6) relapsed. In multivariate analysis, the use of PSL at the start of b/ts-DMARDs was extracted (29.5% in remission group, 49.3% in relapse group, HR: 1.69, 95% CI: 1.03-2.76, p=0.03) and there were no differences in the disease duration, RF, anti-CCP antibody, or CDAI at the start of b/ts-DMARDs. [Conclusion] Patients who require PSL due to high disease activity before starting of b/ts-DMARDs may relapse more easily after discontinuation of b/ts-DMARDs.

### W63-5

#### A study of rheumatoid arthritis patients according to age of onset

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Conflict of interest: None

[Objective] We report a study of the clinical picture, treatment, disease activity, and QOL of patients with rheumatoid arthritis (RA) according to age of onset. [Methods] The target patients were 243 patients (44 males and 189 females, mean age of onset 58.6 years) undergoing treatment at our hospital who developed RA after 2010. The age of onset was divided into 5 groups: under 44 years, 45-54 years, 55-64 years, 65-74 years, and 75 years or older. There were 46, 38, 67, 57, and 35 cases, respectively. In each of these groups, the initial joint, the positive rate of RF and anti-CCP antibodies, the treatment content of MTX, immunomodulator-targeted drugs such as biologics and JAK inhibitors, and steroids, and the degree of disease activity and functional disability were examined using DAS28CRP and HAQ-DI. [Results] There were more RF and anti-CCP antibody-negative cases and more cases of large joint onset in patients older than 75 years. The number of patients treated with MTX decreased with age, and the number of patients treated with PSL increased. [Conclusions] There was no significant difference in disease activity, but functional impairment was more advanced according to age of onset.

### W63-6

#### Association between frailty and falls in patients with rheumatoid arthritis - multicenter study from T-FLAG study-

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Conflict of interest: None

[Objective] Frailty is a concept that indicates a state of vulnerability, a condition that increases the risk of health problems including falls and disability. Rheumatoid arthritis (RA) is a disease that affects the bones and joints, increasing the risk of falling. The purpose of this study was to investigate the risk factors for falls in patients with RA. [Methods] Among 581 patients with RA who completed a frail questionnaire including Kihon Checklist (KCL) between June and August 2020 (baseline), 487 patients who were still available after 1 year were included. A logistic regression analysis was performed to examine the factors influencing the 1-year fall experience. [Results] 121 patients (25%) had falls (1.7 times) and 22 patients (18.2%) had fractures during 1 year. There were no significant differences in age (66 vs. 66 years), disease duration (12 vs. 11 years), women (72 vs. 74%), or DAS28-CRP (2.38 vs. 2.12) in the group with falls vs. the group without falls, but there were significant differences in grip strength (18 vs. 21 kg) and KCL score (8 vs. 6 points). Multivariate analysis showed that KCL score (OR: 1.15) were independent predictors of falls. [Conclusion] Frailty is a risk factor for falls in patients with RA, even when disease activity is controlled.

### W64-1

#### Usefulness of activity indicators for early diagnosis of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis Shuya Kaneko<sup>1</sup>, Masaki Shimizu<sup>2</sup>, Asami Shimbo<sup>1</sup>, Hitoshi Irabu<sup>3</sup>, Mao Mizuta<sup>4</sup>, Yasuo Nakagishi<sup>4</sup>, Naomi Iwata<sup>5</sup>, Masaaki Mori<sup>3</sup>

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Conflict of interest: None

[Objective] To validate the correlation between cytokine-induced molecules and cytokines in macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (s-JIA), and to identify



which markers are valuable for early diagnosis. [Methods] Eight MAS patients were enrolled. We serially measured WBC, platelets (PLT), fibrinogen (FIB), FDP-Dimer (DD), AST, LDH, TG, and ferritin (FER) levels from an acute phase of sJIA to the diagnosis of MAS. We evaluated the change in values between the value at the acute phase of sJIA and those at the onset of MAS or full-blown MAS diagnosis. The change in values was calculated as the value at the acute phase was set to 1.0. In 3 of the patients, we also measured serum levels of IL-18, IL-6, CXCL9, and sTNFR2 and validated their correlation with the activity indices. [Results] There was a positive correlation between CXCL9 and FDP-DD, sTNFR2 and AST, LDH, FER ( $r$ : 0.4–0.7), and a negative correlation between CXCL9 and PLT ( $r$ : -0.44). There was a significant change in PLT between the acute phase of sJIA and the onset of MAS. The changes in PLT, FIB, and LDH were significant between the onset of MAS and full-blown MAS. [Conclusions] PLT was the most useful index for the diagnosis of MAS.

## W64-2

### Clinical characteristics of juvenile idiopathic arthritis with atlantoaxial arthritis

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Conflict of interest: None

[Backgrounds] Atlantoaxial arthritis (AA) occasionally causes rotatory fixation of atlantoaxial joint (AARF) in Juvenile Idiopathic Arthritis (JIA). However, clinical characteristics of AA in JIA remain unknown. [Objectives] Analysis of clinical characteristics of AA in JIA. [Methods] Medical records of 80 JIA patients were retrospectively reviewed. [Results] AA were observed in 3 out of 42 systemic JIA (sJIA) patients (7.1%) and 4 out of 38 RF-positive polyarticular JIA (RF+pJIA) patients (10.5%) ranging in age at onset from 3.4 to 18 years. AA occurred during flares of chronic arthritis in sJIA and onsets of RF+pJIA. Because early treatment with cervical collar was not effective, one sJIA and two RF+pJIA patients needed cervical tractions (2 to 3 weeks) following by cervical collars (2 weeks to 4 months). These two patients were diagnosed with RF+pJIA after polyarthritis appeared during cervical tractions for AARF. All patients received biologics and showed refractory clinical course, but AA improved without any functional impairments. [Conclusions] JIA should be in consideration as differential diagnosis for refractory AARF. Combination of medications including biologics and orthopedic procedures could improve cervical involvements in JIA.

## W64-3

### Subcutaneous Tocilizumab for Patient with Juvenile Idiopathic Arthritis: Multicenter Retrospective Observational Study

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School of Medical and Dental Sciences

Conflict of interest: None

[Object] To investigate the real-world evidence of subcutaneous TCZ (TCZsc) in juvenile idiopathic arthritis (JIA). [Methods] The subjects were patients with JIA treated with TCZsc. Patient characteristics, clinical and laboratory findings, duration of using TCZsc and adverse events were retrospectively investigated. [Results] Fifty-nine cases were included. JIA classification was as follows: systemic type (sJIA) 13, polyarthritis (pJIA) 43 and oligoarthritis (oJIA) 3 cases. The median age at initiation of TCZsc were 22.6, 18.2 and 23.0 years in sJIA, pJIA and oJIA, respectively. All sJIA cases received intravenous TCZ before switched to TCZsc and 53.8% of sJIA had experience withdrawal. The most common reason for the switch was the extension of hospital visit interval in all types. The median duration of TCZsc and continuation rate at the last observation were as follows: 29, 42 and 5 months, 92.3%, 69.8% and 33.3%, respectively. Reasons for discontinuing TCZsc included insufficient effect 4, arthritis 2, uveitis 1 and injection site reaction 1. The main serious adverse events were relaps in systemic symptoms 2, relaps in arthritis 5 and uveitis 1. [Conclusions] We clarified the real-world evidence of JIA patients who used TCZsc in Japan.

## W64-4

### Predictors of the low disease activity state in systemic lupus erythematosus: results from a prospective cohort study of young patients with systemic lupus erythematosus in Japan (PLEASURE-J)

Tomo Nozawa<sup>1</sup>, Takako Miyamae<sup>2</sup>, Kayoko Kaneko<sup>3</sup>, Nobuya Abe<sup>4</sup>, Sakiko Isojima<sup>5</sup>, Hideyuki Iwai<sup>6</sup>, Yasunori Iwata<sup>7</sup>, Masako Utsunomiya<sup>8</sup>, Kae Onishi<sup>8</sup>, Moeko Ochiai<sup>9</sup>, Hiromi Shimada<sup>10</sup>, Tsuyoshi Shirai<sup>11</sup>, Yumi Tsuchida<sup>12</sup>, Shingo Nakayamada<sup>13</sup>, Hironari Hanaoka<sup>14</sup>, Yoko Miura<sup>5</sup>, Mayuko Moriyama<sup>15</sup>, Akane Watanabe<sup>16</sup>, Kenji Oku<sup>17</sup>, Yuko Kaneko<sup>14</sup>, Yoshiya Tanaka<sup>13</sup>, Keishi Fujio<sup>12</sup>, Masakazu Matsushita<sup>18</sup>, Nobuyuki Yajima<sup>5</sup>, Takashi Wada<sup>7</sup>, Ayako Nakajima<sup>19</sup>, Atsuko Murashima<sup>3</sup>

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Conflict of interest: None

[Objective] To identify the predictors of low disease activity state (LLDAS) in systemic lupus erythematosus (SLE). [Methods] This is a prospective cohort study on SLE in Japan (Pleasure-J study) from November 2017 to September 2021, and for whom data were available at 2 or more time points. LLDAS was defined as SELENA-SLEDAI  $\leq 4$  and prednisolone (PSL)  $\leq 7.5$  mg/day ( $\leq 7.5$  mg/day or  $\leq 0.15$  mg/kg/day for childhood-onset cases). We conducted an exploratory Cox regression analysis and logistic regression analysis to examine the factors. [Results] The

median age of SLE diagnosis was 25.0 (20.0-31.0) years. The Childhood-onset cases (<18 years) and adult-onset cases ( $\geq 18$  years) was 25 (male: female=3:22) and 140 (male: female=15:125). The Total observation period was 331 person-years. One hundred nine (66%) patients achieved LLDAS within observation period, and the months from diagnosis to LLDAS was 16.6 (11.8-23.4). Only CRP level (HR; 1.077,  $p=0.037$ ) was related to LLDAS. In the 145 patients observed at 18 months after diagnosis, methylprednisolone pulse therapy (OR; 0.290,  $p=0.005$ ) and C4 (OR; 0.937,  $p=0.014$ ) were associated with failure to achieve LLDAS. [Conclusions] CRP level can be a predictor of LLDAS. Methylprednisolone pulse therapy was shown to contribute to achievement of LLDAS.

## W64-5

### The work productivity of adulthood juvenile idiopathic arthritis patients

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Conflict of interest: Yes

[Objective] The aim of this study was to evaluate the impact of juvenile idiopathic arthritis (JIA) on the work productivity in long-term follow-up patients. [Methods] A questionnaire survey was administered to 55 patients with adult JIA (age of disease onset <16 years, Female 87%) who were younger than 60 years of age. The questionnaire included job description, commuting methods, commuting time, and annual income. [Results] The median age at onset of disease was 14 years, and at evaluation was 36 years. Of the 55 patients, 45 (82%) were employed and 80% had full-time jobs. The type of jobs was categorized into three types. Patients who have mainly engaged in a sedentary job were 35 (71%), a job that mainly walk around was 7 (14%), and a job that requires much standing were 3 (6%). Significantly more patients with a disability certificate were engaged in sedentary work. 16% of patients had changed jobs because of JIA. The most common method of commuting was public transportation with 24 (49%) patients. Commuting time was less than 15 minutes in 47%, and an annual income was fewer than 4 million yen in 59% of patients. [Conclusion] In the long-term disease course, the majority of the adult JIA patients were working, and the impact of the disease on work productivity was limited.

## W64-6

### Study of correlation between pediatric rheumatic diseases and oral flora

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Conflict of interest: None

[Objective] We report the correlation between pediatric rheumatic diseases and oral flora in Japan. [Methods] Saliva was collected from patients and compared with control subjects. A 16 S metagenome analysis was performed and Quantitative Insights Into Microbial Ecology 2 was used for sequence analysis and diversity analysis of next-generation sequence data. Bacterial differences and effects were assessed by Linear Discriminant Analysis (LEfSe). This study has been approved by the ethics committee and the written consent of parents were obtained. [Results] 21 patients participated, including 14 with JIA, 6 with pediatric Sjögren's syndrome (pSS) and 1 with Behçet's disease. Alpha diversity did not differ from control. Bray-Curtis dissimilarity and Unweighted UniFrac distance in beta diversity were significantly different from control ( $p = 0.008$ ,  $p = 0.027$ ), but weighted UniFrac distance was not different ( $p = 0.454$ ). LEfSe showed that *Clostridia* steel tended to be prevalent in patient group. There

were differences in the composition of bacteria between the JIA group and the pSS group. [Conclusions] The oral flora of pediatric rheumatic patients in Japan was different from previously reported results in other countries and there was difference among diseases.

## W65-1

### Efficacy of anti-tumor necrosis factor-alpha blockers in cutaneous polyarteritis nodosa: A Case Series

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Conflict of interest: None

[Objective] This study aimed to investigate the efficacy of anti-TNF- $\alpha$  blockers in patients with refractory leg ulcers associated with Polyarteritis nodosa (PN). [Methods] The study involved PN patients with treatment-resistant refractory leg ulcers, who received anti-TNF- $\alpha$  blockers in the period 2006-2021. Patients' data were retrospectively collected, and patient backgrounds, steroid doses before and after anti-TNF- $\alpha$  drug therapy and leg ulcer sizes were investigated. [Results] The patients in the analysis comprised five women and four men. The mean age was 49 years. The mean dose of prednisolone prior to anti-TNF- $\alpha$  drug therapy was 25 mg/day. As immunosuppressants, cyclophosphamide was used for six cases, and tacrolimus was used for one case. As anti-TNF- $\alpha$  drugs, infliximab, etanercept and adalimumab were used for one case, four cases and four cases, respectively. In all cases, leg ulcers epithelised within a few months, and the dose of prednisolone was reduced after anti-TNF- $\alpha$  drug administration. No adverse events including infections were noted. [Conclusions] In the present study, all PN patients with treatment-resistant refractory leg ulcers responded favourably to the anti-TNF- $\alpha$  therapy, enabling steroid dose reduction.

## W65-2

### A case of polyarteritis nodosa for which PET-CT was useful for early diagnosis

Makoto Koichi, Shunsuke Tsuge, Kiyooki Ito, Hiroyuki Kawahara, Hajime Sanada, Misaki Yoshida, Yoshinori Takahashi, Ryo Nishioka, Takeshi Zoshima, Satoshi Hara, Ichiro Mizushima, Mitsuhiro Kawano

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Conflict of interest: None

A 65-year-old man was admitted to our hospital because of high-grade fever for 2 weeks. He also had pain in his right groin and feeling of coldness in his lower limbs for half a year. The investigation into the origin of prolonged fever, including contrast-enhanced CT, showed no significant findings as the clue to diagnosis. Therefore, we conducted FDG-PET to investigate middle-large vessel arteritis. FDG-PET showed subclinical inflammation in the subclavian, brachial, axillary, iliac, femoral, popliteal and arteries at the extremities. We diagnosed polyarteritis nodosa (PAN) and treated him with prednisolone. The treatment was effective and his symptoms improved. FDG-PET seems to be useful for diagnosing PAN, particularly in patients with non-specific systemic features. Although he did not meet the diagnostic criteria, we diagnosed PAN based on the size of the affected vessel and previous reports of similar cases. Diagnostic criteria for PAN include vascular stenosis / occlusion, symptoms associated with rupture, or histological evidence, but FDG-PET can detect vasculitis earlier than structural changes in blood vessels. We believe that there are some cases in which early diagnosis and treatment should be performed without being bound by existing diagnostic criteria.

## W65-3

### A case of Segmental Arterial Mediolysis (SAM) that required differentiation from Polyarteritis Nodosa

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Conflict of interest: None

[Case Presentation] The patient was 37-year-old man. Since the age of 30, abdominal pain had appeared once every few years. In March of X-1, Abdominal 3D-CT Angiography showed a superior mesenteric artery aneurysm and a splenic artery aneurysm. In July X, CT scan showed dissection of bilateral renal arteries, multiple small aneurysms in the mesentery, and new small aneurysms in the lumbar and intercostal arteries. The patient was suspected to have active vasculitis. However blood tests showed no inflammatory findings, various autoantibodies were negative, and PET-CT showed no significant accumulation in the arterial wall. Based on the examination findings and the distribution of aneurysms and dissecting lesions, a comprehensive diagnosis of SAM was made. [Discussion] SAM is a rare disease of unknown aetiology in which the tunica media smooth muscle of the abdominal visceral arteries degenerates and melts, causing vascular dissection of the tunica media, resulting in an aneurysm. Disruption of the formed aneurysm can sometimes cause fatal intra-abdominal bleeding. The affected vessels are similar to those of polyarteritis nodosa, and it is an important disease that Rheumatologist should consider as a differential.

## W65-4

**A case of multiple drugs-resistant IgA vasculitis (IgAV) with gastrointestinal involvement successfully treated with intravenous cyclophosphamide (IVCY) for remission induction and mycophenolate mofetil (MMF) for maintenance therapy**

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Conflict of interest: None

<Case>17-years old woman <Chief complaints (CC)>Abdominal pain and bloody stools <Present illness>In X-5 year, she was diagnosed with IgAV because of knee joint pain and CC, and treated by PSL 60 mg/d. PSL tapering led to repeated relapses and colchicine (Col) was added. Although abdominal pain attacks decreased, purpura, arthralgia, and fatigue persisted. In Mar X-1, she was referred to our hospital, and definitely re-diagnosed as IgAV based on skin biopsy showing leukocytoclastic vasculitis (LV) with IgA/C3 deposition. Col was stopped, and PSL 30 mg/d and CyA were added. In Oct X-1, after tapering PSL, azathioprine (AZP) was added to PSL 11 mg/d and CyA against recurrent abdominal pain. In Feb X, CC appeared, and S-colon biopsy showed LV. PSL was increased to 30 mg/d, and CyA/AZP were switched to MMF. CC improved, and PSL was reduced to 27.5 mg/d. In Mar X, however, she was admitted to our hospital because of CC. <Progress after admission>Although CC improved by fasting, MMF did not seem to induce remission. Thus we started IVCY for induction therapy. After 6 cycles, IVCY was switched to MMF resulting in maintained remission. <Discussion>Our case revealed that remission induction by IVCY and maintenance therapy by MMF might be efficacious for multiple drugs-resistant IgAV.

## W65-5

**A case of alveolar hemorrhage in IgA vasculitis**

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Conflict of interest: None

IgA vasculitis commonly occurs in children, with a purpura, abdominal pain, arthralgia and nephritis. Adult onset of IgA vasculitis is a rare systemic vasculitis and would be associated with severe disease. We here reported A 41-year-old man who was suffering from IgA vasculitis with alveolar hemorrhage. Despite of intravenous prednisolone therapy, plasma

exchange and mechanical ventilation and percutaneous cardiopulmonary support, he passed away on day 15 of hospitalization. Alveolar hemorrhage is a rare but life-threatening complication in IgA vasculitis.

## W65-6

**A case of elderly onset IgA vasculitis newly occurred after COVID-19 Vaccination**

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Conflict of interest: None

[Case] A 75-year-old woman had multiple breast cancer metastases. Two weeks after the second COVID-19 vaccine, purpura appeared bilateral lower legs to dorsal legs. Loss of abdominal pain and appetite didn't improve by fasting and fluid replacement. Upper gastrointestinal endoscopy showed multiple duodenal erosions. Biopsy showed neutrophil infiltration and vascular wall fibrinoid necrosis from the superficial to middle dermal layer of skin and submucosa of duodenal mucosa. She was diagnosed IgA vasculitis. Moderate-dose steroid therapy in view of the risk of tumor lysis syndrome was rapidly relieved. On the other hand, with no decreased renal function and glomerular erythrocytes, low selectivity nephrotic-range proteinuria increased by a week after treatment started. Renal biopsy was withheld because of hypoxia. Steroid therapy to prevent nephritis in IgA vasculitis and symptomatic treatment for nephrotic syndrome were continued. [Discussion] There have been several reports of exacerbations IgA vasculitis in the 30s to 50s after COVID-19 vaccination, but it is first report to new onset in the elderly. The lesions in this case were mainly in the gastrointestinal tract, so association with IgA vasculitis and a vaccine against COVID-19 induced to mucosal infection was suggested.

## W66-1

**Evaluation of pulmonary lesions and prognosis in patients with ANCA-associated vasculitis**

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Conflict of interest: None

[Objective] This study aimed to investigate the clinical features of anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) with pulmonary lesions. [Methods] The study included patients with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis who were treated at university of Yamanashi Hospital and Fujieda Municipal General Hospital between June 2007 and August 2019. We retrospectively examined recurrence-free survival (RFS) and overall survival (OS). [Results] In total, 147 patients with AAV (118 with MPA) were identified and 100 had pulmonary lesions. Pulmonary lesions included interstitial pneumonia in 83 patients (usual interstitial pneumonia pattern, 32 patients; non-specific interstitial pneumonia pattern, 34 patients; organising pneumonia pattern, 17 patients), multiple nodular shadows in 10 patients, and pulmonary alveolar haemorrhage in 9 patients. In treatment, 74 patients in the induction phase, and 59 patients in the maintenance phase were each treated with immunosuppressive agents. In the comparison of RFS and OS between patients with and without pulmonary lesions, both were shorter in patients with lesions. [Conclusions] Pulmonary lesions in AAV may be associated with disease prognosis.

## W66-2

**A case of refractory ANCA-associated vasculitis with orbital apex syndrome successfully treated with rituximab**

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Conflict of interest: None



[Case] A 50s-year-old man was diagnosed with ANCA-associated vasculitis (AAV) because of sinusitis, lung lesions, and positive MPO-ANCA in the sera, and received the treatment with prednisolone (PSL) from 50 mg/day. Then, PSL was reduced together with azathioprine. After 5 months, ocular pain, decreased visual acuity, and visual field narrowing were gradually developed and he received methylprednisolone (mPSL) pulse therapy although there were no findings on contrast-enhanced MRI of the head. At 9 months of the onset, abnormal sensation in the ophthalmic nerve (V1), ptosis of the left eyelid, and paralysis of the left full external ophthalmic muscle were further developed, and MRI showed contrast-enhancing soft tissue at the left orbital apex, which was diagnosed with orbital apex syndrome caused by AAV. After treatment with intravenous cyclophosphamide, MRI showed the shrinkage in the lesions. However, since there were still diplopia and V1 deficits, rituximab was then administered. After that, the symptoms subsequently improved and he is currently being treated with PSL 7 mg/day alone without relapse. [Clinical significance] Since AAV indicates ocular symptoms due to various mechanisms, we should treat those accordingly understanding the pathogenesis of each case.

### W66-3

#### **A case of hypocomplementemic urticarial vasculitis presenting with peripheral neuropathy of both lower limb and Gastrointestinal perforation due to necrotizing vasculitis during untreated follow-up**

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Department of Rheumatology, Itami City Hospital

Conflict of interest: None

[Case] A 50-year-old woman was admitted to our hospital because of recurrent painful wheal. Her laboratory findings showed hypocomplement and normal of antinuclear antibodies. Her skin biopsy showed leukocytoclastic vasculitis with immunocomplex deposition. Because of these results, she was diagnosed with hypocomplementemic vasculitis (HUV). She had only mild skin symptoms with repeated exacerbations and remissions, then she was under observation without treatment. Seven months later, she was suddenly presented with the ileal perforation. Histopathological examination of it showed necrotizing vasculitis in the medium-sized blood vessel. Subsequently, peripheral motor sensory neuropathy of both lower limbs appeared. Therapy with high dose prednisone (PSL) was started, then all symptoms reduced and disappeared excluding peripheral neuropathy. With the addition of tacrolimus, the neurological symptoms improved. [clinical significance] HUV is known to affect multiple organs, The patient suffered from ileal perforation and peripheral neuropathy that is rare organ involvement. Despite the rapid organ involvement and the lack of established treatment, this case showed a suggestive course with successful treatment with PSL and tacrolimus, and we report this valuable case with discussion.

### W66-4

#### **A refractory granulomatosis with polyangiitis (GPA) case with hearing impairment, and nodular lesions associated with pulmonary non-tuberculous mycobacteriosis (NTM) infection**

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Conflict of interest: None

A 72-year-old female was referred to our hospital with hearing impairment, fever, nasal discharge, and elevated CRP and MPO-ANCA levels. Multiple nodular opacities suspected of NTM infection were indicated one year in advance. While treatment for otitis media with antibiotics and myringotomy was not effective for hearing loss, high dose of steroid therapy was. We diagnosed as localized GPA presenting otitis media with ANCA-associated vasculitis (OMAAV), by inflammatory findings of eardrum, nasal septum and ear canal, and a relapse of hearing impairment after rapid taper of steroid. Though ENT manifestations improved with pulse and high dose steroid therapy and intravenous cyclophosphamid, multiple nodules appeared and enlarged around known NTM lesions. In consider-

ation of the possibility of worsening of NTM and pulmonary involvement of GPA, combination therapy for NTM using CAM, RFP and STFX, and consecutive immunosuppressive therapy were performed and resulted in size reduction of nodules in two months. For the recurrent OMAAV, combination use of mycophenolate Mofetil and methotrexate enabled dose reduction of steroid. We report a case of refractory GPA/OMAAV with pulmonary lesions difficult to distinguish from NTM infection.

### W66-5

#### **A case of eosinophilic granulomatosis with polyangiitis (EGPA) with fatal sinus thrombosis following thrombocytopenia**

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Conflict of interest: None

[Case] A 44-year-old woman visited a doctor by abdominal pain with bilateral pneumonia and enterocolitis on CT. After admission, eosinophilia, numbness in both upper and lower limbs, and purpura in the abdomen and left lower limb appeared. After admission, the platelet count decreased. On day 11, she had consciousness disorder and convulsions, and head CT showed subcortical bleeding in the left parietal lobe. She was transferred to our hospital's neurosurgery. CT angiography revealed cerebral bleeding due to sinus thrombosis. The diagnosis of EGPA was made. Glucocorticoid pulse therapy was started. The platelet count was 19000 /μL, and heparin was started. Clot recovery was performed. After that, platelet did not increase after transfusion. Hematoma in right abdominal muscle was confirmed on day 16, and heparin was discontinued. Head CT showed severe cerebral edema and spontaneous breathing disappeared on day 24. Anti-HLA antibody was found positive on day 31. She died on day 33. [Clinical significance] EGPA may be accompanied by thrombocytopenia, which may attribute from consumption by thrombosis, and early treatment may be considered.

### W66-6

#### **Two cases of juvenile-onset Granulomatosis with polyangiitis (GPA) presenting with strawberry gums**

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Conflict of interest: None

Case 1: A 14-year-old girl. She had been suffering from with refractory sinusitis with nasal bleeding for several months. She presented with strawberry gums, fever, weight loss, and cough. She had multiple lung nodules and PR3-ANCA positive. Case 2: A 14-year-old boy. He had been suffering from refractory sinusitis and eyelids swelling with severe pain for several months. He presented with strawberry gums, fever, cough, hearing loss and visual loss. He had multiple lung nodules and PR3-ANCA positive. MRI showed he also had granulomatosis in middle ears and orbital inflammatory pseudotumor. We diagnosed both of them as Granulomatosis with polyangiitis (GPA) because of necrotizing vasculitis with granuloma in their tissue specimens. They received methylprednisolone pulse and cyclophosphamide pulse therapy. She achieved serological remission, however refractory subglottic stenosis (SGS) occurred. The other achieved clinical remission and keeps it. Discussion: Two cases had presented with various eye-nose-throat manifestations such as refractory sinusitis, strawberry gums, SGS and orbital inflammatory pseudotumor. In order to diagnose earlier, we should consider a serological test and a histopathological examination for the patients with refractory severe sinusitis or strawberry gums.

### W67-1

#### **Impact of COVID-19 on rheumatoid arthritis patients' lifestyle and their news source of COVID-19 from NinJa 2020 cohort study**

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Conflict of interest: Yes

[Objective] To investigate the Impact of COVID-19 on rheumatoid arthritis patients' lifestyle and their news source of COVID-19 using NinJa 2020 cohort study. [Methods] At the collection of patients' data of NinJa2020, questionnaire about their lifestyle and news source of COVID-19 was given. Questionnaire includes questions about frequency of scheduled visit, going out and exercise, weakness and news source. [Results] 6677 patients out of 15553 patients answered questionnaire. Most patients did not change the interval of scheduled visit. Frequency of going out and exercise was clearly decreased in 80% of patients. 50% of patients felt their weakness and older patients felt more than younger patients. Their news source was mainly newspaper, tabloid show and acquaintance not official website. [Conclusions] The provision of accurate information about COVID-19 was important to avoid infodemic. From this questionnaire, more practical information delivery system was required in Japan.

## W67-2

### Study of adverse Reactions to COVID-19 Vaccination in Patients with Rheumatic Diseases

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Conflict of interest: None

[Objective] Some patients are not vaccinated due to concerns about adverse reactions. The purpose of this study is to investigate the adverse reactions of COVID19 vaccination in rheumatic diseases and to guide the decision-making of patients and physicians. [Methods] A questionnaire was sent to patients with rheumatic diseases, and when they consented to this study, were surveyed. [Results] Patients were 123 (male: female=10:113), 84 with rheumatoid arthritis and 39 with other immune diseases. The therapeutic agents used were PSL 31 (25.2%), MTX 65 (52.8%), NSAID 28 (22.8%), bDMARDs 42 (34.1%). Adverse reactions after the first and second vaccination were fever 17 (13.8%)/50 (40.7%), joint symptoms 7 (5.7%)/22 (17.9%), local injection reactions (pain/erythema) 93 (75.6)/98 (79.7), systemic skin symptoms 0 (0%)/2 (1.6%), other symptoms (malaise, myalgia, etc.) 59 (48.0%)/85 (69.1%), and changing treatment 5 (4.1%)/12 (9.7%). These responses differed in occurrence only for fever with and without PSL medication (22.5%: 47.3% (p=0.02)). [Conclusions] No specific adverse reactions were observed, but some patients experienced worsening of symptoms. Based on this study, it is thought that adverse reactions to vaccination are acceptable. We plan to accumulate more cases and analyze them in the future.

## W67-3

### Three cases of adult-onset Still's disease following COVID-19 vaccinations

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Conflict of interest: None

[Background] Virus infection is an environmental factor of AOSD, and cases of the onset of vaccination have been reported. We report a case that was suggested to be related to COVID19 vaccination. [Case] 1.75 year old female. Remittent fever, sore throat, arthralgia, and myalgia persisted from the next day after the first inoculation of the mRNA vaccine. A typical eruption appeared later. AOSD was diagnosed with neutrophil-dominant leukocytosis, mild liver damage, and marked increase in ferritin. Treatment with 1 mg / kg of prednisolone (PSL) was inadequate, and tocilizumab (TCZ) was added to improve the condition. However, she developed drug eruption due to TCZ and changed to sarilumab. 2.81 year old female. Remittent fever persisted from the next day after the first inoculation of vaccine.

Similar course. 3.78 year old male. Similar course. Elevated levels of various inflammatory cytokines were observed in the sera of each patient. In particular, IL-18 increased significantly to  $2-5 \times 10^5$  pg / ml, which was consistent with the profile of AOSD. [Conclusion] It cannot be ruled out that AOSD may have developed as part of the hypersensitivity reaction to the mRNA vaccine. If high fever persists after inoculation, it may be necessary to consider it as a differential disease.

## W67-4

### Three Cases of reactive arthritis after covid-19 vaccination

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Conflict of interest: None

**Purpose** of this study was to report three cases of enthesitis after covid-19 vaccination. All three cases were seronegative, revealed tenderness in the entheses, and joint echography findings showed active enthesitis. The age and sex, the time of onset, the location of the enthesitis, the presence of arthritis, and the course of the disease are as follows. **Case 1**, 78/M, 2 weeks after the second vaccination, shoulders' biceps, none, diagnosed as polymyalgia rheumatica (PMR) at outpatient and started prednisolone (PSL) 10 mg. **Case 2**, 76/F, 2 weeks after the second vaccination, knees' quadriceps, biceps' shoulder, and knees and hands had arthritis. Patient was admitted to the hospital, diagnosed as elderly onset rheumatoid arthritis (EORA), and started on PSL 20 mg + MTX 6 mg. **Case 3**, 63/F, 1 week after the first vaccination, right Achilles, none, outpatient diagnosis of arthritis in response to vaccine, started with PSL 5 mg + SASP 0.5 g. **Discussion** These three cases are considered to be reactive arthritis after Covid-19 vaccination. The only similar report is that of a case of remission after 1 month. Although our hospital is a community hospital, we have already experienced three cases. So we believe that these cases are common in Japan.

## W67-5

### Two Cases of COVID-19 with Rheumatoid Arthritis treated with JAK inhibitors

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Conflict of interest: None

[Background] Studies on the effects of COVID-19 infection on patients with rheumatoid arthritis (RA) have been conducted, but there are few reports on its effects on patients treated with Janus kinase inhibitors (JAKi). We report two cases of COVID-19 infection found in patients with RA treated with JAKi. [Case 1] 60s-year-old female, developed RA three years ago, has been treated with JAKi for two years. She was well treated with JAKi, MTX and PSL. She was diagnosed with COVID-19, followed by hospitalization. Pneumonia was improved with oxygen and dexamethasone, but her joint symptoms remained. At the time of COVID-19 infection, she was not inoculated against COVID-19. [Case 2] 40s-year-old female, developed RA two years ago, was treated with IL-6 inhibitor one year ago, followed by JAKi six months later due to diminished effect. She was well treated with JAKi and MTX, and has been vaccinated with COVID-19 in Y-4 months. She was diagnosed with COVID-19 and followed up at home. Symptoms such as fatigue and joint pain persisted even at Y+2 months. [Clinical significance] Since the symptoms of RA may be exacerbated by COVID-19 infection, it is necessary to carefully examine the patients' condition and provide medical care even after the COVID-19 has improved.

## W67-6

### Impact of COVID-19 outbreak in Shizuoka Prefecture on perceptions and behaviors in patients with rheumatic diseases: A cross-sectional study using questionnaire

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Conflict of interest: None

[Objective] We undertook this study in order to analyze responses against the coronavirus disease-2019 (COVID-19) pandemic in patients with rheumatic diseases. [Methods] Patients belonging to the Shizuoka Rheumatism Network were subjected for the study. A questionnaire was mailed to the patients from June to October 2021. Questions included were as follows; demographics, medications, source of information, fear levels and therapeutic compliance, etc. [Results] A total of 75 questionnaires were collected. 96.0% were patients with rheumatoid arthritis. They obtained the knowledge about COVID-19 mainly from mass media (89.3%), and social media (29.3%). Fear of COVID-19 were born from the risk of infection due to usual visits (65.3%), and from the increase of risk by disease (49.3%) or by medication (36.0%). However, 86.7% continued their usual visits (interval 46.4 ± 21.9 days), and there were no patients who spontaneously stopped their visits and/or medication. 93.0% were received vaccination twice because they thought it is effective for infection and/or for reducing severity of the disease. [Conclusions] In our study, patients with rheumatic diseases were influenced by the COVID-19 outbreak in Japan. However, most patients continued to receive necessary health management as usual.

## W68-1

### Analysis of the effectiveness and safety of recombinant zoster vaccine (RZV)

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Conflict of interest: Yes

[Objective] To analyze the effectiveness and safety of RZV in Japanese patients with rheumatic diseases. [Methods] We analyzed the patients who received RZV during October 2020 to September 2021 retrospectively. [Results] A 82 YO female RA patient died due to pneumonia after the 1st shot. We evaluated 30 (4M, 26F) patients: 27 RA, one with dermatomyositis, two MPA, one with UC and one GPA. The mean age was 74.7±9.2 YO and disease duration was 16.5±12.9 Y. Two patients were vaccinated of COVID-19 after the 1st shot. Twelve patients had a past history of herpes zoster (HZ). Twelve patients used TNFi. Two patients used ABT and one patient used RTX. JAKi were introduced in eight patients around the 1st shot. After the 1st shot, two patients developed fever. Among them, one patient developed arthralgia, lumbago and anorexia. one patient developed herpes simplex of the lip and local heat of the injection site and one patient had itching of the injection site. After the 2nd shot, one patient who had fever after the 1st shot developed fever again. One patient developed HZ after the 1st shot. [Conclusions] Although the flare of the rheumatic diseases after RZV was reported in Western countries, RZV appeared to be relatively safe. No patients developed HZ after the 2nd shot.

## W68-2

### Diagnostic utility of alpha-defensin assay for possible prosthetic joint infection

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Conflict of interest: None

[Objective] Periprosthetic joint infection (PJI) occurs in about 1% of primary surgical cases. Early diagnosis is important, but the diagnostic criteria for PJI have not been established. Recently, the usefulness of  $\alpha$ -defensin as a biomarker of joint fluid has been recognized. In this study, we investigated the usefulness of alpha-defensin assay for the diagnosis of PJI. [Methods] 20 patients who visited our department with suspected PJI from 2017 to 2019 were included in this study. There were 11 cases of THA and 9 cases of TKA with a mean age of 71 years. Blood tests, joint fluid culture, and  $\alpha$ -defensin assay using "synovasure" were performed. [Results] There were 16 Synovasure positive cases, of which 11 were diagnosed as PJI. 4 cases were negative for Synovasure, of which one was diagnosed as PJI. Sensitivity was 68.8%, specificity was 75%, positive predictive value was 91.7%, and negative predictive value was 37.5%. Among the false positive cases, two were pseudogout, one was polymyalgia rheumatica and another one was a patient with rheumatoid arthritis. [Conclusions] We investigated the usefulness of alpha-defensin assay using Synovasure for the diagnosis of PJI.  $\alpha$ -defensin may be useful as a diagnostic tool for PJI when used with other clinical tests.

## W68-3

### Clinical analysis of RA patients with nontuberculous mycobacteria infection

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Conflict of interest: None

[Objective] Treatment for rheumatoid arthritis (RA) has recently reached a more advanced stage but simultaneously posed a potential risk of infection like nontuberculous mycobacteria infection (NTM). We, herein, assessed clinical aspects of RA patients with NTM. [Methods] Seventeen RA patients that were diagnosed as NTM in our hospital from 2005 to 2021 were included and analyzed with the clinical records. [Results] Out of 17 patients including 13 women, 13 developed new-onset NTM in lung. The median age of onset for and the median RA disease duration until the lung NTM was 66 years old and 9 years, respectively. Accidental abnormalities in chest imaging were found in 6 patients with asymptomatic lung NTM. At the onset of lung NTM, 11, 10 and 6 patients used oral steroids, methotrexate and biologics, respectively. *M. avium* or *M. intracellulare* was detected in all cases of lung NTM. A combination of 3 antibiotics was selected for 10 patients but no treatment for 3 patients. Unfortunately, 3 patients, who were coincidentally suspected of other lung infections, passed away within two years after the diagnosis of lung NTM. In addition, two of them also had pulmonary fibrosis. [Conclusions] Some kinds of pulmonary complications might exacerbate the prognosis of RA patients with lung NTM.

## W68-4

### Predictor of necessity for anti-cytomegalovirus (CMV) agents in connective-tissue disease (CTD) patients with CMV reactivation, single-center prospective cohort study

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Conflict of interest: None

[Object] To investigate the predictor of necessity for anti-CMV agents in CTD with CMV reactivation. [Methods] Consecutive CTD cases with CMV reactivation after remission induction therapy for CTD from February 2017 until February 2019 were enrolled. CMV pp65 antigen was monitored weekly, and anti-CMV drug was started for CMV disease or CMV pp65 antigen  $\geq 6$  cells/2 slides. The predictor for necessity of anti-CMV agents were statistically analyzed. [Results] 52 cases were enrolled; the mean age was 65 y/o, and female was 71%. The underlying CTDs were vasculitides 19, PM/DM 10, SLE 9, RA 4, and others 10. The mean initial PSL dose was 52.2 mg/day, and mPSL pulse therapy was conducted in 20 (39%). Immunosuppressants were IVCY 26, CN1 10, MMF 3, and MTX



1, and biological agents were 8 including RTX. CMV disease was occurred in 5 cases with hepatitis 3, retinitis 1, and hematopoietic injury 1. Multiple regression analysis revealed that PSL  $\geq 37.5$  mg/day, serum Alb  $< 3.0$  g/dl, and CMV pp65 antigen  $\geq 2$  cells/2 slides at CMV reactivation were the predictors of necessity for anti-CMV agents in CTD patients with CMV reactivation. [Conclusions] The predictors of necessity for anti-CMV agents in CTD patients with CMV reactivation were prospectively detected.

## W68-5

### A case of disseminated *Scedosporium apiospermum* infection with brain abscesses and simultaneous nocardiosis in a patient with systemic lupus erythematosus

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Conflict of interest: None

[Case] A 61-year-old woman was diagnosed with systemic lupus erythematosus (SLE) and lupus nephritis, and treated by glucocorticoid and mycophenolate mofetil. After 6 months, a CT scan revealed nodules in her right lung. At the same time, valganciclovir was prescribed for her cytomegalovirus antigenemia. One month later, she was hospitalized due to a sudden seizure. A CT scan showed mass lesions in the brain and her blood  $\beta$ -D-glucan level was elevated. Meropenem and liposomal amphotericin B (L-AMB) were administered for febrile neutropenia. Her brain mass lesions kept expanding, and she was transferred to our hospital. Considering that L-AMB was ineffective, voriconazole (VRCZ) and micafungin (MCFG) were started, and she became afebrile. *Scedosporium apiospermum* was detected in the bronchial lavage fluid culture and *Nocardia nova* was detected in the sputum culture. VRCZ, MCFG, imipenem/cilastatin, and trimethoprim-sulfamethoxazole were continued, and her clinical symptoms improved. [Discussion] *Scedosporium* is known as a cause of "tsunami lung". VRCZ and posaconazole are often effective, but L-AMB is ineffective. Nocardiosis can also show elevated serum  $\beta$ -D-glucan levels. To our knowledge, this is the first report of brain abscesses by *scedosporium* infection with an SLE patient.

## W68-6

### A case of meningitis due to disseminated nontuberculous mycobacterium infection with anti-interferon-gamma autoantibody treated with adjunctive rituximab therapy in a patient with chronic recurrent multifocal osteomyelitis

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Conflict of interest: None

A 55-year-old male was admitted to our hospital due to a syncope. He was diagnosed with chronic recurrent multifocal osteomyelitis at the age of 38, and with disseminated nontuberculous mycobacterium (NTM) infection (DNTMI) by *Mycobacterium Intracellulare* at the age of 51. At the initial diagnosis of DNTMI, anti-interferon-gamma (IFN- $\gamma$ ) autoantibody was confirmed by enzyme-linked immunosorbent assay. After admission, NTM was also detected in his cerebrospinal fluid, and he was diagnosed with meningitis due to DNTMI. He underwent 5 combined antibiotics, by adding intravenous amikacin (AMK). Positive control of QuantiFERON (QFT) assay was not detectable. He was administered rituximab (RTX),

and discharged on the 99th hospital day. Although positive control of QFT assay was still undetectable, when we mixed a healthy donor's peripheral blood mononuclear cells (PBMCs) with the patient's serum before and after RTX treatment and recombinant IFN- $\gamma$  in vitro, STAT1 phosphorylation in the PBMCs was confirmed only with the serum after RTX treatment using flow cytometry. He is still in remission 3 months after discharge without AMK. To our best knowledge, this is the first report of a rescued case with meningitis due to DNTMI with anti-IFN- $\gamma$  autoantibody.

## W69-1

### Eighty-three cases of cytomegalovirus reactivation during immunosuppressive therapy for rheumatic diseases

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Conflict of interest: None

[Objective] In order to estimate risk factors for cytomegalovirus (CMV) infection, we revealed the profile of CMV-infected patients during the treatment for rheumatic diseases. [Methods] The subject is patients admitted to our department from January 2006 to October 2021 whose CMVC7-HRP antigen was evaluated. We collected their age, sex, primary problem and its lesion, lymphocyte counts, and serum immunoglobulin G (IgG). We also investigated the administration of steroid, immunosuppressants, and anti-CMV drug. [Results] Among the patients (N=502), 83 cases were positive for CMVC7-HRP. Primary problems are as follows; microscopic polyangiitis (MPA) 17, rheumatoid arthritis-related interstitial lung disease (RA-ILD) 8, dermatomyositis 7, lupus nephritis 4, eosinophilic granulomatosis with polyangiitis 4. Pulmonary (29) and renal (16) lesion are the main manifestations. The average lymphocyte counts and serum IgG are 589 / $\mu$ L and 985 mg/dL. 40 cases were treated with steroid pulse, and maximum dose of prednisolone was 44.7 mg/day on average. Immunosuppressants were combined to 62 cases. Anti-CMV drug was administered to 41 cases. [Conclusions] Among rheumatic diseases, pulmonary and renal lesion will require intensive immunosuppression, which can be risk factors for CMV reactivation.

## W69-2

### Progressive multifocal leukoencephalopathy in a dermatomyositis patient treated with low dose prednisolone

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Conflict of interest: None

[Case] A 63-year-old man was diagnosed with dermatomyositis (DM) nine years ago and was treated with prednisolone (PSL) and immunosuppressants. He has received a PSL monotherapy since he developed methotrexate-associated lymphoproliferative disorder two years ago. He was admitted to our hospital with a 2-week history of ambulate difficulty, dysarthria, and dysphagia. A flare of DM was suspected, but concentration of CPK was normal. Brain MRI showed hypointensity on T1 and hyperintensity on T2/FLAIR from pons to cerebellar peduncle, which suggested progressive multifocal leukoencephalopathy (PML). JC virus (JCV) DNA quantification in the cerebrospinal fluid by PCR was 329 copies/mL and we diagnosed as PML. Although we initiated mirtazapine 7.5 mg/day and tapered PSL to 5 mg/day, clinical symptoms worsened. We added mefloquine 275 mg daily for three days followed by 275 mg once a week, under permission by the Ethics Committee in our hospital, and clinical symptoms have gradually improved. [Conclusion] PML is caused by the infection of JCV to glial cells due to immunologic abnormality. Since there is no specific treatment, the basis of the treatment is to remove the cause to restore the immunological function. Our case suggests the efficacy of mefloquine on PML, as some studies report.

## W69-3

### A case of polyarteritis nodosa associated with miliary tuberculosis

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Department of Internal Medicine, Gifu University Hospital

Conflict of interest: None

[Case] 74 year-old man [Chief complaint] Fever [Current medical history] Pancreaticoduodenectomy and chemotherapy were performed for pancreatic head cancer in January X. In May of X+1, he was hospitalized with a fever. Cholangitis was suspected and antibacterial drugs were started, but no improvement in fever type was observed. He had red papules on his right lower leg and gastrocnemius muscle pain. Fasciitis and myositis were suspected on lower leg MRI. He biopsied and found findings suggestive of polyarteritis nodosa. PET-CT showed accumulation of FDG in the mediastinal lymph nodes and hepatic nodules, and biopsy confirmed acid-fast bacilli. IGRA positive rotation was also confirmed. Excretion was confirmed by smearing sputum acid-fast bacillus, and the diagnosis was miliary tuberculosis. Treatment with anti-tuberculosis drug improved fever type and myalgia, and both lower leg MRI were normalized. [Clinical significance] An association between cutaneous nodular polyarteries and tuberculosis infection has been reported. Polyarteritis nodosa was complicated with miliary tuberculosis, but antituberculosis drug also improved vasculitis. It is considered that tuberculosis was indirectly involved in the development of polyarteritis nodosa through an immunological mechanism.

## W69-4

### A case of Whipple's disease in a treatment-resistant rheumatoid arthritis patient with a history of methotrexate-associated lymphoproliferative disorder

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Conflict of interest: None

[Case] A 60-year-old man with ulcerative colitis (proctitis type) for 11 years and rheumatoid arthritis for 8 years was admitted to our hospital. Although he was treated by methotrexate (MTX), adalimumab, infliximab, tocilizumab (TCZ), and golimumab, his arthritis was not improved. He was also diagnosed with MTX-associated lymphoproliferative disorder (LPD) by axillary lymph node biopsy 3 years ago. The LPD was not regressed by withdrawal of MTX. The administration of tacrolimus, TCZ, tofacitinib or cyclosporine was discontinued for their ineffectiveness or adverse events. Methylprednisolone alleviated the symptoms. His lymphadenopathy was a diagnosis with Whipple's disease by a biopsy of para-aortic lymph node. [Discussion] Whipple's disease is an opportunistic infection that causes arthritis, lymphadenopathy, and diarrhea due to infection with *Tropheryma whipplei*, a gram-positive bacillus. It is a relatively rare disease with only about 1000 cases reported in Europe and the United States and more than 10 cases reported in Japan. Whipple's disease may have contributed to the progression of arthralgia. In the case of seronegative arthritis with refractory to usual treatments or an atypical clinical course, it is necessary to consider a possibility of Whipple's disease.

## W69-5

### Immunogenicity of the BBV152 Vaccines in Patients with Autoimmune Diseases

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Conflict of interest: None

[Objective] We investigated about seroconversion after SARS-CoV-2 vaccination and impact of various drugs on seroconversion rates in the treatment of patients with autoimmune diseases. [Methods] 107 patients with rheumatic diseases being treated at our hospital who had completed

vaccination with the BBV152 vaccines were recruited. Serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins were measured 2-11 weeks after the second vaccine dose. Seropositivity was defined as IgG  $\geq 50$  binding antibody units (BAU)/ml. [Results] In serum of 2 patients with rheumatoid arthritis, it was antibody titer negative, one is a man in his 80s who uses subcutaneous injections of abatacept and tacrolimus, and the other is a woman in her 50s who uses MTX10 mg and betamethasone 0.5 mg. In addition, the antibody concentration of 9 patients was 250 BAU/ml or less, indicating a low value. 6 of the 9 patients were over 65 years of age and were used in combination with two of the biologics, MTX, tacrolimus, 5-aminosalicylates (5-ASA), and iguratimod. [Conclusions] A combination of biologics and immunomodulators resulted in an attenuation of immunologic response over and above that of biologics monotherapy. 5-ASA and iguratimod may also reduce the effectiveness of vaccines in combination with other DMARDs.

## W69-6

### A case of *Mycobacterium marinum* (*M. marinum*) bacteremia with polyarthralgia

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Conflict of interest: None

[Case] 70-year-old male [Chief complaint] Polyarthralgia [Clinical course] He had received a renal transplant 22 years ago due to end-stage renal failure and was treated with prednisolone 10 mg/day, azathioprine 50 mg/day, mizoribine 50 mg/day and tacrolimus 1 mg/day. He underwent surgery for pyogenic tendinopathy of the left 3rd finger and synovitis of the left elbow at the orthopedic department 3 years ago. He had nodular lesions on the left leg and swelling in the bilateral wrist joints the last year, for which he received antibacterial treatment, which was not effective. Afterward, new ulcerative lesions and multiple elevated lesions were found on the dorsum of the left foot. On admission, blood culture and biopsy of skin ulcer and synovium revealed *M. marinum* and the patient was diagnosed with disseminated mycobacteriosis due to *M. marinum*. We treated with clarithromycin 400 mg/day, rifampicin 600 mg/day and doxycycline 200 mg/day. Five months later, the ulcer lesions showed a steady tendency to regress. [Discussion] We need to differentiate non-tuberculous mycobacterial infections as a cause of polyarthralgia in immunosuppressed patients. In this case, *M. marinum* was identified with blood cultures and synovial specimens, and the symptoms were similar to those of rheumatic diseases.

## W70-1

### Examination of the use of body composition meter in objective muscle strength measurement of patients with inflammatory myopathy

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Conflict of interest: None

[Objective] Quantitative measurement of muscle strength is important to evaluate and clarify the changes of a disease and its treatment. Handheld dynamometer (HHD) can measure muscle strength but requires time and practice. Non-invasive body composition analyzer is simpler and evaluates muscle mass, but its usefulness has not been well established in clinical practice. In this study, the relationship of muscle mass and muscle strength was investigated aiming to examine the usefulness of the body composition analyzer in patients with myositis. [Methods] We measured the muscle mass and knee extensors strength in 56 patients with myositis using a body composition analyzer and HHD, respectively. The relationships between muscle mass, muscle strength and clinical findings (CK level, ILD, dysphagia, malignant tumor, albumin level, BMI) were also investigated. [Results] There was a significant correlation between muscle mass and muscle strength (rt:  $r=0.50$ , lt:  $r=0.52$ ,  $p<0.059$ ). Muscle mass

was correlated with BMI. Muscle strength was correlated with albumin, BMI and CK variance. [Conclusions] The correlation between muscle mass and muscle strength suggests the usefulness of the body composition analyzer as a quantitative measurement of muscle strength in patients with myositis.

## W70-2

### Evaluation of apremilast, an oral phosphodiesterase 4 inhibitor, for refractory cutaneous dermatomyositis: A Phase 1b clinical trial

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Conflict of interest: None

[Objective] Dermatomyositis, an idiopathic inflammatory myopathy, is characterized by cutaneous itchy manifestations, which are frequently refractory and recurrent even after intensive immunosuppressive treatments. The objective of this study is to evaluate the effectiveness and safety of apremilast, an oral phosphodiesterase-4 inhibitor, in treating skin-dominant dermatomyositis. [Methods] We performed this prospective, single-arm, interventional study using apremilast. We collected adverse events, and evaluated cutaneous dermatomyositis disease area and severity index (CDASI), visual analogue scale (VAS) of itching, and quality of life by dermatology life quality index (DLQI), during a 12-week treatment phase. [Results] Among 5 patients (1 male and 4 females, median age, 64 years), 3 patients experienced diarrhea, 2 of which withdrew from the study and recovered quickly afterwards. In 3 patients who received apremilast for 12 weeks, a 39.4% reduction from baseline CDASI total activity score, but not the damage score. VAS of itching, and DLQI were slightly improved in 1 and 2 patients, respectively. [Conclusions] This first Phase Ib study suggested that apremilast can be as a possible treatment for refractory and recurrent dermatomyositis-associated cutaneous manifestations.

## W70-3

### Standard combination therapy is associated with decreased risk of relapse or death in patients with anti-MDA5 antibody-positive dermatomyositis

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Conflict of interest: None

[Objective] To investigate factors associated with relapse or death in patients with anti-MDA5 antibody-positive dermatomyositis (DM). [Methods] Patients with anti-MDA5 antibody-positive DM treated at our hospital from November 2017 to October 2021 were included. The combination therapy of steroid, tacrolimus, and cyclophosphamide was defined as standard treatment (S-Tx), and the others as non-standard treatments (NS-Tx). The relapse or death were defined as events. Event-free survival (EFS) was analyzed between two groups according to treatment regimens, ferritin levels, and ILD scores using Kaplan-Meier method. [Results] Nine patients were included (S-Tx: 4, NS-Tx: 5 for initial treatments). Six events were seen; 1 death in S-Tx and 5 relapses in NS-Tx group. The EFS showed no difference between treatments, ferritin levels, or ILD scores. During the median follow up period of 38.9 months, 5 relapses were additionally reported after first relapses. Among all 20 treatments, EFS tended to be better in S-Tx regimens and more events were seen in NS-Tx regimens (S-Tx /NS-Tx: 11.1%/100%,  $p < 0.001$ ). [Discussion] Standard combination therapy is associated with fewer events and better EFS. [Conclusions] Our study suggests that treatment regimen is mainly associated with relapse or death.

## W70-4

### A case of anti-MDA5 antibody positive dermatomyositis after COVID-19 vaccination

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Conflict of interest: None

[Case] 60-year-old man [Chief complaint] skin rash [Clinical history] He received the Pfizer-BioNTech COVID-19 mRNA vaccine BNT162b in September 20XX. On the second day, skin rashes appeared on the both fingers and gradually worsened. The dermatologist diagnosed as an allergic reaction after vaccination, but no improvement was observed. He developed a fever on 16th day. He was referred to our hospital on the suspicion of rheumatic disease. [Progress] Gottron's sign, mechanic's hand, nail fold bleeding, and V-neck sign were evident and the chest CT findings showed interstitial pneumonia with organizing pneumonia (OP) pattern. In addition, anti-MDA5 antibody was positive titer 3595 Index, which led to the diagnosis of anti-MDA5 antibody positive dermatomyositis (anti-MDA-5-positive DM). Combined immunosuppressive therapy with prednisolone, cyclophosphamide, and tacrolimus was started immediately. The skin rash showed improvement after the start of treatment within 1 week, and the interstitial shadows improved on the chest CT. [Consideration] Although the causal relationship between vaccination and the onset of the disease is not clear, we experienced a case of anti-MDA-5-positive DM immediately after vaccination, and we report this case with some literature review.

## W70-5

### Four cases of anti-ARS antibody positive dermatomyositis developed after COVID-19 vaccine (Tozinameran) inoculation

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Conflict of interest: None

Case 1: 70-year-old female recognized fever the next day of inoculation with COVID-10 mRNA vaccine (Tozinameran). Two weeks after the inoculation, she had respiratory distress. She had desaturation of oxygen. Her chest CT showed cNSIP pattern, and her anti-ARS antibody was positive. We administrated her with mPSL pulse and 1 mg/kg PSL and Tac with plasma exchange. Case 2: 68-year-old female became aware of dyspnea 2 weeks after inoculation of Tozinameran. Her chest CT showed cNSIP pattern and her anti-ARS antibody was positive. We cured her with mPSL pulse, 1 mg/kg PSL, and IVCY. Case 3: 58-year-old female recognized pitting edema of her hands 9 days after Tozinameran inoculation. After second inoculation, she had dyspnea. We found that she had ILD and was anti-ARS antibody positive. We administrated her with mPSL pulse, 1 mg/kg PSL and Tac. Case 4: 54-year-old female, who had been already administrated with 5 mg PSL and Tac, was inoculated Tozinameran. The next day of inoculation, she had dyspnea. We found she had ILD, and cured her with mPSL pulse. Conclusion: Tozinameran is extremely helpful vaccine against COVID-19. But we cannot deny relation between these 4 cases and Tozinameran at this point. We need more information about effect of Tozinameran to Rheumatic disease.

## W70-6

### Poor prognostic factors in patients with anti-MDA5 antibody-positive dermatomyositis treated with plasma exchange therapy

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Conflict of interest: None

[Purpose] Plasmapheresis (PEX) was reported to be effective in patients with anti-MDA5 antibody (Ab)-positive dermatomyositis (DM) who had an inadequate response to glucocorticoid (GC), calcineurin inhibitor and intravenous cyclophosphamide (IVCY) combination therapy. We retrospectively analyzed the medical records of anti-MDA5 Ab-positive



DM patients with interstitial lung disease (ILD) who underwent PEX, and examined the prognostic factors. [Methods] In this study, 8 patients (mean age 60.3 years, 3 males, 5 females) were included. Clinical and laboratory findings before the start of initial treatment and PEX were analyzed by dividing into 4 survived and 4 deceased groups. [Results] All patients were treated with triple-drug combination. In the deceased group, serum albumin before the start of treatment was lower ( $2.3 \pm 0.19$  vs  $2.9 \pm 0.06$  g/dL,  $p < 0.01$ ) and more elderly ( $69.0 \pm 2.0$  vs  $51.5 \pm 7.9$  years old,  $p < 0.05$ ) compared to the survived group. Also, before the start of PEX, serum albumin was lower in the deceased group ( $2.2 \pm 0.25$  vs  $2.8 \pm 0.33$  g/dL,  $p < 0.05$ ). Serum CRP, ferritin, KL-6, SP-D, and IgG levels were not different between both groups. [Conclusion] In anti-MDA5 Ab-positive DM with ILD treated with PEX, old age and low serum albumin levels can be a poor prognostic factor.

## W71-1

### The clinical and serological features of recurrent anti-MDA5 Ab positive DM patients

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Conflict of interest: None

[Objective] Anti-melanoma differentiation-associated gene 5 (MDA5) antibody (Ab) positive dermatomyositis (DM) often complicates rapidly progressive interstitial lung disease (RP-ILD), which has a fatal prognosis at early phase. However, the long-term clinical course after remission remains unclear. Therefore, we investigated the clinical and serological features of recurrent cases. [Methods] DM patients with anti-MDA5 Ab who were treated between 2014 and 2021 were enrolled. [Results] 35 patients were enrolled. 57% (17/30) were discharged from the hospital. 20% (4/20) showed recurrence. Interestingly, anti-MDA5 Ab titers of all female cases elevated at the recurrence and both required the intensive treatment as same degree as their initial treatment. On the other hands, these titers of all male cases remained under cut-off level, and both patients showed good response to moderate dose of PSL. The ferritin levels in all and the KL-6 levels in 3 cases were within normal range at the recurrence, and both of male cases stayed within their normal ranges. [Conclusions] At the early detection of recurrence, exacerbation of physical symptoms such as skin and muscle are sometimes proceeded to serological findings. Exacerbation of physical findings is the key to early detection of recurrence.

## W71-2

### Identification of YKL-40 positive inflammatory cells in polymyositis and dermatomyositis

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Conflict of interest: None

[Background and purpose] YKL-40 is a chitinase-like protein that has received attention as a biomarker for estimating disease activity in autoimmune diseases, including polymyositis (PM), dermatomyositis (DM). In myopathology, YKL-40-positive inflammatory cells were identified in immunohistochemical staining of anti-synthetase syndrome in 2021. However, they have not been identified. The aim of this study was to identify these cells. [Methods] Muscle biopsy specimens from patients each with PM and DM were HE-stained and immunofluorescence staining was performed using anti-YKL-40 and anti-CD68 antibodies. [Results] HE staining showed myofibrils of different sizes and inflammatory cell infiltration into the interstitium in all cases. Immunofluorescence staining showed YKL-40 and CD68 positive cells. [Conclusion] CD68 is known as a marker for macrophages. Last year, we predicted that YKL-40 positive cells were macrophages. Immunofluorescence staining to verify this prediction showed that CD68 was expressed in YKL-40 positive cells. We have shown that serum YKL-40 is elevated during myositis without ILD. Our

results suggest YKL-40 positive macrophages may be one of the sources of serum YKL-40, and we considered them to be important for elucidating the pathogenesis of myositis.

## W71-3

### Fasciitis might predict clinically amyopathic dermatomyositis -single center, retrospective, case series study-

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Conflict of interest: None

[Objective] Dermatomyositis can be accompanied by fasciitis. It was reported that fasciitis on MRI correlated with RP-ILD, but there is no report to examine whether fasciitis can predict CADM in combination with other biochemistry test. So, we investigated the association between fasciitis and CADM. [Methods] From 2010 to 2020, we retrospectively analyzed 94 patients with inflammatory myopathy who were treated at the Department of Internal Medicine for Collagen Disease and Rheumatology, Kobe University Hospital. Symptoms clinically associated with fasciitis were examined using logistic regression. We also analyzed whether there were any test values related to CADM using logistic regression. [Results] Patients with fasciitis on MRI had a significantly higher proportion of CADM (2% vs 16%,  $p = 0.04$ ). Paronychia had association with fasciitis (odds ratio = 4.48,  $p = 0.019$ ). Blood biochemistry tests showed that CK and C4 were associated with fasciitis. Furthermore, the combination of fasciitis, CK, C4, and paronychia predicted MDA5 (AUC 0.926). VIF of each item are nearly equal to 1 and there was no multicollinearity. [Conclusions] Fasciitis reflects angiopathy and can be predicted as MDA5.

## W71-4

### Characteristics of Anti-MDA-5 dermatomyositis associated with thrombotic microangiopathy: two case reports

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Conflict of interest: None

[Objective] There are few reports of TMA complicated with anti-MDA-5 dermatomyositis. We present two cases of anti-MDA-5 antibody-positive dermatomyositis complicated with TMA, comparing the clinical features with non-TMA cases. [Methods] We evaluated 20 anti-MDA-5 dermatomyositis cases treated from November 2009 to October 2021. [Results] 2 patients were complicated with TMA. [Case 1] The patient was a 34-year-old man. Prednisolone (PSL), cyclosporine, and cyclophosphamide pulse therapy (IVCY) were administered. Thrombocytopenia, hemolytic anemia and renal dysfunction occurred which indicated TMA. Rituximab (RTX) improved TMA. [Case 2] The patient was a 65-year-old man. Treatment was initiated with PSL, tacrolimus, and IVCY. Hemolytic anemia, thrombocytopenia, and renal function worsened, which led to the diagnosis of TMA. RTX improved TMA. [Conclusions] We found that 2 out of 20 patients with TMA were refractory to triple therapy and one patient had hypocomplementemia. Among non-TMA patients, 9 (50.0%) patients were refractory to triple therapy and 3 (16.7%) patients had hypocomplementemia. We found no difference in serum levels of ferritin and anti-MDA5 antibody titer. In the cases of anti-MDA-5 dermatomyositis complicated with TMA, RTX may be important for successful treatment.

## W71-5

### Subtype analysis of anti-ARS antibody positive cases

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Conflict of interest: None

[Purpose] To clarify the characteristics of anti-ARS antibody-positive cases in the subtype. [Methods] We analyzed the anti-ARS antibody subtypes of anti-ARS antibody-positive cases measured in our hospital from October 2016 to September 2020 for 4 years. (EUROLINE Myositis Profile 3, Euroimmun) was used for the measurement. [Results] EUROLINE Myositis Profile 3 was measured in 68 cases. The average age was  $62.3 \pm 14.0$ , and the gender was 25 males, 43 females, 27 IPs alone, 17 PM + IPs, 15 DM + IPs, 6 ADMs, and 2 others. Anti-Jo-1 antibody 20 cases, PL-12 antibody autoantibody 12 cases, anti-EJ antibody 11 cases, anti-PL-7 antibody 7 cases, anti-PM75 antibody 1 case, detailed autoantibody was not detected in 17 cases. Interstitial pneumonia complications were observed in almost all cases in which autoantibodies could be detected. Skin symptoms were noted in half of the cases. PL-12 had less onset of muscle symptoms. [Conclusion] In the analysis of the anti-ARS antibody subtype group, there were many interstitial pneumonia groups, skin symptoms were observed in about half, and the appearance of muscle symptoms was different for each autoantibody. It was suggested that more detailed examination of each autoantibody is important.

## W71-6

### A case of dermatomyositis with a positive cross-compatibility test after intravenous immunoglobulin

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Conflict of interest: None

[Case] A 94-year-old woman was admitted for anti-TIF1- $\gamma$  antibody-positive dermatomyositis, and received glucocorticoids and intravenous immunoglobulin (IVIG). On day 6 of admission, she developed hemorrhagic shock due to left femoral intramuscular hematoma. Her blood type was A Rh D positive and no irregular antibodies were detected, but compatibility tests were positive for four units of type-A red blood cells (RBCs). Two units of type-O RBCs were compatible, suggesting ABO incompatibility due to IVIG. She received type-O RBCs without hemolysis. She needed another blood transfusion on day 12 of admission, and compatibility tests turned negative for two of the four type-A RBCs units. The compatible unit was administered and no signs of adverse reactions occurred. [Clinical significance] IVIG potentially contains anti-A and anti-B antibodies, but their titers are low and hemolytic anemia is rare (D. Branch et al., Transfusion, 2015). On the other hand, blood compatibility testing can be positive after IVIG. This case suggests that it is better to select type-O RBCs in emergency, and that the incompatibility will be resolved over time. IVIG is often used to treat dermatomyositis, and it is important to know that IVIG affects on blood transfusions.

## W72-1

### Impact of dysphagia and its severity on long-term survival and swallowing function outcomes in patients with dermatomyositis and polymyositis

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Conflict of interest: None

[Objective] To investigate the impact of dysphagia on long-term survival and swallowing function outcomes in dermatomyositis and polymyositis patients. [Methods] Impact of dysphagia and its severity assessed using the Food Intake LEVEL Scale (FILS) on long-term survival and swallowing function outcomes were retrospectively studied. [Results] 26 dysphagic, including 8 severe (FILS score 2, 3) and 6 most severe (FILS score 1) cases, 210 non-dysphagic cases were identified. Although dysphagic cases had significantly shorter survival, multivariate analysis showed dysphagia was not significantly associated with shorter survival (hazard ratio (HR) 1.46 [95% confidence interval (CI) 0.69-3.10]), but the age-adjusted Charlson Comorbidity Index was significantly associated (HR 1.57 [95% CI 1.36-1.82]). Dysphagia severity was significantly asso-

ciated with delayed recovery of dysphagia. The most severe cases had a significantly higher cumulative probability of death before recovery from dysphagia than the severe cases. [Conclusions] The poor survival of dysphagic myositis patients was largely confounded by advanced age and comorbid malignancies. However, patients with the most severe dysphagia had a significantly worse swallowing function and survival prognosis than those with milder dysphagia.

## W72-2

### Tofacitinib 20mg/day for interstitial pneumonia associated with anti-MDA5 antibody-positive dermatomyositis

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Conflict of interest: None

Anti-MDA5 antibody-positive dermatomyositis is associated with rapidly progressive interstitial pneumonia and has a poor prognosis. Triple therapy (high-dose glucocorticoids, cyclophosphamide, and calcineurin inhibitor) and tofacitinib 10 mg/day are effective, but there are still refractory cases despite these treatments. In this case series, we report five cases in which the dose of tofacitinib was increased from 10 mg to 20 mg/day due to poor response to multidrug therapy. The median age was 47 years with three males. All patients were receiving triple therapy and tofacitinib 10 mg/day. After the tofacitinib dose was increased, three of five patients improved. Three survivors started the triple therapy by the second day of hospitalization, whereas the deceased started it more than one week later. As to opportunistic infections, four patients developed cytomegalovirus infection. It was reported that tofacitinib 20 mg/day had a higher remission rate than 10 mg/day in patients with rheumatoid arthritis or ulcerative colitis. However, reports regarding 20 mg/day of tofacitinib in dermatomyositis are limited. We report five cases with refractory anti-MDA5 antibody-positive dermatomyositis treated by 20 mg/day of tofacitinib with some literature review.

## W72-3

### Long-term outcome of maintenance therapy with immunosuppressants for polymyositis/dermatomyositis (PM/DM)

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Conflict of interest: None

[Objective] The differences of various immunosuppressants regarding long-term outcomes and the effect on new occurrence of malignancy are not known in the maintenance therapy of PM/DM. [Methods] We retrospectively reviewed 75 patients with PM/DM who were patients in our department or who had been newly diagnosed between 2015 and 2020. [Results] The mean age was 63.4 years; the mean disease duration was 91 months. Immunosuppressants were used in 53/75 patients, with a mean duration of 48 months. Tacrolimus (TAC) was used in 31 cases, azathioprine (AZP) in 12 cases, cyclosporine (CsA) in eight cases, and methotrexate in four cases. The most common side effects were tremor with TAC in five cases, liver dysfunction with AZP in eight cases, and nephropathy with CsA in five cases. Malignancies were screened and diagnosed in three cases at the time of remission induction. There was only one case of early gastric cancer at the time of relapse who was taking TAC during maintenance therapy. [Conclusions] Immunosuppressants can be safely used for the long-term in patients with PM/DM. Although the most common side effects differed depending on the drug, there was no obvious increase in the occurrence of malignancy during maintenance therapy.

## W72-4

### High-intensity induction therapy combining tofacitinib, rituximab, and plasmapheresis in rapidly progressive interstitial lung disease associated with anti-MDA5 antibody positive dermatomyositis

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Department of Rheumatology, Tohoku University Hospital

Conflict of interest: None

[Object] Although triple therapy is used in rapidly progressive interstitial pneumonia (RP-ILD) associated with anti-MDA5 antibody-positive dermatomyositis (anti-MDA5+DM), the survival rate of patients with poor prognostic factors is poor. This study aimed to analyze therapeutic effects of high-intensity induction therapy utilizing tofacitinib (TOF) for patients with multiple poor prognostic factors. [Methods] Thirty-one patients with anti-MDA5+DM during 2014 to 2021 were retrospectively analyzed for the survival, relapse, and adverse events. [Results] 18 cases were treated before the introduction of TOF. Although RTX or PE were used, eight out of 10 RP-ILD cases with a ferritin level ( $>400$  ng/mL) died in 2.5 months. High-intensity induction therapy, consisting of triple therapy with very high dose of steroid, liposteroid, TOF, PE, and RTX was performed in eight patients with poor prognostic factors. Although, deaths at two months and at eight months were observed, significant improvement of survival was observed. Several adverse effects including infections and cytopenia existed. [Conclusions] Significant improvement of survival was observed in patients treated with high-intensity induction therapy. Meanwhile, stratification of patients for prognosis is needed.

## W72-5

### Long-term use of abatacept in patients with refractory polymyositis and dermatomyositis

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Conflict of interest: Yes

[Objective] Effectiveness of abatacept (ABT) in some cases of polymyositis and dermatomyositis (PM/DM) have been reported. We investigated the effectiveness and safety of ABT in clinical practice. [Methods] The ethics committee in our institute approved off-label use of ABT. Written informed consent was obtained from participants. Clinical information was collected from medical records retrospectively. [Results] ABT was administered to three patients with PM and four with DM. Among 7 cases, four had interstitial lung disease (ILD) with positive anti-ARS antibodies (Abs), two had anti-HMGCR Abs and the other one had no myositis-specific Abs. All cases were refractory to two or more kinds of immunosuppressants besides glucocorticoids (GCs). ABT ameliorated the disease activities in five cases, but not in the other two. In the five cases responding to ABT, the median follow-up period was 3.8 years. The median dose of prednisolone was decreased from 10 mg/day at the initiation of ABT to 3 mg/day at their latest visits. No severe infectious-adverse events occurred. Two cases were diagnosed with lymphoproliferative disorder and prostate cancer after 3.8 and 4.1 years, respectively. [Conclusions] ABT demonstrated GC-sparing effects in refractory PM/DM including cases complicated with ILD.

## W72-6

### Peficitinib is effective for anti-MDA5 antibody positive dermatomyositis refractory to triple therapy

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Nephrology Center and Rheumatology, Toranomon Hospital Kajigaya

Conflict of interest: None

[Background] Anti-MDA5 Antibody positive dermatomyositis (DM) is characteristic with its amyopathic DM, skin manifestation, and intersti-

tial lung disease (ILD). Although triple therapy with steroids, calcineurin inhibitors, and cyclophosphamide (IVCY) is effective, there are refractory cases. [Case presentation] A 50-year-old woman. She came to the hospital for hepatopathy. She showed Gottron and reverse Gottron signs and ILD. Anti-MDA5 antibody titer was high at 6860 IU/mL, and we diagnosed her as anti-MDA5 antibody-positive dermatomyositis. The patient was immediately started on triple therapy with prednisolone (PSL) 50 mg (1 mg/kg/day), tacrolimus 4 mg, IVCY 500 mg/m<sup>2</sup> every 2 weeks. The PSL was reduced every 2 weeks because the skin rash and ILD improved and the anti-MDA5 antibody decreased, but when the PSL was reduced to 40 mg, the skin rash worsened and the ILD marker showed an upward trend. Peficitinib was added on her and improved her skin rash and ILD. The patient was discharged after the PSL was reduced to 30 mg. In the 6 months after discharge, anti-MDA5 antibody continued to decrease and PSL was reduced to 10 mg. [Conclusions] In addition to the JAK inhibitor tofacitinib, peficitinib was shown to be effective in the treatment of anti-MDA5 antibody-positive dermatomyositis.

## W73-1

### Clinical and imaging features of hyperuricemia cases with ankle joint arthritis

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Conflict of interest: None

[Objective] We examined the imaging features of gout cases with ankle arthritis. [Methods] Ultrasonography were examined in 145 ankle gout patients. 10 cases were examined by HR-pQCT. [Results] In the ankle joint, there were 56 cases of synovitis, 21 cases of Achilles tendinitis, 117 cases of bone formation, and 75 cases of periarticular tendinitis. There were 12 cases of hand pain, 3 cases of wrist synovitis, 5 cases of finger synovitis, 3 cases of extensor tendinitis, and 8 cases of nail bed inflammation. There were 9 cases of elbow pain, 6 cases of triceps tendon enthesitis, 2 cases of bone formation, and 2 cases of bursitis. One case of shoulder joint was supraspinatus tendon enthesitis. There were 32 cases of knee joint, 13 cases of synovitis, 12 cases of femoral quadrilateral tendinitis, 10 cases of bursitis, 10 cases of patellar ligament enthesitis, and 22 cases of bone formation. HR-pQCT showed calcification in 4 cases of ankle lateral malleolus, osteophytes in 5 cases of Chopard joints, in 9 cases of Achilles tendon enthesitis, and in 8 cases of plantar aponeurosis. [Conclusions] Enthesitis and osteophytes are often found in the large joints. It was considered that uric acid in plasma exuded by enthesitis may have been deposited in the joints and around the tendons.

## W73-2

### Comparison of clinical features of the patients with pseudogout and rheumatoid arthritis

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Conflict of interest: None

[Objective] Pseudogout is an acute arthritis induced by calcium pyrophosphate dihydrate (CPPD) crystal deposition and its etiology is unclear. In clinical practice pseudogout is difficult to differentiate from rheumatoid arthritis (RA). In this study, we compared the clinical features of the patients with pseudogout and RA. [Methods] Seventeen patients with pseudogout and 11 patients with RA referred to our hospital with symptoms of acute arthritis and had been undergone arthrocentesis. The clinical data was collected and analyzed. [Results] The age (pseudogout group;  $82.8 \pm 8.9$  years, RA group;  $72.7 \pm 10.4$  years;  $p=0.01$ ), the levels of C-reactive protein (pseudogout group;  $14.1 \pm 9.1$  mg/dL, RA group;  $1.6 \pm 2.4$  mg/dL;  $p<0.01$ ), that of hemoglobin (pseudogout group;  $11.3 \pm 1.5$  g/dL, RA group;  $12.6 \pm 1.69$  g/dL;  $p=0.044$ ), that of serum albumin (Alb) (pseudogout group;  $11.3 \pm 1.5$  g/dL, RA group;  $12.6 \pm 1.69$  g/dL;  $p=0.044$ ), and white



blood cell count (WBC) (pseudogout group;  $10150 \pm 3089/\mu\text{L}$ , RA group;  $6600 \pm 2465/\mu\text{L}$ ;  $p < 0.01$ ) were significantly different between both groups. [Conclusions] Patients with pseudogout showed higher inflammation status accompanied with higher WBC, lower levels of Alb, and lower levels of Hb compared with patients with RA, suggesting that pseudogout is debilitating disease compared with RA.

### W73-3

#### Calcium pyrophosphate dihydrate crystal in operated rheumatoid arthritis of the knee

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Conflict of interest: None

[Objectives] To investigate the relationship between CPPD crystal and operated rheumatoid arthritis (RA) of the knee. [Methods] Seventy-seven TKAs were performed for RA knees from January 2016 to September 2021. At the operation, joint fluids were collected from 70 knees (average age 71.6: male 8: female 72). We evaluated the relationship between CPPD crystals and age, gender, FTA, BMI, CRP, ESR, MMP-3, degree of osteophyte formation and alignment. [Results] CPPD crystals were detected from 19 RA knees (27.1%). There were no significant differences between CPPD (+) and (-) groups about age, gender, FTA, BMI, CRP, ESR and MMP-3. The more severe osteophyte formation showed higher CPPD (+) rate tendency, however, there are no significance. CPPD (+) rates were 34.2% in varus knees, 23.1% in valgus knees and 18.2% in neutral knees, respectively. We reported that age, valgus knee, severe osteophyte and low BMI were the risk factors of CPPD (+) in operated osteoarthritis (OA) knees, previously. In this study, there was no difference between CPPD (+) and (-) groups about these factors. In especially, CPPD (+) rate in RA valgus knees was one third of that of OA valgus knees. [Conclusions] It may be suggested that CPPD production mechanism in RA knees is different from that in OA knees.

### W73-4

#### Is Calcium Pyrophosphate (CPPD) Spondylitis / Epidural Abscess Underestimated? -Potential Spondylitis Proposal-

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Conflict of interest: None

[Objective] We have reported that CPPD spondylitis may have been diagnosed as infectious spondylitis, but it is unclear if CPP is the true cause. It has not yet been fully debated as to whether diseases that have been diagnosed as spondylitis with no identified causative agent may be false-negative, due to the limitations of culture testing, CPPD spondylitis, or whether there may be new spondylitis that is currently undiagnosable or due to other causes. [Methods] We would like to present 7 patients who were clinically and radiologically suspected of having infectious spondylitis/epidural abscesses positive for CPP crystal with negative culture test of specimens from the intervertebral disc or epidural space, and consider the above. [Results] The average age was 69.6 years. CRP at the first visit was 0.13 to 22.3 mg/dL, body temperature was 36.3 to 39.1 degrees Celsius. They responded well to treatment, but did not seem respond to antibacterial agents. [Conclusions] Considering that there are various forms of arthritis due to CPPD, from asymptomatic to fulminant, the same possibility is considered in the spine. Until this pathological condition is explained to our satisfaction, we propose to term it "potential spondylitis" and try to elucidate the pathological condition.

### W73-5

#### Dual energy CT as a diagnostic tool of gouty tendinitis. A case report

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Conflict of interest: None

[Case] The patient was a 49-year-old man with asymptomatic hyperuricemia with a serum uric acid level of around 9 mg/dL. He experienced swelling and pain in his joints once or twice a year from a few years ago. In addition, he was aware of dull pain in his right knee without obvious swelling. These episodic joint symptoms were relieved by analgesics, lasting about 1-2 weeks. About 2 weeks before the visit, swelling and pain in the right shoulder appeared again, and brought him to our department. A blood test showed a uric acid level of 9.1 mg/dL. Musculoskeletal ultrasonography showed tendinitis and hyperechogenic crystal-like deposits in acromioclavicular joint, triceps brachii and patellar tendon enthesis. Dual energy CT showed the urate crystal deposits in these areas. The gouty tendinitis was diagnosed, and urate lowering therapy and colchicine were started. [Discussion] In gouty tendinitis, it is difficult to collect and prove urate crystals which are the gold standard for the diagnosis of gout. Dual energy CT can show urate deposition and lead to the diagnosis in gouty tendinitis which is difficult to obtain specimens for microscopic crystal examination. [Clinical significance] We experienced a case of gouty tendinitis confirmed by dual energy CT.

### W73-6

#### A case of highly refractory gouty arthritis that could be controlled by the treatment of tocilizumab (TCZ) and a surgery

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Conflict of interest: None

[Case] A 77-year-old man was hospitalized for gout attack with CRP 30 mg/dL at December 20XX. NSAIDs could not be used due to renal dysfunction. Prednisolone (PSL) 20 mg/day was initiated and his arthritis was improved, then PSL was gradually reduced to 10 mg/day with febuxostat. However, 3 days later, the arthritis was flared again with CRP 35 mg/dL. PSL dosage was increased to 20 mg/day again and CRP decreased to 1 mg/dL, but his gout activity remained. Colchicine 3 mg/day was also combined, but he could not continued due to severe diarrhea and hepatic injury. His gout was intractable with repeated relapse even with PSL 20 mg/day; therefore, IL-6 receptor antibody tocilizumab (TCZ) 480 mg (8 mg/kg)/4 weeks intravenous infusion was initiated from April 20XX+1. His gout arthritis was improved and CRP was negative after a week. PSL was gradually reduced to 7.5 mg with combination of TCZ every month. However, he was flared again on reducing PSL to 5 mg. Then, we decided the synovectomy of his inflamed joints because of very refractory gout at June 20XX+1 with dose up of febuxostat, low dose of colchicine and TCZ. After the therapies, his gout activity was improved enough and became stable. Currently, TCZ 162 mg sc /week was continued without relapse, and PSL could be discontinued at June 20XX+2.

### W74-1

#### Efficacy and safety of mepolizumab (MEP) as remission induction therapy in patients with eosinophilic granulomatosis with polyangiitis (EGPA)

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Conflict of interest: None

[Objective] To clarify the efficacy and safety of MEP as remission induction therapy in patients with EGPA. [Methods] We retrospectively investigated the medical records of 9 EGPA patients (8 females) treated with MEP for initial remission induction (6 cases) or re-remission induction for

relapse (3 cases) at our hospital. [Results] MPO-ANCA was positive in 4 cases. At diagnosis of EGPA, the clinical features were as follows; mononeuritis multiplex 9, cutaneous symptoms 7, otolaryngological lesions 3, cardiac lesions 3, pulmonary lesions 3, and renal lesions 3, 1996-FFS  $\geq$  1:2, geometric mean eosinophil count 13074/ $\mu$ L. At the start of MEP, the average age: 59.7 years, the average PSL dose: 37 mg/day and 1 patient received IVCY. All cases achieved BVAS=0. The average PSL dose was 8.3 mg/day (6 months (M), N=8), 4.3 (12M, N=5), 3.0 (18M, N=4), 1.5 (24M, N=4), and 2 patients discontinued steroids by 24M. Six adverse events (the observation period of 160 person-months) were seen in 4 patients; 3 infections, 1 bilateral femoral head necrosis, 1 injection site wheal, and 1 urticaria. [Conclusions] BVAS=0 was finally achieved in all patients. PSL dose could be reduced in all patients, and PSL was successfully discontinued in 2 cases. There were no serious adverse events directly related to MEP.

## W74-2

### Efficacy and safety of mepolizumab (MEP) as remission maintenance therapy in patients with eosinophilic granulomatosis with polyangiitis (EGPA)

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Conflict of interest: None

[Objective] To clarify the efficacy and safety of MEP as maintenance therapy in patients with EGPA. [Methods] We retrospectively investigated the medical records of 6 EGPA patients (4 females) treated with MEP for remission maintenance at our hospital. [Results] At the start of MEP, average disease duration was 110 months, age was 60.5 years, geometric mean eosinophil count 297/ $\mu$ L, and the reasons for starting MEP were as follows; 3 asthma, 2 eosinophilia, 2 peripheral neurosensory disorder, 1 difficulty in reducing steroids, 1 deafness, and 1 skin lesion. After the start of MEP, eosinophils decreased in all cases but increased slightly (less than 1000/ $\mu$ L) in one case. The average PSL dose was as follows; 4.8 mg/day (MEP start, N=6), 4.2 (6 months (M), N=5), 4.7 (12M, N=5), 2.7 (24M, N=3), 2.5 (36M, N=2), and 1 patient discontinued steroid. Six adverse events (the observation period of 147 person-months) were seen in 2 patients; 5 Infections (bacterial pneumonia 2, sinusitis 2 and 1 enteritis), and 1 local site-reaction and 1 discontinued MEP because of the pain of injection region and patient's hope. [Conclusions] PSL dose could be reduced in all patients, and PSL was successfully discontinued in 1 case. There were no serious adverse events directly related to MEP.

## W74-3

### The efficacy of mepolizumab in patients with eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

Objective: The relapse rate of eosinophilic granulomatosis with polyangiitis (EGPA) is approximately 30%, and mepolizumab (MEP) has been recently applied in such cases. This study investigated the efficacy of MEP in our hospital. Methods: Fifty-three patients with EGPA who visited our hospital were retrospectively analyzed for the clinical characteristics, efficacy, and steroid sparing effect. Results: Relapse was observed in 34%. MEP was used in 20 (37.7%) patients out of 53 patients with EGPA. The mean age at the initiation of MEP was 49.6 years, the mean disease duration was 77 months, 45% was male, and the positivity for MPO-ANCA was 50%. MEP was introduced for allergic manifestations, relapse of vasculitis, and steroid sparing effects in seven, four, and five patients, respectively. The dose of prednisolone (PSL) was reduced in six, two, and five patients in whom MEP was used for allergic manifestations, relapse of vasculitis, and tapering PSL. The reduction of PSL was difficult in patients with refractory vasculitis, refractory bronchial asthma, and lower doses of PSL at the beginning of MEP. Conclusions: MEP is particularly effective for allergic manifestations. Meanwhile, effects for refractory vasculitis

were limited.

## W74-4

### Clinical results of treatment of four cases with eosinophilic granulomatosis with polyangiitis complicated by myocarditis

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Department of Rheumatology and Collagen Diseases, Hiroshima University Hospital, Hiroshima, Japan

Conflict of interest: None

[Introduction] Eosinophilic granulomatosis with polyangiitis (EGPA) affects multiple organs and can be fatal if myocarditis develops. Case 1: A 49-year-old female with bronchial asthma became aware of peripheral numbness. She was diagnosed with EGPA based on the findings of eosinophilia and ANCA positivity. Echocardiography (ECG) showed cardiac involvement of EGPA. We administered intravenous cyclophosphamide (IVCY) combined with intravenous methylprednisolone (IVMP). Case 2: A 47-year-old male presented with eosinophilia and hypokinesia of cardiac wall. IVMP was initiated for the treatment of myocarditis. Because he had a history of bronchial asthma, we diagnosed him with EGPA and started treatment with IVCY. Case 3: A 45-year-old male presented with eosinophilia. Hypokinesia of cardiac wall were observed. Myocardial biopsy revealed eosinophilic infiltration, indicating myocarditis. After diagnosis of EGPA, IVMP with IVCY was started. Case 4: A 39-year-old male developed bronchial asthma. He was diagnosed with EGPA according to eosinophilia and ANCA positivity. Because myocarditis were observed, we started IVMP and IVCY. [Discussion] The poor prognosis of myocarditis in EGPA has been reported, but the combination of high-dose steroid and IVCY was effective for all presented cases.

## W74-5

### Three cases of eosinophilic granulomatosis with polyangiitis (EGPA) with flare-ups of sinusitis under the use of mepolizumab (MPZ)

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Conflict of interest: None

Case 1. A 56-year-old woman presented with asthma, sinusitis, numbness, and limb weakness. We diagnosed it as EGPA and initiated PSL and MPZ. Nasal obstruction appeared after reducing the dosage of PSL. Despite the lack of eosinophilia, the nasal mucosa was infiltrated with eosinophils. We diagnosed as relapse of eosinophilic sinusitis. Case 2. A 52-year-old woman was diagnosed with EGPA with asthma, nasal obstruction, and lower leg purpura which was proved as necrotizing vasculitis. We administered PSL and MPZ. As the dosage of PSL was reduced, wheezing, bilateral leg rashes, and nasal congestion were exacerbated. The eosinophil infiltrated nasal mucosa without eosinophilia. Case 3. A 72-year-old man was diagnosed with EGPA with asthma onset at age 40, fever, myalgia, hemoptysis, and nasal polyps, and numbness in his extremities. Laboratory tests revealed eosinophilia and MPO-ANCA positive. We treated with PSL, MPZ, and IVCY. After the dosage of PSL reduction. The nasal polyps worsened despite the lack of eosinophilia. Discussion. MPZ is effective in sparing glucocorticoid and preventing relapse in EGPA. However, flare cases under MPZ use were reported. We noted that nasal mucosa was infiltrated with eosinophils, though eosinophilia was lacking in peripheral blood.

## W74-6

### A case of eosinophilic granulomatosis with polyangiitis despite treatment with benralizumab

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Conflict of interest: None

A 79-year-old man was diagnosed with bronchial asthma four years ago and was being treated with medication. Two years ago his asthma worsened, and he started benralizumab injections last December. The last injection was administered in May. Five weeks later, the patient experienced worsening nasal obstruction and headache, followed by joint pain, purpura, decreased sensation in the lower limbs, and fatigue. Blood test showed increased eosinophils (1600 / $\mu$ L), CRP (17.83 mg/dL), and elevated MPO-ANCA levels (1100 U/mL). A skin biopsy was performed and a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA). Steroid pulse therapy and intravenous immunoglobulin were administered. On the 17th day after the start of treatment, CRP and eosinophils were elevated, and fever was observed. It was judged to be a relapse. After another steroid pulse therapy, intermittent intravenous cyclophosphamide therapy (IVCY) was administered. After the second dose of IVCY was administered, it was discontinued due to the presence of pulmonary aspergillosis, but no recurrence of EGPA was observed. Benralizumab is an anti-IL-5 receptor alpha monoclonal antibody that suppress eosinophils. In this case, the patient developed EGPA despite treatment with benralizumab.

## W75-1

### Retrospective study of initial data of patients with PMR resistant to glucocorticoid tapering

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Inflammation and Immunology, Kyoto Prefectural University of Medicine

Conflict of interest: None

[Objective] In polymyalgia rheumatica (PMR), some patients are resistant to maintenance treatment with corticosteroids (GCs) monotherapy. Although ESR and neutrophil to lymphocyte ratio (NLR) have been reported to be useful factors associated with resistance to treatment, the association with MMP-3 is not clear. In this study, we divided PMR patients into successful and resistant cases of GC tapering and compared the data including MMP-3 at initial diagnosis. [Methods] We retrospectively analyzed 51 cases who were diagnosed with PMR between 2008 and 2020, and were followed for at least 1 year. Patients with no relapse for more than 6 months under treatment with 5 mg/day of prednisolone or less at the end of the observation period were defined as successful cases of GCs tapering, and those who did not meet this definition were defined as cases of GCs tapering resistance. [Results] A total of 35 patients were successful cases of GCs tapering, and 16 patients were those of GCs tapering resistance. There was no difference in ESR or NLR between the two groups, whereas MMP-3 was significantly lower in cases of GCs tapering resistance. [Conclusions] When MMP-3 levels are low at the time of initial diagnosis, it may be difficult to reduce the dose of GC monotherapy.

## W75-2

### Clinical characteristics of polymyalgia rheumatica at our hospital

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Conflict of interest: None

[Object] Polymyalgia rheumatica (PMR) often occurs in elderly people and clinical symptoms are improved by steroid, but many patients relapse during steroid taper. We investigated clinical characteristics of PMR patients experienced at our hospital. [Methods] We examined 67 patients diagnosed with Bird's criteria or 2012 EULAR/ACR criteria from January 2015 to March 2021. [Results] The average of age was 73.3 $\pm$ 12.1 years for 22 males and 45 females. The average levels of CRP and ESR were 6.88 $\pm$ 5.70 mg/dL and 67.6 $\pm$ 31.0 mm/h, respectively. The initial dose of prednisolone (PSL) was 15.1 $\pm$ 4.3 mg/day. 34 cases (50.7%) had peripheral arthritis and 20 (29.9%) had swelling of hands. 8 cases were diagnosed as malignant tumor. 1 case was HBs antigen positive and 6 were HBs or HBc antibody positive. PSL could be discontinued in 8 cases (11.9%) in one year. 20 cases (29.9%) relapsed and 6 were administrated with MTX or TAC. 26 cases (38.8%) achieved PSL-free remission. [Conclusion] Many cases required long-term PSL treatment. In patients with peripheral

arthritis or swelling of hands, it is necessary to distinguish PMR from elderly-onset RA or RS3PE syndrome. It should be careful about the complication of malignant tumor and HBV reactivation in patients treated with PSL and immunosuppressants.

## W75-3

### Treatment prognosis for Polymyalgia rheumatica: Can drug-free remission be predicted?

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Conflict of interest: None

[Objective] Polymyalgia rheumatica (PMR) eventually leads to remission without medicine, while there are cases in which relapse requires increased doses of steroids and DMARD such as MTX. We verified the final outcome and the relationship between treatment prognosis, and inflammatory markers at diagnosis. [Methods] Patients diagnosed with PMR fulfilling Bird's criteria at our hospital between April 2016 and July 2020 and treated with PSL (10-20 mg/day) were included. They were followed for 10 months or more. In each case, we extracted the data related to relapse. The final outcomes were classified into 4 groups by the type of drugs. [Results] Fifty-one cases were included and 69% were females. Median age was 73 years. Baseline markers were as follows: CRP 4.54 mg/dL, MMP-3 177.4 ng/mL, and ESR 67.0 mm/h. Final outcome was PSL only: 14 (27%), DMARD only: 7 (14%), PSL+ DMARD: 8 (16%), and no drug: 22 cases (43%). Relapse was observed in 27 cases (53%). There were no significant differences in CRP, MMP-3, and ESR among the 4 groups, similarly in the relapse or non-relapse group. [Conclusions] About 40% of PMR patients achieve drug-free without relapse, while about half patients have relapse. It is difficult to predict the final outcome with inflammatory markers at diagnosis.

## W75-4

### A case of anti-MDA5-positive dermatomyositis with interstitial pneumonia developing in the use of statins successfully treated with plasma exchange

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Conflict of interest: None

A 74-year-old woman with past medical history of dyslipidemia and hypertension presented to our hospital for muscle pain of upper legs which started one month before her visit. On physical exam, she had heliotrope rash and Gottron's papules. The laboratory data revealed significant elevation of creatine phosphokinase (CPK) and the statin therapy was discontinued. Her myalgia and CPK were improved by discontinuing statins but her heliotrope rash lasted and inverse Gottron's papules were newly found. The lung CT scan showed bilateral interstitial pneumonia and anti-MDA-5 antibody was strongly positive (4845 index). She was diagnosed with anti-MDA5-positive dermatomyositis with rapidly progressive interstitial lung disease and started combined immunosuppressive therapy. She also received 10 sessions of plasma exchange (PE) as an additional therapy because of aggravating dyspnea two weeks after starting the treatments. She has no recurrences after initiation of PE. In this case, the patient's drug history of statins and symptoms of muscle pain made the diagnosis of anti-MDA5-positive DM difficult. PE could be an effective additional therapy as reported and it is important to start aggressive treatments including PE as soon as possible to improve the prognosis of the disease.

## W75-5

### Eosinophilic fasciitis as a manifestation of angioimmunoblastic T cell lymphoma

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Conflict of interest: None

An 84-year-old woman presented with 2-month history of edema. Her



extremities were swollen in January. Her edema expanded to whole body, and she gained 10 kg when she was hospitalized in March. She presented with hard edema, hypereosinophilia, increased serum aldolase level and thickening of the fascia on MRI. She was diagnosed with eosinophilic fasciitis from fascia biopsy. The small lymph nodes were noticed in the axilla and the inguinal region, but they were flat and didn't support the diagnosis of lymphoma. The serum sIL-2R level increased to 4,062 U/ml, which was reported to be also increased in eosinophilic fasciitis and was compatible with it. She was treated with prednisolone 30 mg/day and her edema was improved rapidly. She complained rash, fever and cervical lymphadenopathies in May. The PET/CT showed lymphadenopathies with uptake of FDG, and the biopsy of a lymph node showed angioimmunoblastic T cell lymphoma. She couldn't receive chemotherapy because of severe asthma and enteritis, and died in July. Eosinophilic fasciitis is occasionally associated with malignancies, especially hematological malignancies including T cell clone. Even though steroid therapy is effective as this case, we should examine and follow-up the possibilities of malignancies more carefully in elderly.

## W75-6

### Standardization of summary descriptions using an automatic summary visualization system based on machine learning

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Conflict of interest: Yes

**Background:** It has become common to include a summary at the top of the chart to solve the electric medical record referring problem. However, the method of writing summaries varies significantly from doctor to doctor, and standardization is required. We have developed a system that automatically visualizes summaries according to standardized description rules and verified whether summary expressions could be standardized. **Methods:** We developed a browser-based application (React/Redux) to visualize summaries and used machine learning methods for language analysis. We randomly selected 20 cases of rheumatoid arthritis patients who visited the hospital between January and December 2020 and wrote more than 20 lines of summaries. We randomly selected 20 cases of rheumatoid arthritis patients who came to the hospital between January and December 2020, divided them into (A) a visual confirmation group and (B) an automatic conversion group, and examined the time spent on standardization in each group. **Results:** (A) The average validation time was 8.0 minutes  $\pm$  2.1, and (B) the average validation time was 6.1 minutes  $\pm$  1.5 ( $p < 0.05$ ; t-test). **Conclusion:** By visualizing the summary in real-time, we were able to verify that it is possible to standardize the summary description.

## W76-1

### Evaluation of diagnostic criteria for Relapsing Polychondritis and relationship with drug free remission

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Hamamatsu University School of Medicine

Conflict of interest: None

[Purpose] From our RP cohort ( $n = 10$ ), we calculate three clinically commonly referred test characteristics, examine whether diagnostic criteria contribute to prognosis. [Method] Clinical information has been extracted retrospectively from patients diagnosed with RP from 2007 at our hospital using medical records, and McAdam criteria (1976), Damani and Levine criteria (1979), and Michele criteria (1986) have been used. Divide into a true positive group (TP) and a false negative group (FN), calculate the sensitivity for each diagnostic criterion, and determine whether there is a difference in the rate of drug free remission between TP and FN for each diagnostic criterion. [Results] The average number of symptoms at the onset of 6 symptoms according to the McAdam standard was 2.1 (SD1.04), and the sensitivities of the McAdam standard, Damani and Levine standard, and Michele standard were 40%, 100%, and 50%, respectively.

Although 50% of cases achieved drug free remission, there was no difference in the prognosis of drug free remission between TP and FN according to McAdam and Michele criteria ( $p = 0.52, 1.00$ ). [Conclusion] RP is a disease with a relatively high rate of drug free remission, but was not associated with the number of symptoms at onset.

## W76-2

### A case of relapsing polychondritis with interstitial nephritis

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Kitano Hospital Osaka Japan

Conflict of interest: None

A 69-year-old man was hospitalized for the left ophthalmalgia, swelling and pain of nose and right ear. In addition, high fever, conjunctival hyperemia of both eyes, and knee joint pain also appeared. His blood test showed high inflammatory reaction and no significant increase in various autoantibodies, also no abnormal findings on the CT examination. Antibiotic treatments were poor response. The ophthalmologic examination revealed episcleritis, and the biopsy of the right auricular cartilage revealed degeneration of cartilage tissue, infiltration of inflammatory cells, and fibrosis. Although renal function was normal, his urinary test showed hematuria, proteinuria, and increased  $\beta$ 2MG and NAG. We performed renal biopsy, specimen showed strong tubular injury and interstitial nephritis, and immunofluorescence provided findings suggestive of the immune complex. Skin biopsy and bone marrow biopsy were also performed, but no findings suggestive of other collagen diseases or hematologic diseases, we diagnosed relapsing polychondritis. We started to treat with prednisolone 30 mg, his various symptoms and urinary findings were improved. This is rare case of Japanese patient with relapsing polychondritis performed renal biopsy, so we report this case with literature review.

## W76-3

### Clinical significance of enthesitis in classical collagen diseases and others

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Conflict of interest: None

[Purpose] We investigated enthesitis in patients with rheumatoid arthritis (RA) and other collagen related disorders. [Method] Patients who attended our outpatient in 2019 or later were included. Rheumatic symptoms and signs were evaluated based on the examination findings at the first visit for the presence of arthritis (A) and enthesitis (E). [Results] 100 cases were evaluated. In 70 cases of RA, 68 patients had A and 40 patients had E. 7 Sjogren's syndrome, 3 had A and 2 had E. 7 other classical collagen diseases, 4 had A and 3 had E. 6 Psoriatic arthritis (PsA), 4 had A and 5 had E. 6 reactive arthritis (ReA), 3 had A and 6 had E. [Discussion] It has been reported that about half of the patients with rheumatic disease had enthesitis. We also found E in 60% of patients with RA, and confirmed it at all sites. In other classical collagen diseases, E was found in 30-50% of patients. E was found in almost all patients with PsA, ReA. E was also found in some patients who complained of rheumatic symptoms but had no arthritis and were serum CRP negative. [Conclusions] Even if there is no arthritis and the serum CRP is negative, enthesitis may be present. In order to improve the quality of life of patients with RA, it is necessary to take into account the treatment of enthesitis.

## W76-4

### A case report of central venous obstruction due to pustulotic arthro-osteitis (PAO) and introduction of guselkumab

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Conflict of interest: None

[Case report] A 66-year-old man. Keratinized lesions of limbs were observed from X-6 years, and pain around the neck and shoulders were

observed from March X-1. With regard to pustulotic arthro-osteitis (PAO), prednisolone 30 mg, azulfidine 1000 mg, and bisphosphonate were started. Teriparatide was started due to right clavicle fracture, but he was self-interrupted at the end of September X-1. From May X, swelling of the entire left arm and exacerbation of skin eruption of both limbs were observed. Left internal jugular vein, subclavian to distal vein, obstruction of right subclavian vein, stenosis of right brachiocephalic vein were observed, and effects of chronic thoracic arthritis and clavicle enlargement were considered. Prednisolone 10 mg / azulfidine even after resuming 1000 mg, residual eczema and poor control of arthritis led to introduction of guselkumab. After that, improvement of eczema and arthritis were observed. [Discussion] This case was accompanied by persistent inflammation of the thoracic chain joint due to PAO, and clavicle hypertrophy caused chronic central vein occlusion. We report the relationship between PAO and vein obstruction with a review of literature.

## W76-5

### Comparison of clinical features between TAFRO syndrome (or TAFRO syndrome mimics) and idiopathic multicentric Castleman's disease in our hospital

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Conflict of interest: None

**Background:** TAFRO syndrome has some similarities with idiopathic multicentric Castleman's disease (iMCD) and is considered a subtype of iMCD, but there are some differences in its clinical course, and some consider it an independent disease concept. In this study, we compared the clinical features of the two types diagnosed at our hospital. **Aims:** The TAFRO group was diagnosed according to the TAFRO Syndrome Diagnostic Criteria 2019, and the iMCD group was diagnosed according to the diagnostic criteria of the Castleman Disease Collaborative Network. The clinical symptoms, Hb, PLT, Cre, IgG, ALP, Alb, Ferritin (Fer), CRP, IL-6, PCT, and treatment in both groups were compared retrospectively. **Results:** Five of six patients in the TAFRO group had renal cell carcinoma, myelodysplastic syndrome, SJS, or SLE in the background, and two patients in the iMCD group had scleroderma. In the TAFRO group, Cre and Fer were significantly higher and PLT and Alb were significantly lower. PCT was elevated in all patients in the TAFRO group (median: 2.74, range: 1.08-9.19). **Conclusions:** In the TAFRO group, PCT was positive in all patients and many patients had underlying diseases, suggesting that it is important to carefully search for background diseases when diagnosing TAFRO syndrome.

## W76-6

### Anti-glomerular basement membrane disease and secondary thrombotic microangiopathy treated with rituximab

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Conflict of interest: None

**Case:** A 68 year-old man presented with malaise and anuria. The patient was lethargic and the vital signs were temperature 35.7°C, pulse 108 beats/min BP 162/81 mmHg, respiratory rate 24 breaths/min and SpO2 93% with oxygen mask at the rate of 5 L/min. Bilateral crackles were heard. A chest X-ray showed diffuse ground-glass opacities and infiltrate. Laboratory study showed acute kidney injury, then renal replacement therapy with hemodialysis was instituted. Anti-glomerular basement membrane (GBM) antibody was detected and the titer was 3060 U/mL. A diagnosis of anti-GBM disease was made. The patient was started on high-dose glucocorticoid and plasmapheresis, and respiratory status improved, but hemolytic anemia and thrombocytopenia were progressed and schistocytes appeared. ADAMTS13 level was normal. Secondary thrombotic microangiopathy (TMA) was strongly suspected, rituximab was started. The

patient never recovered his kidney function but anti-GBM antibody titers decreased to 9.9 U/mL and there was a significant improvement of hemolytic anemia and thrombocytopenia. Glucocorticoid was tapered and 2 months after admission, he was discharged home. **Discussion:** Rituximab may have been effective for both anti-GBM disease and secondary TMA.

## W77-1

### Real-world treatment for rheumatoid arthritis patients with chronic kidney diseases-the ANSWER cohort study-

Shinsuke Yamada<sup>1</sup>, Kazuo Fukumoto<sup>1</sup>, Ryu Watanabe<sup>1</sup>, Tadashi Okano<sup>2</sup>, Wataru Yamamoto<sup>3</sup>, Akira Onishi<sup>4</sup>, Hideo Onizawa<sup>5</sup>, Kosuke Ebina<sup>6</sup>, Yuichi Maeda<sup>7</sup>, Yuzuru Yamamoto<sup>8</sup>, Hirotaka Yamada<sup>8</sup>, Yonsu Son<sup>9</sup>, Hideki Amuro<sup>9</sup>, Masaki Katayama<sup>10</sup>, Ryota Hara<sup>11</sup>, Tohru Takeuchi<sup>12</sup>, Hidehiko Makino<sup>12</sup>, Motomu Hashimoto<sup>1</sup>

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Conflict of interest: None

**Introduction:** Treatment strategy for the rheumatoid arthritis (RA) patients with chronic kidney diseases (CKD) is not well established. **Purpose:** To clarify the real-world treatment for RA patients with CKD. **Methods:** CKD was defined by eGFR. Disease activity and the real-world treatments were compared in 4,197 RA patients with or without CKD. In the total 2,633 patients treated by bio/ts DMARDs, drug retention rates and disease activities were compared between patients with and without CKD for each bio/ts DMARDs treatment. **Results:** 44% of RA patients were accompanied by CKD. CKD patients were older, advanced RA Stage/Class, and higher disease activities. CKD patients were more frequently treated by MTX, less by PSL, and similarly bio/ts DMARDs. Among bio/ts DMARDs treated patients, abatacept was more frequently used in CKD patients than in non-CKD patients, while TNF inhibitors were less frequently used in CKD patients. There was no apparent difference in the drug retention rates between patients with and without CKD in bio/ts DMARDs-treated patients. Disease activities were similarly controlled in those patients.

## W77-2

### Assessment of nutritional status in patients with rheumatoid arthritis who achieved SDAI remission and low disease activity in the Nin-Ja2019 database

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Conflict of interest: None

[Purpose] To examine the nutritional status of patients with rheumatoid arthritis who have achieved remission and low disease activity using the clinical nutrition index CONUT (Controlling Nutrition Status). The subjects were 5277 patients who had no deficiency in score). Of these, 4017 patients who achieved SDAI remission and low disease activity were nutritionally evaluated. CONUT used for nutritional evaluation is a nutritional index that scores serum albumin level, plasma total cholesterol level, and total lymphocyte count. The subjects were 66.4 ± 12.9 years old, 920 males and 3097 females, 1048 glucocorticoids administered (mean

3.9 ± 2.9 mg), and the duration of illness was 12.8 ± 10.5 years. [Results] The average CONUT score was 1.4 ± 1.3. The number of malnutrition cases was 1650 (41.1%), 64.7% of malnutrition was 65 years or older, and in multivariate analysis with CONUT abnormality as the objective variable, age 75 years or older (OR 1.226), CRP (per1, OR 1.301), BMI (per1, OR 0.921) and bDMARDs (OR 0.738) were analyzed. Nutritional intervention should be taken into account as well as achieving remission and low disease activity.

### W77-3

#### **The behavioral restriction of COVID-19 pandemic and the change of body composition of patients with rheumatoid arthritis**

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Conflict of interest: None

[Object] The behavioral restriction (BR) of COVID-19 pandemic influenced for the lifestyle. The change of exercise (EX) and daily life activity (DLA) of RA patients were investigated and body composition and muscle function were compared pre- and post-BR. [Methods] We used the date from prospective observational study (CHIKARA study). 70 from 100 RA were followed-up and evaluated the change of EX and DLA. They were measured body compositions and grip strength. The relationship between the change of EX and DLA and body composition was investigated. [Results] Mean age was 69.7 years. The rate of decrease of EX and DLA was mean 20% and 44%. Muscle mass at post-BR decreased significantly compared that at pre (34.0 vs 34.7 kg, P<0.001). Fat mass at post-BR increased significantly compared that at pre (16.2 vs 15.5 kg, P=0.014). Grip strength at post-BR decreased significantly compared that at pre (16.2 vs 17.2 kg, P=0.026). The change of EX was significantly positively correlated with the change of muscle mass and basal metabolic rate. [Conclusions] Muscle mass and grip strength decreased and fat mass increased in RA by the BR of COVID-19 pandemic. Muscle mass and basal metabolic rate decreased in patients without exercise. The maintain of muscle mass is important at COVID-19 pandemic era.

### W77-4

#### **Biomarkers of response to treatment for acute exacerbation of Connective tissue disease-associated interstitial lung disease**

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Division of Rheumatic Diseases, National Center for Global Health and Medicine

Conflict of interest: None

[Objective] We investigated relation between the response to treatments and serum LDH, CRP, KL-6, and SP-D in acute exacerbation of connective tissue diseases-associated interstitial lung diseases (CTD-ILD). [Methods] 76 patients with acute exacerbation of CTD-ILD hospitalized between 2005 and 2021 were analyzed. Serum LDH, CRP, KL-6, and SP-D at the time of diagnosis were evaluated for response to treatment. [Results] 48 were in the good response group and 28 were in the poor group (19 died). The proportion of males in the favorable group was significantly lower than that in the unfavorable group (p=0.027). The age of onset was significantly lower in the favorable group (p=0.0006), and the percentage of patients with a history of smoking was significantly lower (p=0.043). Serum SP-D tended to be lower in the group with good response to treatment with more drugs among steroid pulse, high-dose intermittent cyclophosphamide (IVCY), and calcineurin inhibitor (CI) (p=0.02), and the same trend was observed for serum CRP (p=0.26). [Conclusions] In patients with acute exacerbation of CTD-ILD and little increase in serum SP-D or CRP, IVCY or CI may be used in addition to steroid pulse to relieve the symptoms.

### W77-5

#### **The analysis of obstructive sleep apnea in patients with knee osteoarthritis and rheumatoid arthritis**

Yasuo Kunugiza

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Conflict of interest: None

[Objective] Obstructive sleep apnea (OSA) is the common sleep-related breathing disorder and is characterized by recurrent episodes of complete or partial obstruction of the upper airway leading to reduced or absent breathing during sleep. Epidemiologic data support a link between OSA and age, obesity and hypertension. The purpose of this study was to examine the rate of OSA in the patients with knee osteoarthritis (OA) or rheumatoid arthritis (RA). [Methods] 280 cases of knee arthritis patients (264 OA and 16 RA, average age 74.0) who planned to undergo knee arthroplasty were enrolled in this study. Polysomnography was performed to detect OSA and the severity of OSA (Respiratory Disturbance Index (RDI)), average SpO<sub>2</sub>, and subjective symptoms were examined. [Results] 230 patients showed the OSA. 119 patients (OA108, RA11) showed the mild OSA, 111 patients (OA108, RA3) showed the moderate or severe OSA. The association between the severity of OSA and subjective symptoms was observed. [Conclusion] The average rate of OSA in Japanese adults is reported to be 3 to 7% in male and 2 to 5% in female. The rate of OSA was high in knee arthritis patients, and the proportion of patients with moderate and severe OSA was higher in OA patients than in RA patients.

### W77-6

#### **Clinical features and outcome of rheumatic diseases with a history of malignancy, and management considerations in those cases**

Ikuko Naka, Takashi Nakazawa

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Conflict of interest: None

(Objective) Recently, lifetime risk of developing cancer has been over 50% in Japan. There is an increasing need for precise management of rheumatic diseases with a history of cancer. We analyzed clinical features and outcome of rheumatic diseases with a history of cancer in our hospital. (Methods) We retrospectively reviewed the medical records of 96 patients in our hospital with a history of demanding cancer specific management fee and prescription of medicine for rheumatic diseases between April 1, 2019 and September 30, 2021. (Results) The mean age was 70.7 years at cancer diagnosis and 59% were female. Malignant diseases included 95 cases of solid tumors, 11 cases of malignant lymphoma, and two cases of leukemia. 92.7% were alive on September 30, 2021. Among 55 cases of RA, 9 cases were receiving bDMARDs and one case JAK inhibitors at the time of cancer diagnosis. The bDMARDs were discontinued in 4 cases after diagnosing cancer, two of which were resumed bDMARDs 4 or more years later. Cancer relapsed in one of 5 patients continuing bDMARDs after cancer treatment. One case using a JAK inhibitor was revealed to have malignant lymphoma and died of it. (Conclusions) Further analysis is required to consider management of rheumatic diseases with a history of cancer.

### W78-1

#### **Changes of gray scale and power doppler signals of ultrasonography in salivary glands and disease activity in patients with Sjogren's syndrome**

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Division of Rheumatology, Mitsui Memorial Hospital

Conflict of interest: None

[Objective] We previously reported utility of power doppler signals (PDs) in salivary glands by ultrasonography in patients with Sjogren's syndrome (SS). Here we studied changes of gray scale (GS), PDs and disease activity after one year. [Methods] GS score (0-3), PDs score (0-3) of parotid and submandibular glands, and ESSDAI, ESSPRI, OHIP-14 of patients with SS were investigated in 0 and 12 months. Treatments were decided by attending physicians. [Results] Among 29 SS patients, 25 were



female, primary SS was 19, and average age was 58.1 years. There were no significant changes in GS and PDs scores of salivary and submandibular glands overall, but patients who had improved scores were mostly administered prednisolone or mizoribine. There was a significant correlation between PDs score of parotid glands in 0 M and GS score of parotid glands in 12 M. OHIP-14 was significantly decreased, and ESSDAI had a tendency to decrease. Improvement of PDs scores of parotid glands had a tendency to correlate with improvement of ESSPRI. [Conclusions] PDs in parotid glands may predict changes of glandular parenchyma after one year and have a tendency to correlate with changes of disease activity.

## W78-2

### Efficacy of immunosuppressive treatment against tubulointerstitial nephritis associated with primary Sjogren syndrome

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<sup>1</sup>Hiroshima University Hospital, <sup>2</sup>Kure Medical Center and Chugoku Cancer Center

Conflict of interest: None

[Background] Tubulointerstitial nephritis (TIN) has been known as one of the major complications of primary Sjogren syndrome (pSS). However, the efficient treatment of TIN has not been confirmed. We present 5 cases with TIN associated with pSS (pSS-TIN) who showed good response to immunosuppressive treatment. [Case] All five patients with pSS-TIN were female, with a median age at SSc diagnosis of 34.0 (interquartile range 32.5 - 43.5) yrs. Among them, four patients were diagnosed with TIN based on the pathological findings of renal biopsy. All the patients were complicated with distal renal tubular acidosis, and one patient with lymphocytic interstitial pneumonia, while none had any other rheumatic diseases except for pSS. All the patients showed anti-SS-A positivity and an elevation of urinary  $\beta$ 2-microglobulin ( $\text{u}\beta$ 2-MG). Four out of five were treated with prednisolone (PSL), three with mycophenolate mofetil (MMF) and one with azathioprine. In all patients, immunosuppressive therapy improved or kept kidney function stable with ameliorating the elevated  $\text{u}\beta$ 2-MG levels. [Discussion] Clinical courses of our cases suggest immunosuppressive therapy improves the declined kidney function in patients with pSS-TIN.

## W78-3

### Clinical features and prognosis of pulmonary manifestations in patients with primary Sjögren's syndrome (pSS)

Akira Kawashima, Hiroto Tsuboi, Nana Uematsu, Fumina Kawashima, Ryota Sato, Mayu Terasaki, Fumika Honda, Mizuki Yagishita, Ayako Ohyama, Saori Abe, Shinya Hagiwara, Yuya Kondo, Isao Matsumoto  
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Conflict of interest: None

[Objective] To clarify clinical features and prognosis of pulmonary involvements in pSS. [Methods] We retrospectively examined 1) prevalence of pulmonary involvements and background, 2) image findings, 3) autoantibodies, 4) pulmonary function tests, 5) ESSDAI, 6) treatments and response, and 7) comparison between progressors and non-progressors after corticosteroid (CS) treatment, in pSS patients based on 1999 ministry of health criteria who admitted to our hospital from Jan 2015 to Oct 2021. [Results] 1) 22 of 89 cases (24.7%) had pulmonary involvements (17 females/5 males, 65.0 $\pm$ 9.6 years old). 2) 19 cases had interstitial, 2 had cystic, and 1 had bronchial lesions. 3) Anti SS-A and B antibodies were detected in 86.4% (19/22) and 50.0% (10/20). 4) 12 of 21 cases (57.1%) had abnormal pulmonary function. 5) ESSDAI before treatment was 11.0 $\pm$ 4.3. 6) 13 of 22 cases (59.1%) were treated by initiation or escalation of CS. 9 of 13 underwent CT 16.6 $\pm$ 16.2 months later, and 5 of 9 (55.6%) had progression. 7) Clinical features and CS doses were comparable between progressors (N=5) and non-progressors (N=4). [Conclusions] Lung lesions were found in 24.7% of pSS, and interstitial lesions were common. Although 55.6% of CS treated cases had progression, predictors for progression could not be identified.

## W78-4

### The characteristics of non-MALT lymphoma associated with Sjögren's syndrome

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Conflict of interest: None

[Objective] The aim of this study is to elucidate the features of patients with Sjögren's syndrome overlapped non-MALT lymphoma. [Methods] Eleven patients with Sjögren's syndrome accompanied by malignant lymphoma, who visited our department from 2008 to August 2021, were included. We analyzed the differences in the backgrounds between the patients with MALT lymphoma (n=7) and those with non-MALT lymphoma (n=4: three patients with diffuse large B-cell lymphoma and one with Hodgkin lymphoma). [Results] The mean age of 11 Sjögren's syndrome patients was 65.5 $\pm$ 13.2 years, and 7 (64%) were female. All patients with non-MALT lymphoma were in the advanced stage, while those with MALT lymphoma were in the localized stage (p=0.003). In addition, serum soluble IL-2 receptor (sIL-2R) was significantly higher in the non-MALT lymphoma group compared to the MALT lymphoma group (1682 $\pm$ 1361 U/mL vs 434 $\pm$ 250.5 U/mL, p=0.012). There were no differences between those two groups in complement titers, serum IgG level or ESSDAI, which were previously reported as the risks of malignant lymphoma in patients with Sjögren's syndrome. [Conclusions] The serum sIL-2R might be a useful marker to identify Sjögren's syndrome with the complication of advanced-stage non-MALT lymphoma.

## W78-5

### Effect of Long-term hydroxychloroquine treatment in patients with primary Sjögren's syndrome

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Conflict of interest: None

[Objective] The aim of this study was to examine the efficacy of HCQ in pSS at 8 and 52 weeks after treatment. [Methods] Twenty-six pSS patients with CLE were studied. The clinical indexes were evaluated by ESSDAI, ESSPRI, IgG and CH50 before and 8 and 52 weeks after HCQ treatment. [Results] The ESSPRI and fatigue and pain domain were significantly lower at 8 and 52 weeks than HCQ pre-treatment (ESSPRI: 4.14 $\pm$ 1.48 vs 3.38 $\pm$ 1.57, 3.34 $\pm$ 1.56, p=0.005, p=0.045, fatigue: 4.68 $\pm$ 2.12 vs 3.68 $\pm$ 1.96, 3.58 $\pm$ 1.87, p=0.010, p=0.036, pain: 3.32 $\pm$ 1.94 vs 2.09 $\pm$ 1.60, 1.79 $\pm$ 1.51, p=0.0043, p=0.0014). There was also a significant decrease in ESSDAI and constitutional, articular, cutaneous and biological domain at 52 weeks compared to HCQ pre-treatment (ESSDAI: 9.68 $\pm$ 6.14 vs 4.74 $\pm$ 6.43, p=0.0004; constitutional: 1.41 $\pm$ 1.50 vs 0.63 $\pm$ 1.26, p=0.034, articular: 1.00 $\pm$ 1.02 vs 0.21 $\pm$ 0.63, p=0.0027, cutaneous: 2.86 $\pm$ 3.27 vs 1.11 $\pm$ 2.49, p=0.010, biological: 1.14 $\pm$ 0.83 vs 0.79 $\pm$ 0.86, p=0.014). An improvement of at least 1 point or 15% in ESSPRI and at least 3 points in ESSDAI compared to previous values were observed in 31.8% and 63.6% at 8 weeks and 68.4% and 73.7% at 52 weeks. [Conclusions] HCQ treatment was useful in improving ESSPRI and ESSDAI, and the number of effective cases increased from 8 weeks to 52 weeks.

## W78-6

### Usefulness of abatacept for patients with secondary Sjögren's syndrome associated with rheumatoid arthritis. An open label, multi-center, prospective study: ROSE (Rheumatoid Arthritis with Orenicia trial toward Sjögren's syndrome Endocrinopathy) and ROSE II trials

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Conflict of interest: Yes

[Objective] To clarify usefulness of abatacept (ABT) for patients with secondary Sjögren's syndrome (sSS) associated with RA. [Methods] Patients with sSS with RA were enrolled in ROSE and ROSE II trials. 1) The primary endpoint was achievement of SDAI remission at 52 W after ABT administration. 2) Secondary endpoint included Saxon's and Schirmer's test. 3) In ROSE II, ESSDAI and ESSPRI were included in secondary endpoint. 4) Adverse events (AE) and adherence rates during the 52 W of study period were analyzed. [Results] 68 patients (all female) were enrolled (36 in ROSE and 32 in ROSE II). 1) SDAI significantly decreased from 23.6±13.2 (0 W) to 9.9±9.5 (52 W) ( $P<0.05$ ), and patients who achieved SDAI remission significantly increased from 0 (0 W) to 19 patients (27.9%) (52 W) ( $P<0.05$ ). 2) Saxon's and Schirmer's test significantly improved from 2015.1±1695.4 (0 W) to 2311.3±1804.4 (24 W) mg/2 min ( $N=66$ ,  $P<0.05$ ), and 5.0±6.0 (0 W) to 5.6±6.3 (52 W) mm/5 min ( $N=52$ ,  $P<0.05$ ). 3) ESSDAI and ESSPRI significantly decreased at 12 W, and these responses were maintained up to 52 W. 4) The rate of adherence to ABT over the 52 W period was 83.8% (57/68). 22 AE occurred in 15 patients, and 9 of AE were infections. [Conclusions] ABT was effective for both RA and SS related manifestations in patients with sSS with RA.

## W79-1

### Quantification of skin sclerosis and examination of skin structure by ultrasonography

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Conflict of interest: None

[Objective] We investigated whether the skin lesions of scleroderma patients could be evaluated by ultrasonography. [Methods] The subjects were 30 patients who were positive for anti-Scl-70 Ab or anti-centromere Ab. From the fingers to the forearm, the skin strain was classified into 4 patterns of Strain Elastography, the E Elastocity value (kPa) was measured by Shear Wave Elastography, and the skin structure was examined in high B mode. [Results] In the fingers, strain patent 1 was 249 places, pattern 2 was 195 places, Pattern 3 was 46 places, and pattern 4 was 33 places. The average values of E Elastocity were 18.2 ± 8.4 kPa for pattern 1, 30.2 ± 11.9 kPa for pattern 2, 89.0 ± 48.56 kPa for pattern 3, and 155.0 ± 49.2 kPa for pattern 4. Patterns 3 and 4 were considered to have skin sclerosis. Dermis layer tightness was observed in 60.9% for pattern 3 and 4, and 87.9% for pattern 4. The epidermis thickness became thinner with skin sclerosis, but no change was observed in the dermis thickness. [Conclusions] The results of the two types of Elastography and the results of B mode are correlated, and ultrasonic Elastography is a modality that can objectively quantify skin stiffness, and is considered to be extremely useful for diagnosis and evaluation of therapeutic effect.

## W79-2

### The long-term changes in KL-6 and their correlation with %FVC in patients with SSc-ILD

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Conflict of interest: None

[Objective] The aim of this study is to clarify the long-term KL-6 changes and their correlation with %FVC and predict an annual %FVC decline  $\geq 5\%$  at any observation points during the clinical course using an annual KL-6 change in SSc-ILD. [Methods] We retrospectively analyzed consecutive SSc-ILD patients from 2008 and 2019. [Results] Forty-six patients were included. The median age was 62 years, 54% were female and %FVC was 86.1%. KL-6 was 1612 U/ml. The median observation periods were 4.9 years and 185 cases were calculated for both the annual change of %FVC and KL-6. The annual changes in KL-6 had a significantly negative correlation with those in %FVC in the first year ( $r = -0.70$ ) and over the observation periods ( $r = -0.41$ ). The ROC curve analysis for predicting the annual %FVC decline  $\geq 5\%$  was used to determine the optimal annual KL-6 change. AUC was 0.71 and a threshold of the annual KL-6 change was determined at +200 U/ml. Sensitivity and specificity were 45.5% and 93.8% (PPV and NPV were 71.4% and 83.3%) at the first year, and 40.4% and 90.6% (59.4% and 81.7%) over the observation periods. [Conclusions] The negative correlation between the annual changes in %FVC and those in KL-6. The annual KL-6 change  $\geq 200$  U/ml was a useful indicator of disease activity in patients with SSc-ILD.

## W79-3

### Longitudinal measurement of SP-D is useful in predicting the progression of interstitial pneumonia in scleroderma

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Conflict of interest: None

[Objective] To determine whether changes in KL-6 and SP-D could predict the progression of interstitial pneumonia (IP) in scleroderma. [Methods] A retrospective observational study. Subjects were patients with scleroderma who visited our clinic. Medical records were reviewed; progression of IP was judged by CT images and symptoms. KL-6 and SP-D levels were recorded at the time of initial diagnosis and of IP worsening. [Results] Among 74 patients with scleroderma, 43 patients had IP. Analysis was conducted on patients with IP. A correlation was detected between KL-6 and SP-D levels; however, no correlation was found between changes in KL-6 and SP-D, 17 patients had progression of IP, and 15 did not. There was no difference between these two groups in KL-6 levels and at the worsening, nor in the change in KL-6 levels. However, there was a difference in SP-D levels at the worsening between the two groups. There was also a tendency for a difference between the SP-D levels at the diagnosis and the change in SP-D levels. The analytical ROC curve of SP-D levels at the time of the worsening showed that SP-D below 110 ng/ml had a small risk of IP progression. [Conclusions] The longitudinal measurement of SP-D may be more useful than KL-6 in predicting the progression of IP in scleroderma.

## W79-4

### Analysis of the role of mediator of RNA polymerase II transcription subunit 30 which identified by immune complexome analysis in systemic sclerosis

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Conflict of interest: None

**Objectives:** Identification of disease-specific immune complexes (ICs) in SSc by immune complexome analysis and investigating the role of that protein. **Methods:** We used immune complexome analysis to comprehensively identify antigens incorporated into ICs in serum samples from patients with SSc (n=47) and compared them with IC-antigens identified in patients with systemic lupus erythematosus (SLE). The serum mediator of RNA polymerase II transcription subunit 30 (MED30) was investigated by ELISA and expression and localization of MED30 were examined by immunocytochemistry. **Results:** 13 IC-antigens was identified in SSc patients, not in SLE patients. Among these ICs, MED30 was mostly detected and further analyzed. The increase of serum MED 30 in SSc patients was detected by ELISA and immunohistochemistry showed the significantly high *in situ* expression of MED30 in fibroblasts and vascular structures of SSc skin. **Conclusion:** We detected MED30-IC in SSc patients. MED30 is involved in the function of vascular endothelium and cell invasion and proliferation. When MED30 forms ICs, its function is lost because of structural abnormalities, and this is related to the pathogenesis of SSc. Moreover, MED30 fibroblasts might be related to fibrosis through their increase of proliferation.

## W79-5

### Survey on dysphagia using videofluoroscopic examination of swallowing in patient with systemic sclerosis

Tatsuaki Naganawa<sup>1</sup>, Naoki Dosoden<sup>1</sup>, Ayako Kuwabara<sup>3</sup>, Marika Sawada<sup>1</sup>, Masashi Suzuki<sup>1</sup>, Ai Umeda<sup>1</sup>, Konomi Akamatsu<sup>1</sup>, Megumi Kurumizawa<sup>1</sup>, Daisuke Hirano<sup>1</sup>, Takako Hashimoto<sup>1</sup>, Jo Nishino<sup>1</sup>, Shusaku Fukaya<sup>1</sup>, Yohei Otake<sup>2</sup>, Hidekata Yasuoka<sup>1</sup>

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Conflict of interest: None

[Objective] Our aim was to investigate the actual condition of dysphagia in patient with SSc. [Methods] SSc patients who visited outpatient clinic in Fujita Health University Hospital between 2018 and 2021 were involved. The feature of dysphagia was evaluated by Eating assessment tool-10 (EAT-10) and videofluoroscopic examination of swallowing (VF). Dysfunction of the oropharyngeal and esophageal phase of swallowing was detected by VF. Demographic and clinical characteristics were retrospectively collected by medical charts. [Results] Nineteen SSc were included. The mean age was 63.7±13.9 years, Male: Female ratio was 4:15. By EAT-10, there were 11 cases (57.9%) who were suspected to have dysphagia based on the score. Seven patients had penetration in the laryngeal aditus, by which we stratified patients with SSc. Patients with penetration in the laryngeal aditus show higher prevalence of oral after-swallow residual (p=0.044) and premature spillage. (p=0.002). There was a significant positive correlation between esophageal dilation on CT and high score of mRSS (p=0.067). [Conclusions] These results suggest that patients with SSc have a relatively high prevalence of swallowing problems, and dysfunction of the pharyngeal phase of swallowing may be independent with esophageal lesion in SSc.

## W79-6

### Causes and risk factors for death in Japanese systemic sclerosis

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Conflict of interest: None

[Objective] SSc is characterized by tissue fibrosis, vascular damage, and immune abnormalities. Complications of interstitial pneumonia (IP) and pulmonary hypertension (PH) have been reported as poor prognostic factors. The purpose of this study was to investigate the causes and risk

factors of death in SSc. [Methods] This is a retrospective cohort study using the SSc database of our hospital between 2013 and 2021. We examined the cause of death, age at death, gender, comorbidities, and treatment. [Results] Of 458 SSc patients, there were 42 confirmed deaths (9 males, 33 females). The mortality rate was 9.1%. The mean age at death was 63.9 ± 14.4 years. Of the 35 patients with known causes of death, 21 (63.6%) were SSc-related. Of which, 12 (57.1%) were cardiovascular diseases mostly involving PH, respiratory diseases with IP were 4 (19%), gastrointestinal disorders were 4 (19%). Of the 14 non-SSc-related deaths, 7 (50%) were infections and 3 (20.1%) were malignancies. In the comparison between the death group and the survival group, PH, IP, skin ulcer, diffuse type, male, and steroid treatment group were significantly higher in the death group (P<0.01). [Conclusions] Disease related deaths were the most common cause of death in SSc, especially cardiovascular diseases involving PH.



# International Concurrent Workshop

## ICW1-1

### Glucocorticoid discontinuation in patients with systemic lupus erythematosus with prior severe organ involvement: A single-center retrospective analysis

Takehiro Nakai, Futoshi Iwata, Genki Kidoguchi, Sho Fukui, Hiroki Ozawa, Satoshi Kawaai, Yukihiro Ikeda, Ayako Kitada, Atsushi Nomura, Hiromichi Tamaki, Ken-ichi Yamaguchi, Masato Okada  
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Conflict of interest: None

[Objective] Long-term glucocorticoid use in systemic lupus erythematosus (SLE) may have significant side effects; however, glucocorticoid discontinuation is occasionally associated with disease flare-ups. Therefore, we evaluated the risk factors for disease flares and the flare rate upon glucocorticoid tapering in patients with prior severe organ involvement. [Methods] Patients with SLE with glucocorticoid tapering at our institution were retrospectively analyzed. We divided the patients according to the presence of prior severe organ involvement and compared flare rates and time to first flare after glucocorticoid discontinuation. Furthermore, we determined risk and protective factors for flares after glucocorticoid discontinuation. [Results] A total of 309 patients with SLE were screened; 298 had prednisolone tapered to less than 7.5 mg/day and 75 had glucocorticoid discontinuation. Overall, 73 patients met the inclusion criteria; 49 were classified as SLE with prior severe organ involvement. No statistical differences were noted in the 52-week flare rate and time to first flare after glucocorticoid discontinuation between patients with and without prior severe organ involvement (52-week flare rate: 16.7% vs. 18.2%,  $p = 1.0$ ; time to first flare: 322 [280, 1169] vs. 385 [304, 2345] days,  $p = 0.33$ ). Hypocomplementemia, elevated anti-dsDNA antibody titers of more than twice the upper limit of the laboratory reference range, and positive anti-Smith/anti-ribonucleoprotein antibody were negatively associated with flare-free remission. [Conclusions] Glucocorticoid discontinuation can often be achieved in patients with SLE without increasing flare risk in most patients with prior severe organ involvement, especially when the disease is clinically and serologically stable.

## ICW1-2

### Usefulness of Belimumab to achieve lupus low disease activity: a single-center retrospective study

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Conflict of interest: None

[Objective] Lupus Low Disease Activity Status (LLDAS) is considered as one of the realistic treatment goals for systemic lupus erythematosus (SLE) in real-world practice. We investigated the effect of Belimumab (BEL) for achieving LLDAS. [Methods] SLE patients treated with BEL by February 2021 were collected and compared with those without BEL (control). The observation was started at the time of BEL initiation or from July 1st, 2020 for control. Clinical information was retrospectively collected and the LLDAS achievement rate was compared after propensity score matching. The rate of LLDAS-5; PSL tapered to  $\leq 5$  mg/day was also evaluated. We calculated factors contributing to LLDAS and LLDAS-5 achievement by Cox proportional hazard model. [Results] After propensity score matching with BEL ( $n=100$ ) and control ( $n=342$ ), 60 patients in each treatment group were matched for analysis. Increased achievement of LLDAS (hazard ratio (HR) 1.993, 95% confidence interval (CI) 0.943-4392,  $P=0.071$ ) and significantly increased achievement of LLDAS-5 (HR 2.393, 95%CI 1.175-5.512,  $P=0.016$ ) was observed at 12 months. Arthritis and use of calcineurin inhibitors (CNI) were extracted by univariate analysis as baseline patient background factors contributing to achieve LLDAS (HR 4.097, 95%CI 1.843-8.744,  $P=0.001$ , HR 3.363, 95%CI 1.005-

5.046,  $P=0.026$ ) or LLDAS-5 (HR 3.568, 95%CI 1.652-7.291,  $P=0.002$ , HR 1.819, 95%CI 0.897-3.652,  $P=0.096$ ). Multivariate analysis revealed that arthritis ( $P=0.008$ ), BEL ( $P=0.040$ ) and CNI ( $P=0.035$ ) were significant risks to achieve LLDAS while BEL was the only significant factor to achieve LLDAS-5 ( $P=0.005$ ). [Conclusions] Our results emphasize the utility of BEL with concomitant CNI for PSL tapering in SLE patients especially in those involving joint inflammation. BEL was the factor to achieve not only LLDAS but also LLDAS-5, which is a more stringent treat to target that could lead to sustained improved quality of life by preventing accumulative organ damages.

## ICW1-3

### Efficacy and safety of belimumab for maintenance therapy in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objective] The efficacy of belimumab (BEL) for maintenance therapy in patients with systemic lupus erythematosus (SLE) remains unclear. We analyzed the efficacy and safety of BEL in patients with SLE for maintenance therapy. [Methods] This study included patients with SLE in the maintenance phase (SELENA-SLEDAI $<10$ , glucocorticoid (GC) dose  $\leq 0.2$  mg/kg/day). The efficacy of BEL combined with standard-of-care (BEL+SoC group,  $n=100$ ) was compared with SoC alone (SoC group, patients using either mycophenolate mofetil or hydroxychloroquine,  $n=103$ ). Selection bias was adjusted by propensity score-based inverse probability of treatment weighting (IPTW). We analyzed the trajectories of changes in GC dosage using growth mixture modeling (GMM). The primary endpoint was the GC dose at 52 weeks. [Results] No significant difference was observed in patient background between the two groups after adjustment by IPTW. The BEL+SoC group had significantly lower GC doses at 52 weeks compared to the SoC group (BEL+SoC,  $2.2 \pm 2.7$  vs. SoC,  $4.4 \pm 3.9$  mg/day,  $p<0.01$ ). The BEL+SoC group had a lower relapse rate compared to the SoC group (BEL+SoC, 0.9% vs. SoC, 6.3%,  $p<0.03$ ). The incidence of infections was significantly lower in the BEL+SoC group compared to the SoC group before IPTW (BEL+SoC, 4.0% vs. SoC, 17.5%,  $p<0.01$ ). The trajectory of the GC dose was divided into four groups by GMM; in a group (GC-free group), GC dosage could be reduced to 0 within 26 weeks, without any relapse. The majority of the GC-free group (87.5%) consisted of cases with concomitant BEL administration. In the BEL+SoC group, the patients had lower SELENA-SLEDAI scores ( $p=0.03$ ) and were more likely to belong to the GC-free group (multivariable analysis,  $p=0.02$ ). [Conclusions] In maintenance-phase SLE, administration of BEL was able to achieve a reduction or discontinuation of GC dose while suppressing flare-ups. The present study suggests that BEL is suitable for patients with SLE for maintenance therapy.

## ICW1-4

### Efficacy of Anifrolumab in Serological Subgroups of Patients With SLE Participating in 2 Phase 3 Trials

Ian Bruce<sup>1</sup>, Ronald Van Vollenhoven<sup>2</sup>, Yoshiya Tanaka<sup>3</sup>, Eric F Morand<sup>4</sup>, Richard A Furie<sup>5</sup>, Konstantina Psachoulia<sup>6</sup>, Emmanuelle Maho<sup>7</sup>, Catharina Lindholm<sup>8</sup>, Christi Kleoudis<sup>9</sup>, Raj Tummala<sup>6</sup>

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Conflict of interest: Yes

**Objectives:** To compare BICLA response rates in serological subgroups in the TULIP trials of anifrolumab, a mAb targeting the type I interferon receptor. **Methods:** TULIP-1 (NCT02446912) and TULIP-2 (NCT02446899) were phase 3, randomized, placebo-controlled, 52-week trials of IV anifrolumab Q4W for 48 weeks in patients with moderate to severe SLE receiving standard therapy. Week 52 BICLA response rates for anifrolumab vs placebo were compared post hoc in pooled TULIP data across subgroups of baseline active (low complement C3/C4, anti-dsDNA autoantibody positive, or low C3/C4 and/or anti-dsDNA positive) or normal (normal C3/C4, anti-dsDNA negative, or normal C3/C4 and/or anti-dsDNA negative) serologies. **Results:** Across TULIP-1 and -2 (anifrolumab 300 mg, n=360; placebo, n=366), overall BICLA treatment differences ( $\Delta$ ) favored anifrolumab over placebo (47.5% vs 30.8%;  $\Delta$ =16.6%; 95% CI 9.7-23.6). Anifrolumab BICLA response rates were higher in serologically active vs normal subgroups (49.2-53.0% vs 42.4-46.2%); patients with low C3/C4 had the highest anifrolumab response rate (53.0%). Placebo BICLA response rates were lower in serologically active vs normal subgroups (25.4-30.4% vs 30.2-35.0%). In both treatment groups, response rates were similar regardless of anti-dsDNA status, and subgroup response rates did not vary more than  $\pm$  6% from the overall population. Treatment differences favoring anifrolumab were greater in patients with low C3/C4 vs the overall population, alone ( $\Delta$ =27.6%; 95% CI 17.0-38.2) or with anti-dsDNA positivity ( $\Delta$ =24.1%; 95% CI 10.9-37.3). **Conclusion:** Subgroup analyses indicate efficacy of anifrolumab across evaluated serological subgroups. Treatment effect was greater in patients with low vs normal complement, in support of anifrolumab's mechanism of action. A treatment effect was observed regardless of baseline anti-dsDNA antibody status.

## ICW1-5

### SLE Treatment History and Anifrolumab Efficacy by Baseline Standard Therapies in Patients With SLE From 2 Phase 3 Trials

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Conflict of interest: Yes

**Objectives** To determine whether baseline standard therapies impacted anifrolumab efficacy in pooled data from the phase 3 TULIP-1 and TULIP-2 trials. **Methods** TULIP-1 (NCT02446912) and TULIP-2 (NCT02446899) were 52-week trials of intravenous anifrolumab or placebo every 4 weeks for 48 weeks in patients with moderate to severe SLE who were receiving  $\geq$  1 of the following therapies: oral glucocorticoids (GCs), antimalarials, immunosuppressants (azathioprine, mizoribine, mycophenolate mofetil, mycophenolic acid, and/or methotrexate). Patients were divided into subgroups of baseline therapy; BICLA response at Week 52 was compared post hoc across subgroups. **Results** Across TULIP-1 and -2, 726 patients received anifrolumab 300 mg (n=360) or placebo (n=366). The median time from SLE diagnosis to randomization was 84.5 months, during which most patients had received GCs (89.5%), antimalarials (84.3%), and immunosuppressants (68.0%); 100%, 34.3%, or 57.3% of patients had received  $\geq$  1, 2, or  $\geq$  3 SLE-related immunomodulatory therapies, respectively. At baseline, patients were receiving GCs (82.0%), antimalarials (70.2%), and/or immunosuppressants (48.2%). Anifrolumab resulted in higher BICLA response rates vs placebo across all evaluated subgroups. In the 190 patients likely to have refractory disease (ie, those receiving GCs + antimalarials + immunosuppressants at baseline), the BICLA response rate and treatment difference for anifrolumab vs placebo (53.6% vs 32.2%;  $\Delta$ =21.4%; 95% CI 7.4-35.4, nominal  $P$ =0.003) was consistent with responses seen in the overall population (47.5% vs 30.8%;  $\Delta$ =16.6%; 95% CI 9.7-23.6, nominal  $P$ <0.001). **Conclusion** Anifrolumab resulted in higher BICLA response rates than placebo, regardless of baseline standard therapy usage, including in patients with potentially more treatment-refractory SLE who required GCs, immunosuppressants, and antimalarials.

## ICW2-1

### Deletion of Mir223 exacerbates lupus nephritis by targeting S1pr1 in Fas<sup>lpr/lpr</sup> mice

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Conflict of interest: None

[Objective] The micro RNAs (miRNAs) and their target mRNAs are differentially expressed in various immune-mediated cells. Here, we investigated the role of *Mir223* and sphingosine-1-phosphate receptor 1 (*S1pr1*) in the pathogenesis of systemic lupus erythematosus. [Methods] We analyzed miRNA and mRNA profiling data of CD4<sup>+</sup> splenic T cells derived from MRL/MpJ-Fas<sup>lpr/lpr</sup> mice. We performed 3' untranslated region (UTR) luciferase reporter gene assay using human umbilical vein endothelial cells (HUVEC). We generated the B6-Mir223<sup>-/-</sup>Fas<sup>lpr/lpr</sup> mice and the lupus phenotypes were analyzed. [Results] In CD4<sup>+</sup> splenic T cells, we identified upregulation of miR-223-3p and downregulation of the possible target, *S1pr1* by RNA sequencing of MRL/MpJ-Fas<sup>lpr/lpr</sup> mice. The transfection with miR-223-3p mimic significantly suppressed a luciferase activity in HUVEC treated with a Lentivirus vector containing 3' UTR of *S1pr1*. The mRNA levels of *S1pr1* were significantly decreased after miR-223-3p overexpression. In B6-Mir223<sup>-/-</sup>Fas<sup>lpr/lpr</sup> mice, the proportion of CD3<sup>+</sup> T cells, CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup> cells, B cells, plasma cells, and S1PR1<sup>+</sup>CD4<sup>+</sup> T cells in the spleen was significantly increased compared with that in B6-Mir223<sup>+/+</sup>Fas<sup>lpr/lpr</sup> mice by flow cytometry. B6-Mir223<sup>-/-</sup>Fas<sup>lpr/lpr</sup> mice demonstrated the elevation of glomerular and renal vascular scores associated with enhanced intraglomerular infiltration of S1PR1<sup>+</sup>CD4<sup>+</sup> T cells. [Conclusions] Unexpectedly, the deletion of *Mir223* exacerbated the lupus phenotypes associated with increased population of S1PR1<sup>+</sup>CD4<sup>+</sup> T in spleen and the enhanced infiltration of S1PR1<sup>+</sup>CD4<sup>+</sup> T cells in inflamed kidney tissues, suggesting compensatory role of *Mir223* in the pathogenesis of lupus nephritis.

## ICW2-2

### Role of hematopoietic PAD4 in arthritis: collagen and G-CSF induced arthritis model in C57BL/6 mice

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Conflict of interest: None

[Objective] Genome-wide association studies connected *PADI4*, encoding peptidylarginine deiminase 4 (PAD4), with rheumatoid arthritis (RA). PAD4 promotes neutrophil extracellular trap (NET) formation. We studied *Padi4* and NETs in an arthritis model in C57BL/6 mice that is relatively resistant to the conventional collagen-induced arthritis model. [Methods] We modified a CIA model with administrations of granulocyte colony-stimulating factor (G-CSF) for four consecutive days around the second injection of collagen as an effective arthritis model in C57BL/6 mice. The model evaluated global and hematopoietic lineage-specific *Padi4*-deficient (*Padi4*<sup>-/-</sup> and *Padi4*<sup>flav1Cre/+</sup>) mice. [Results] G-CSF significantly increased the incidence and severity of arthritis in CIA. G-CSF-treated mice showed increased citrullinated histone H3 (H3Cit) and double-stranded DNA (dsDNA) in plasma while vehicle-treated mice did not. Immunofluorescent microscopy revealed deposition of H3Cit on synovial tissue and immunoblotting confirmed deposition of citrullinated histone H4 (H4Cit) in G-CSF-treated mice. Sera of G-CSF-treated mice contained more antibodies to H3Cit antigen than vehicle-treated mice did. *Padi4*<sup>-/-</sup> mice developed less arthritis, presented less serum interleukin 6, plasma H3Cit, and plasma dsDNA. *Padi4*<sup>-/-</sup> mice also showed less H4Cit on synovial tissue in immunoblotting, less bone erosion in micro-computed tomography, and fewer antibodies to H3Cit antigen than *Padi4*<sup>+/+</sup> mice in G-CSF-modified CIA. *Padi4*<sup>flav1Cre/+</sup> mice developed less arthritis compared with *Padi4*<sup>flav1</sup> mice, and presented the same phenotype as *Padi4*<sup>-/-</sup> mice. [Conclusions] We succeeded in developing an arthritis model in C57BL/6 mice compliant with animal welfare standards, with over 90%

incidence, detectable NET markers, and antibodies to H3Cit by injecting G-CSF in the CIA model. This model, mimicking human RA, shows that hematopoietic PAD4 is crucial for arthritis development and would be beneficial for RA research.

## ICW2-3

### JAK1 regulates autophagy and reinforces the inflammatory and autoimmune potentials in rheumatoid arthritis synovial fibroblasts

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Conflict of interest: Yes

[Objective] Rheumatoid arthritis (RA) is pathologically characterized by autoimmunity against citrullinated proteins, ultimately leading to joint destruction. Synovial fibroblasts (SFs) of RA patients produce large amounts of proinflammatory mediators including IL-6 and have high autophagy activity, probably contributing their active phenotype. Besides, our recent study suggests SFs' autoimmune potential by demonstrating the increase of citrullinated vimentin (cVIM) and its interaction with MHC class II when treated with autophagy inducers. JAK1 is an emerging therapeutic target in RA, but its roles in SFs remain unknown. We tried to clarify the role of JAK1 in the regulation of autophagy and in the inflammatory and autoimmune potentials in SFs. [Methods] SFs were derived from synovial tissue of RA patients. To inhibit JAK1, SFs were treated with its inhibitor upadacitinib (Upa, 10  $\mu$ M, 6-24 h). To induce autophagy, SFs were starved using serum-free medium for 2h or treated with MG132 (10  $\mu$ M, 24 h). The expression of autophagy was evaluated by *BECN1*, *ATG5* and *ATG7* in real-time PCR. IL-6 levels were measured in culture supernatants by ELISA. The interaction between cVIM and HLA-DR were analyzed by proximity ligation assays. P values were by ratio paired t-test. [Results] JAK1 inhibition with Upa decreased expression of *BECN1* ( $p=0.01$ ), *ATG5* ( $p=0.03$ ) and *ATG7* ( $p=0.02$ ) in starved SFs ( $n=5$ ). Similar results were obtained in SFs treated with MG132. The treatment with IFN- $\gamma$  (100 ng/mL, 24h) increased the expression of IL-6 ( $p=0.017$ ,  $n=3$ ), which was inhibited by Upa ( $p=0.02$ ,  $n=5$ ). The interaction between cVIM and HLA-DR was increased in SFs following treatment with starvation and IFN- $\gamma$  ( $p=0.003$ ,  $n=6$ ), which was cancelled by treatment with Upa ( $p=0.009$ ,  $n=6$ ). [Conclusions] Our results indicated that JAK1 upregulated autophagy and reinforced the inflammatory and autoimmune potentials in SFs. The mode of action of JAK inhibitors would include the mitigation of SFs' active phenotype.

## ICW2-4

### IL-6 inhibition attenuates neutrophil recruitment and its extracellular traps in joints with autoimmune arthritis

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Conflict of interest: None

[Objective] To investigate neutrophil extracellular traps (NETs) formation in peptide-GPI induced arthritis (pGIA) and their regulation by interleukin-6 (IL-6) inhibition [Methods] 1) Immunohistochemistry (IHC) using anti-modified citrulline antibodies was performed at the immunized skin of pGIA and control mice to detect citrullinated proteins. Western blot (WB) and IHC of citrullinated histone 3 (CitH3) was also performed to detect NETs. 2) WB and IHC of CitH3 was performed at the joints of pGIA and control mice. Immunofluorescence (IF) of CitH3 and neutrophil elastase (NE) was also performed to confirm NETs formation. 3) Gene expression of articular neutrophils in pGIA were explored by quantitative PCR. 4) Anti-IL-6 receptor antibodies were administered to pGIA. Arthritis score, CitH3 and NE expression in the joints, and serum citrullinated protein were examined. 5) Plasma citrullinated protein in RA patients before and 6 months after tocilizumab (TCZ) treatment was compared. [Results] 1) While citrullinated proteins were detected only in the pGIA skin on day7 and 14, CitH3 was detected in the skin of both pGIA and control mice

on day 7, 14, and 28. 2) CitH3 was significantly upregulated in the synovium of pGIA on day 14. Co-localization of CitH3 and NE was detected by IF. 3) The expression of IL-6 receptor tended to increase in articular neutrophils in pGIA on day14, as compared with bone marrow neutrophils. 4) Administration of anti-IL-6 receptor antibodies attenuated arthritis and the expression of CitH3 and NE in the joints. Serum citrullinated protein tended to decrease. 5) After treatment with tocilizumab (TCZ), the plasma citrullinated protein was significantly decreased. [Conclusions] Specific NETs formation was observed in the pGIA synovium. IL-6 inhibition attenuated neutrophil infiltration, NETs formation and blood citrullinated protein. IL-6 inhibition may reduce citrullinated protein via suppression of neutrophil recruitment and function in arthritis.

## ICW2-5

### Characterization of Myeloid-Derived Suppressor Cells in Inflammatory Joint of SKG Mice

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Conflict of interest: None

[Background] Myeloid-derived suppressor cells (MDSCs) are heterogeneous immature myeloid cells with suppressive functions. It is known that MDSCs are expanded in inflammatory sites after migrating from bone marrow (BM) or spleen. Rheumatoid arthritis (RA) is an autoimmune disease characterized as polyarthritis. Although previous reports indicate that MDSCs are increased in BM and spleen of arthritis model mice, detailed analysis of MDSCs in inflammatory joints is very limited. [Objective] The purpose of this study is to characterize the MDSCs in the joints of autoimmune arthritis. [Methods] We isolated CD11b<sup>+</sup>Gr1<sup>+</sup> cells as MDSCs from joints (Jo-MDSCs) bone marrow (BM-MDSCs) and spleen (Sp-MDSCs) of arthritic SKG mice, and investigated differential expressed genes (DEGs) among MDSCs from three tissues by microarray expression analysis. Based on the results, we analyzed the function and the differentiation of each MDSCs. [Results] Microarray analysis revealed that Jo-MDSCs had differential characteristics compared with BM-MDSCs or Sp-MDSCs. One of the characteristics of Jo-MDSCs was their highly expressed immunosuppressive DEGs (*Pd11*, *Arg1*, *Egr2* and *Egr3*). Another characteristic was that Jo-MDSCs highly expressed NF- $\kappa$ B non-canonical pathway DEGs (*Nfkb2* and *Relb*) relevant to osteoclast differentiation. In vitro, Jo-MDSCs suppressed Th17-proliferation and differentiated to osteoclasts. On the other hand, Sp-MDSCs suppressed Th17-proliferation but didn't differentiate to osteoclasts. BM-MDSCs differentiated to osteoclasts but didn't suppress Th17-proliferation. [Conclusions] Jo-MDSCs are different from BM-MDSCs or Sp-MDSCs and characterized as their both immunosuppressive and osteoclastic potentials.

## ICW3-1

### Aging is an independent contributor for seronegative rheumatoid arthritis in patients with female, normal body mass index and non-smoker

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Conflict of interest: None

Objective: The aim of this study is to investigate the effect of aging on seronegativity in patients with rheumatoid arthritis (RA). Methods: We reviewed all consecutive patients with RA in Keio University Hospital between 2016 and 2017. We subdivided patients according to the age at diagnosis, sex, body mass index (BMI), family history and smoking status, and investigated effects of aging on seronegativity. Results: A total of 1709 patients with RA were enrolled. The mean age at diagnosis was 52.0 years old, and 83.3% were women. Prevalence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) gradually declined with increasing age at RA diagnosis after 30s years (RF, 84.2, 81.3, 78.1,



74.6, 63.4, 51.4%; anti-CCP, 87.4, 81.7, 74.0, 70.5, 60.2, 37.1%). This tendency was generated from patients with female, normal BMI and non-smoker if we subdivided by sex, BMI category and smoking status (female, RF, 84.3, 86.9, 83.3, 79.0, 77.3 66.9, 53.8%; anti-CCP 84.2, 89.4, 84.3, 76.3, 73.6, 61.2, 38.5%; normal BMI, RF, 81.6, 83.8, 82.0, 80.1, 74.0, 57.5, 55.0; anti-CCP, 79.4, 88.3, 85.0, 75.5, 72.6, 57.1, 40.0%; non-smoker, RF, 80.6, 85.0, 82.3, 75.7, 74.1, 65.6, 46.2; anti-CCP, 78.9, 87.9, 82.6, 73.0, 69.3, 60.6, 34.6%), while it disappeared in male, BMI<18 or BMI<25 and smoker. Cox's proportional hazard model revealed that aging was an independent contributor for seronegativity in patients with female, normal BMI and non-smoker (RF, odds ratio, 0.971; 95% confidential interval, 0.958-0.984;  $p<0.0001$ , anti-CCP, odds ratio, 0.965; 95% confidential interval, 0.952-0.978;  $p<0.0001$ ) Conclusion: Aging is an independent contributor for seronegative RA in patients with women, normal BMI and non-smoker.

### ICW3-2

#### Patients with rheumatoid arthritis with renal failure require appropriate treatment enhancement to prevent frailty

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Conflict of interest: None

[Objective] To investigate associated factors with frailty in patients with rheumatoid arthritis with renal failure. [Methods] Six hundred twenty-five patients with rheumatoid arthritis (RA patients), who have visited outpatients from June to September 2021, were included. Five patients who failed to record Japanese-Cardiovascular Health Study criteria (J-CHS) and eGFR were excluded. Patients were divided into frailty (J-CHS  $\geq 3$  points) and non-frailty (J-CHS 0-2) groups. Various factor's trend of patients were analyzed by Cochran-Armitage trend test. RA patients with renal failure (eGFR < 60 ml/min/1.73<sup>2</sup>) were examined by Logistic regression analysis. [Results] The worse renal function of patients, the worse DAS28-ESR level ( $p=0.014$ ) and the more frailty there were ( $p=0.028$ ). The worse DAS28-ESE level of patients, the more frailty there were ( $p=0.049$ ). There were older patients (63.3 y.o. vs. 75.4 y.o.,  $p<0.001$ ), lower MTX use rate (67.6% vs. 40.8%,  $p<0.001$ ) in renal failure group compared with normal renal function group (eGFR  $\geq 60$  ml/min/1.73<sup>2</sup>). DAS28-ESR (OR, 95%CI: 1.85, 1.33-2.56,  $p<0.001$ ) and MTX use (0.42, 0.19-0.96,  $p=0.042$ ) were associated factors with frailty in RA patients with renal failure. [Conclusions] RA patients with renal failure need appropriate treatment enhancement to prevent frailty.

### ICW3-3

#### Association between sarcopenia and rheumatoid arthritis in the Korean population: a nationwide cross-sectional study

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Conflict of interest: None

[Objective] Rheumatoid arthritis (RA) includes musculoskeletal symptoms and leads to disuse atrophy of skeletal muscles and change in body composition. The musculoskeletal symptoms and loss of physical function in may be associated with the prevalence of sarcopenia, which is characterized by muscle loss. We aimed to investigate the prevalence of sarcopenia and its association with RA in the general Korean population. [Methods] We conducted a nationwide cross-sectional study using data from the Korea National Health and Nutrition Examination Survey and included 7,389 men and 9,798 women in the study. RA was defined based on a diagnosis made by a physician accompanied by current treatment. Sarcopenia was defined as appendicular skeletal muscle mass/body weight of more than one standard deviation below the mean of a sample of men and women aged 20-40 years. Binominal logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for sarcopenia prevalence in RA patients. [Results] The prevalence of sar-

copenia was 23.0% in men, 25.0% in women, 61.5% in men with RA, 32.3% in women with RA, 22.8% in men without RA, and 24.9% in women without RA. After adjusting for potential confounding variables, the prevalence of sarcopenia was significantly higher in men with RA than in men without RA (OR, 3.11; 95% CI, 1.29-7.46), but this was not seen in women. [Conclusions] The presence of sarcopenia was more than three-fold in Korean men with RA than in those without RA. However, this difference was not seen in women.

### ICW3-4

#### Efficacy and safety of JAK inhibitors for elderly patients of rheumatoid arthritis: a single-center retrospective case-control study

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Conflict of interest: None

[Objective] To evaluate real-world efficacy and safety of approved JAK inhibitors (JAKi) in Japan, including tofacitinib (TOF), baricitinib (BAR), peficitinib (PEF), upadacitinib (UPA), and filgotinib (FIL) for elderly patients of rheumatoid arthritis (RA). [Methods] A single-center retrospective case-control study of patients aged at starting JAKi over 65 (the elderly group, EG) compared with under 65 (the non-elderly group, NEG) treated with JAKi between February 2014 and July 2021. Patient background and clinical findings were collected using medical records. Disease activity was evaluated at the time of starting JAKi, at 3, 6, and 12 months after starting JAKi, and every year thereafter. The log-rank test was used to compare the continuation rates and incidence of herpes zoster (HZ) between the elderly group and the non-elderly group. [Results] A total of 288 patients treated with JAKi (EG, 214; NEG, 74) were enrolled; 150, 85, 31, 21, and 1 were used TOF, BAR, PEF, UPA, and FIL, respectively. There was no significant difference in the type of JAKi use between the groups ( $p=0.74$ ). The rate of concomitant methotrexate use was significantly lower in EG than NEG (37.6% vs. 57.4%,  $p=0.009$ ). The rates of patients with no prior use of biologics and JAKi tended to be higher in EG compared to NEG (47.2% vs. 34.4%,  $p=0.089$ ). There was no significant difference in the 1-year continuation rates of JAKi between the groups (72.9% in EG vs. 70.8% in NEG,  $p=0.54$ ). The incidence of HZ after initiation of JAKi were 4.7 per 100 patient-years in EG and 2.9 per 100 patient-years in NEG, respectively ( $p=0.37$ ). The primary reasons for the discontinuation of JAKi were inadequate efficacy and adverse events (53.1% and 40.6% in EG, and 72.0% and 22.2% in NEG, respectively). [Conclusions] Our study suggests that JAKi may be used effectively and safely in elderly RA patients as well as in non-elderly in clinical practice.

### ICW4-1

#### Characteristics of Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis With Peripheral Neuropathy

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Conflict of interest: None

[Objective] Peripheral neuropathy is one of manifestations of ANCA-associated vasculitis (AAV), which has a major impact on a patient's quality of life. This study aimed to clarify the clinical characteristics of AAV patients with peripheral neuropathy. [Methods] All consecutive patients with active, treatment-naïve AAV who were admitted to our hospital between April 1, 2012 and September 1, 2021 were included. Patients were divided into the two groups according to the presence or absence of peripheral neuropathy, and their baseline characteristics were compared. [Results] A total of 74 patients (MPA: 39, GPA: 21, EGPA: 14) were divided into those with peripheral neuropathy ( $n=26$ ) or those without peripheral neuropathy ( $n=48$ ). The patients with peripheral neuropathy showed younger age, higher frequency of EGPA, higher blood eosinophil counts, higher levels of serum IgE and IgG4 ( $p<0.05$ ). Thus, we next examined the characteristics of EGPA patients with peripheral neuropathy ( $n=11$ ) comparing to those without peripheral neuropathy ( $n=3$ ) and demonstrated

significantly younger age and higher blood eosinophil counts in the former group ( $p < 0.05$ ). We further analyzed the EGPA patients with motor neuropathy ( $n=7$ ) comparing to those with sensory neuropathy ( $n=4$ ), revealing higher blood eosinophil counts in those with motor neuropathy ( $p < 0.05$ ). [Conclusions] Our present study demonstrated that EGPA patients were prone to be complicated with peripheral neuropathy among AAV patients. The severity of peripheral neuropathy, which was reflected by the presence of motor neuropathy, was associated with more intense eosinophilic inflammation, suggesting a peripheral neuropathy as the potential therapeutic target of anti-IL-5 therapy.

## ICW4-2

### Clinical, pathological, and immunological characteristics in patients with Eosinophilic granulomatosis with polyangiitis (EGPA) as a mimicker of IgG4-related disease (IgG4-RD)

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Conflict of interest: None

[Objective] The clinical manifestation of EGPA is different from IgG4-RD. However, these diseases have common clinical phenotypes such as high serum IgE levels and allergic symptoms. In this study, we compared the clinical, pathological, and immunological characteristics between IgG4-RD and EGPA as an IgG4-RD mimicker to investigate their pathogenesis. [Methods] The patients with EGPA or IgG4-RD, who were untreated and newly diagnosed from 2007 through 2018, were enrolled. The clinical findings, histological findings, and immune phenotyping of peripheral blood by flow cytometry were evaluated in both patients. [Results] The levels of eosinophils, CRP, sIL-2R, and C4 were higher in EGPA. Notably, elevated serum IgG4 (IgG4 >135 mg/dl) was seen in all cases of EGPA. The pathological findings in the inflammatory sites showed lymphoplasmacytic infiltration with IgG4-positive plasma cells in 75% of EGPA patients. Namely, most of the EGPA patients met two of the three items of comprehensive diagnostic criteria for IgG4-RD. However, none of the EGPA cases had either mass lesions or hyperplastic lesions, and thus could not fulfill all the diagnostic criteria for IgG4-RD. The immune phenotyping of peripheral blood revealed that the proportions of follicular helper T cells and plasmablasts were increased in both diseases, while activated CD4 and activated CD8 T cells were increased only in EGPA. In other words, a dysregulation of B cell differentiation and activation of T cells were seen in patients with EGPA. [Conclusions] Elevated serum IgG4 levels and IgG4-positive plasma cell infiltration were not specific for IgG4-RD. The similarities of the immune phenotypes indicate the importance of Tfh and plasmablasts for the production and infiltration of IgG4 in both diseases. By contrast, the activation of T cells could be the underlying mechanism of vasculitis. Therefore, the balance between T cell activation and abnormal B cell differentiation may shape these diseases.

## ICW4-3

### CCL2, produced by M2 macrophage, is a useful clinical biomarker of microscopic polyangiitis complicated with interstitial lung disease

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Conflict of interest: None

[Objective] Microscopic polyangiitis (MPA) is often complicated by interstitial lung disease (ILD). However, biomarkers that can diagnose and predict the progression of MPA-ILD have not been identified. In this study, we evaluated various serum biomarkers in MPA-ILD to assess their diagnostic and predictive performance. [Methods] We enrolled 49 patients with anti-neutrophil cytoplasmic antibody (ANCA)+ MPA, with 32 of the MPA patients also presenting ILD. The presence of ILD was assessed by

high-resolution CT and evaluated by ground-glass opacity and fibrosis score. We compared 16 biomarker profiles among MPA-ILD patients, those without ILD, and extracted biomarkers with higher levels in MPA-ILD groups to determine correlations with disease activity. Three lung biopsies were examined by haematoxylin-eosin staining and immunostaining. [Results] Initial serum C-C motif chemokine ligand 2 (CCL2) levels were significantly higher in the MPA-ILD group than those of the MPA group, and were significantly higher in MPA-ILD patients 1 year after immunosuppressive therapy than those before treatment. Initial serum CCL2 levels positively correlated with an increased fibrosis score during the year after treatment. Immunohistochemical staining showed intense CCL2 signals in M2 macrophages and metaplastic epithelial cells in MPA-ILD lungs. [Conclusions] CCL2 is associated with MPA-ILD pathogenesis and suggested its potential efficacy as a useful marker for diagnosing and predicting MPA-ILD progression. Therefore, targeting CCL2 in alveolar M2 macrophages might represent a therapeutic intervention in ANCA+ MPA-ILD.

## ICW4-4

### Predictive factors for irreversible motor neuropathy in patients with eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

[Objective] Eosinophilic granulomatosis with polyangiitis (EGPA) often causes irreversible motor neuropathy (IMN). However, it remains challenging to predict IMN at the time of initiation of remission induction therapy. This study aimed to identify the predictive factors for IMN in patients with EGPA. [Methods] This retrospective observational study enrolled patients with EGPA who met the MIRA trial's classification criteria and received induction therapy at our hospital from January 2006 to April 2021. The clinical and laboratory data at the initiation of induction therapy, specified as the baseline, were collected. IMN was defined as a motor neuropathy with any orthotic devices and/or resulting in 4/5 or lower in manual muscle test, at 6 months after the initiation of the therapy. [Results] A total of 43 patients were enrolled in this study, 21 (49%) had motor neuropathy at the baseline, and 12 (28%) had IMN at 6 months after the initiation of the therapy. The mean age of the patients was  $56.0 \pm 13.2$  years. Although no significant difference in CH50 levels at the baseline was found between the patients with motor neuropathy and those without (median 46.0 vs. 46.1 U/mL,  $p = 0.800$ ), CH50 at the baseline was significantly higher in the patients without IMN than those with IMN (median 48.7 vs. 33.2 U/mL,  $p = 0.016$ ). Multiple logistic regression analysis revealed that CH50 were an independent predictor for IMN (odds ratio = 0.96 [0.92-1.0],  $p = 0.033$ ). [Conclusions] Responders on motor neuropathy for the induction therapy had higher CH50 levels at the baseline compared with non-responders. Higher CH50 would biologically represent the higher extent of inflammation. Thus, intensive anti-inflammatory immunosuppressive therapy would benefit for the EGPA patients with active inflammatory motor neuropathy. Not-elevated CH50 would represent less-inflammatory/more-degenerative damage in the tissue, thus leading to IMN in the affected patients despite the anti-inflammatory treatment.

## ICW4-5

### Efficacy and safety of mepolizumab for eosinophilic granulomatosis with polyangiitis

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Conflict of interest: Yes

[Objective] Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis with eosinophilic inflammation. Mepolizumab, an anti-IL-5 monoclonal antibody, inhibitor, is effective for EGPA with suppressing eosinophils. However, the long-term effects and safety of mepo-

lizumab in comparison with mepolizumab-unused patients have not been clearly verified in real-world settings. We investigated the efficacy and safety of mepolizumab for EGPA in this study. [Methods] We enrolled 25 EGPA patients in this single center study. In comparing patients with and without mepolizumab, 1 case treated with mepolizumab for less than 1 month was excluded. Concomitant corticosteroid dosages, eosinophil counts, the Birmingham vasculitis activity score (BVAS), remission rate defined by BVAS of 0 with prednisolone (PSL) less than 4 mg daily, and adverse events were retrospectively assessed. [Results] Eleven EGPA patients were treated with mepolizumab for more than 1.5 years. Mepolizumab-treated patients, compared with mepolizumab-unused patients, were controlled by lesser PSL dosages (mean, 2.6 mg and 4.5 mg,  $p < 0.05$ ) with smaller number of eosinophils (mean, 36 and 254 cells/ $\mu$ L,  $p < 0.05$ ). In terms of vasculitic disease activity, mepolizumab-treated patients tended to be lower BVAS (0.36 and 0.92) and higher remission state (55% and 31%) without statistically significance. No significant changes of efficacies by mepolizumab were observed in patients with and without MPO-ANCA. Novel safety signals for long-term usage of mepolizumab had not been observed, except for one case of rapid reaction with eyelid edema just after the 1<sup>st</sup> injection of mepolizumab. [Conclusions] Our findings indicate that mepolizumab is effective to reduce corticosteroid and suppress eosinophils without increasing vasculitic activities in EGPA. The efficacies and long-term safety of mepolizumab in real-world settings might clarify the therapeutic position of mepolizumab in EGPA.

## ICW5-1

### The incidence of macrophage activation syndrome in patients with adult-onset Still's disease receiving biological therapy: a single center experience and meta-analysis of the literature

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Conflict of interest: None

[Objective] The macrophage activation syndrome (MAS), a potentially fatal complication of adult-onset Still's disease (AOSD), may be exacerbated by biologics. This study aims to demonstrate the frequency and the clinical features of MAS developed in patients with AOSD receiving biological therapy. [Methods] Consecutive AOSD patients treated with tocilizumab (TCZ) at Yokohama City University Hospital from January 2000 to August 2021 were studied. Data including clinical symptoms, laboratory values, and treatment details were collected by referring to medical records. We also conducted a systematic review and meta-analysis to evaluate the incidence of MAS associated with biologics for AOSD. [Results] A total of seventy-five AOSD patients at our hospital were included in the analysis: all patients met Yamaguchi's criteria, and sixteen patients were treated with TCZ, with a mean age at induction of  $58.4 \pm 19.2$  years and a mean duration of disease of  $25.8 \pm 32.9$  months. Five patients developed MAS after TCZ therapy, and time from TCZ initiation to MAS onset was  $3.23 \pm 6.38$  months. They did not have complication of MAS at the time of AOSD onset, and, after TCZ treatment, showed fever over  $38.5^\circ\text{C}$ , elevated liver enzymes, anemia, thrombocytopenia, hypofibrinogenemia, elevated serum ferritin, and elevated sIL-2R. A total of 334 patients from nine studies were included in the meta-analysis (5 studies for TCZ, and 4 studies for anakinra). In all trials, biologics were used as maintenance therapy during remission. The incidence of MAS in patients with AOSD treated with biologics is as follows: 28.2% for TCZ and 3.0% for anakinra respectively. [Conclusions] Our study found a significant incidence of MAS in patients with AOSD receiving biologics, suggesting the need for careful monitoring during biologic therapy, especially in patients with active AOSD.

## ICW5-2

### Tocilizumab Discontinuation after Remission Achievement in Patients with Adult Still's Disease

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Conflict of interest: None

[Background] Tocilizumab, an interleukin (IL)-6 inhibitor has been proven to be effective in patients with adult Still's disease. However, the possibility of tocilizumab discontinuation has not been fully discussed. [Objectives] To clarify whether tocilizumab can be discontinued after remission achievement and identify factors relevant for its successful discontinuation in patients with adult Still's disease. [Methods] Consecutive patients with adult Still's disease diagnosed according to the Yamaguchi's criteria who were treated with tocilizumab from April 2012 until May 2021 were retrospectively reviewed. Patients who discontinued tocilizumab after remission achievement were included in the analysis, and their clinical courses were collected from their medical charts. [Results] A total of 67 patients with adult Still's disease with a history of tocilizumab use were included in the analysis. Among them, 15 patients discontinued tocilizumab following a good disease control. During the mean observation period of 31.3 months, four patients (27%) remained in remission while eleven patients (73%) recurred after tocilizumab discontinuation. The duration from the last tocilizumab administration to recurrence in the recurrence group was 10.3 months, while the non-recurrent group had been observed without recurrence for the mean period of 38.6 months. The systemic feature score and serum ferritin at tocilizumab discontinuation were comparable. While the duration of tocilizumab use was not different (35.3 vs 25.4 months), the mean interval of tocilizumab infusion at tocilizumab discontinuation in the recurrent group was 3.7 weeks, which was shorter than the 6.8 weeks in the non-recurrent group ( $p=0.04$ ). [Conclusions] More than 70% of patients with adult-onset Still's disease recurred after tocilizumab discontinuation with a mean period of 10 months. Patients remaining in remission with a longer interval of tocilizumab administration are likely to succeed in withdrawal of tocilizumab.

## ICW5-3

### Identification of pathways that discriminate between TAFRO type and NOS type in idiopathic multicentric Castleman's disease

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Conflict of interest: None

[Background] Multicentric castleman's disease (MCD) without human herpesvirus-8 (HHV-8) infection is defined idiopathic MCD (iMCD). iMCD-TAFRO is present in the TAFRO syndrome, and it is thought that pathology of lymph node biopsy shows an MCD-like appearance, and some clinical features overlap with MCD. That do not belong to any of the above categories is classified as iMCD-not otherwise specified (iMCD-NOS). The differences in the pathogenesis and molecular mechanisms between iMCD-TAFRO and iMCD-NOS are still not fully understood. [Objective] The aim of this study was to examine the molecular differences between iMCD-TAFRO and iMCD-NOS in CD4-positive cells from the peripheral blood. [Methods] CD4-positive T cells were isolated from the pre-treatment peripheral blood of three patients diagnosed with iMCD at our hospital and RNA sequencing was performed on the obtained samples using Illumina's Novaseq. We also performed protein arrays using the semi-quantitative RayBio® L-series 507 antibody array on pre- and post-treatment sera from six patients with iMCD. Serum IGFBP-1 levels were measured by ELISA in iMCD-NOS (11 cases), iMCD-TAFRO (7 cases), rheumatoid arthritis (8 cases), and healthy subjects (28 cases) at our hospital and related facilities. [Results] RNA sequencing results showed that mTOR signaling, p70S6K signaling, and HIF-1 $\alpha$  signaling were significantly upregulated in iMCD-TAFRO compared with iMCD-NOS in pathway analysis. The serum protein array before and after IL-6 inhibitor treatment showed that IGFBP-1 was decreased in the effective treatment group. In addition, serum IGFBP-1 levels were highest in the iMCD-TAFRO patient group. [Conclusions] Our results suggest that the mTOR-p70S6K-HIF-1 $\alpha$ -IGFBP-1 pathway may be enhanced in CD4 positive T cells from iMCD-TAFRO patients. Therefore, therapeutic strategies targeting this pathway may be effective for iMCD-TAFRO patients.



## ICW5-4

### Tocilizumab (TCZ) is effective for Tapering Corticosteroid (CS) and Reducing Recurrence in Patients with Adult-Onset Still's Disease (AOSD): a single-center analysis

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Conflict of interest: None

[Objective] Investigate the efficacy of TCZ in maintaining low disease activity and reducing CS dose in patients with AOSD in real-world clinical practice. [Methods] AOSD patients admitted for remission induction therapy from 2010 to 2020 were enrolled. The following were compared with patients treated with Tcz (Tcz group) or without TCZ (standard of care; SOC group), remission rate (no organ damage due to AOSD, negative CRP, and normal ferritin level), cumulative CS dose, recurrence rate (required re-induction therapy with high dose CS) and severe infection. [Results] 19 patients were enrolled; Tcz group (n=11) and SOC group (n=8), age (mean±SD) was 56.5±19.6 y.o. with 16 females (76.5%) and the observation period was 104.7±58.19 and 151.7±11.2 weeks respectively. There were no differences in age, gender, white blood cell counts, ferritin, and CRP on admission. TCZ was initiated 26.2±10.7 days following induction therapy with CS 45.6±11.0 mg/day and concomitant methotrexate (MTX) (n=4) or calcineurin inhibitors (CNI) (n=8). SOC group received CS 42.5±12.2 mg/day with concomitant MTX (n=5) and CNI (n=4). Permanent discontinuation of TCZ (n=2, 27.2%) was due to newly-onset infection. There was no difference in the remission rate during the observation period (Tcz group: 90.9%, SOC group: 100%. p=0.409). However, patients in Tcz group experienced less disease recurrence (9.1% vs. 62.5%, p=0.013) with a significantly higher proportion of patients with CS 3 mg/day (72.7% vs. 50%, p=0.034), and the cumulative CS dose was significantly less (542 mg vs. 877 mg, p=0.032). There was no statistical difference in life-threatening infections between the two treatment groups (18% vs. 37.5%, p=0.47). [Conclusion] Addition of TCZ at the induction treatment phase significantly reduced AOSD flare and cumulative CS dose with no difference in infectious adverse events. Our results indicate the utility of TCZ to reduce organ damage which largely depends on cumulative CS dose.

## ICW5-5

### A novel functional *IKBKE* variant in a patient with remittent fever and arthritis

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Conflict of interest: None

[Background] *IKBKE* is a negative regulator of T cell activation. On the other hand, it is one of the key players that activate type 1 IFN and NFκB signaling via non-classical pathways. The upstream single nucleotide polymorphism of *IKBKE* (rs2297550-G) is a genome-wide association study risk variant of systemic lupus erythematosus, and is associated with decreased *IKBKE* expression in T cells and increased expression in monocytes by expression quantitative trait locus analysis. [Case presentation] A woman in her 50s has had a remittent fever, arthritis, oral ulcers, and bronchial asthma for 30 years. She showed poor response to steroids or DMARDs, including etanercept and tocilizumab. Targeted genetic testing for autoinflammatory diseases was negative. She participated in the Initiative on Rare and Undiagnosed Disease (IRUD), and whole exome sequencing identified a novel heterozygous c.1877G>A, p (Cys626Tyr) variant in *IKBKE*. We transfected plasmids of wild-type *IKBKE* and *IKBKE* with the variant into two types of reporter cells (Type I IFN reporter cells and TNFα reporter cells that monitor NFκB signaling activation). The *IKBKE* variant significantly decreased the type 1 IFN and NFκB signaling than the wild-type variant (p = 1.1e-05, 0.0041). [Conclusions] In

this study, we describe a novel functional heterozygous variant in *IKBKE* in a patient with remittent fever and arthritis. Our data suggest that *IKBKE* is an important negative regulator of inflammation and this *IKBKE* variant might be the cause of novel autoinflammatory pathology.

## ICW5-6

### Caspase-1-mediated secretion of mitochondrial DNA-rich exosomes causes pathological inflammation in a human chronic inflammatory disorder

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Conflict of interest: None

Cell death defends against invasive pathogens by releasing cytoplasmic contents to induce inflammation and send warning signals to neighboring cells. However, it remains unclear how warning signals are transmitted to surrounding cells in response to noxious stimuli. Here, we show that pyroptotic cells secrete mitochondrial DNA (mtDNA) from cells via exosomes, which induce sterile inflammation to transmit warning signals. Activated Caspase-1 induces mtDNA leakage from mitochondria to cytoplasm via Gasdermin-D, as well as generation of intraluminal membrane vesicles that take up the leaked mtDNA and are secreted as exosomes, which further promote leukocyte mobilization and cytokine production via NLRP3 and TLR9. We also found that high levels of serum mtDNA-containing exosomes due to hyper-activation of Caspase-1 cause the pathological manifestations of Behcets syndrome (BS). Collectively, this mechanism of inflammation induced by exosomes containing mtDNA provides new insights into transmission of warning signals and explains the etiology of BS.

## ICW6-1

### A low platelet level during maintenance therapy is associated with failure to achieve definition of remission in systemic lupus erythematosus (DORIS)

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Conflict of interest: None

[Objective] To reduce organ damage in patients with systemic lupus erythematosus (SLE), sustained low disease activity and reduction of glucocorticoids (GCs) during maintenance therapy are essential. However, predictive factors to achieve remission with low-dose GCs, such as the definition of remission in SLE (DORIS), have not been clearly elucidated. This study aimed to identify predictive factors for achieving remission based on the DORIS criteria and risk factors for relapse during maintenance therapy. [Methods] This retrospective observational study enrolled SLE patients on GC tapering. Patients were followed up from the day prednisolone were tapered to 10 mg/day until the first relapse or the last visit. The achievement of DORIS 2021 was set as a primary outcome while the first relapse, an event with one or more organ lesions that met British Isles Lupus Assessment Group Index category A or B and required additional treatment, as a secondary outcome. The clinical data at baseline, including SLE Disease Activity Index (SLEDAI), were collected. Univariate and multivariable Cox regression analyses explored the factors associated with these outcomes. [Results] A total of 200 patients were enrolled and followed up for 59 (32-100) months. Of them, 122 patients (61.0%) achieved DORIS while 73 patients (36.5%) experienced a relapse. The platelet count at baseline was identified as an independent predictive factor for failure to achieve DORIS (every 1 x 10<sup>5</sup>/μL decrease, HR = 0.77 [0.61-0.97], p = 0.02). Consistent with previous studies, high clinical SLEDAI (>4 points, HR = 4.12 [1.90-8.92], p = 0.01) and low C3 levels (<86 mg/dL, HR = 1.78 [1.06-3.00], p = 0.03) at baseline were identified as risk factors for a relapse. [Conclusions] A Low platelet level during maintenance

nance therapy was associated with failure to achieve DORIS, and high clinical SLEDAI and low C3 levels were risk factors for relapse, which may give a hint for GC tapering in SLE patients.

## ICW6-2

### The Association of the visits to substitute physicians and trust in one's physician in SLE patients: a cross-sectional TRUMP2-SLE study

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Conflict of interest: None

[Objectives] Patients trust their personal doctors more when they receive comprehensive and continuous care from them. Patients with systemic lupus erythematosus (SLE) need to be seen by physicians on a long-term basis; however, the effect of seeing a substitute physician, who is not their usual doctor, on patients' trust in physicians is not known. [Methods] This was a cross-sectional study involving 255 SLE patients from five university hospitals. The exposure was the number of visits to substitute physicians for SLE-related issues in a year. The outcomes were a total score of the 11-item Trust in Physician Scale (ranges: 0 to 100). General linear models were fit with covariates (age, sex, length of time with one's physician, SLEDAI-2K, SDI). Missing data were complemented by multiple imputation. [Results] The mean age was 46 (SD 14) years, 88% were female. The number of visits to substitute physicians for SLE was 55.7% (0 visits), 25.5% (1-3 visits), and 18.8% ( $\geq 4$  visits). The mean score on the trust scale was 69.5 (9.3) points. Increased frequency of visits to substitute physicians for SLE was associated with lower trust in physicians ( $\geq 4$  visits vs. 0 visits, -3.1 [95% CI, -5.9 to -0.4]). Before multiple imputation, the result was the same ( $\geq 4$  visits vs. 0 visits, -3.9 [95% CI, -7.0 to -0.8]). [Conclusions] The results of this study suggest that the greater the continuity between the patient and substitute physician, the lower the patient's trust in their physician. Physicians need to consider patient psychology when providing substitute physicians.

## ICW6-3

### Clinical characteristics and phenotypes of peripheral blood immune cells in late-onset systemic lupus erythematosus

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Conflict of interest: Yes

[Objective] The aim of this study was to identify clinical and peripheral blood immune cell characteristics of newly late-onset ( $\geq 50$  years) systemic lupus erythematosus (SLE) requiring remission induction therapy. [Methods] Clinical features and immunophenotypes in peripheral blood by flow cytometry at the diagnosis in new-onset patients with late-onset SLE were compared with those of patients with early-onset ( $< 50$  years) SLE. [Results] Of 51 patients, 19 (38.0%) were late-onset SLE with a mean age of 64.5 years. Late-onset SLE patients compared with ear-

ly-onset patients showed nephritis (26.3% vs. 62.5%), hemolytic anemia (0.0% vs. 18.8%), hypocomplementemia (57.9% vs. 87.5%), anti-dsDNA antibody (19.2 IU/mL vs. 64.6 IU/mL), C1q immune complex (5.9  $\mu$ g/mL vs. 7.8  $\mu$ g/mL), anti-Sm antibody (11.1% vs. 41.9%), and lower SLEDAI (13.9 vs 20.6). Direct Coombs test without hemolytic anemia (94.7% vs 66.7%) and CRP (3.4 mg/dL vs 1.8 mg/dL) were significantly higher in late-onset SLE. Lymphocyte counts were similar, with significantly lower proportions of CD8<sup>+</sup> T cells, naïve CD8<sup>+</sup> T cells, CD27<sup>+</sup>IgD<sup>+</sup>CD19<sup>+</sup> activated B cells and higher central memory CD8<sup>+</sup> T cells (CD8<sup>+</sup>Tcm), HLA-DR<sup>+</sup>Treg and Tfr. Among them, CD8<sup>+</sup> T cells were elevated in all patients with nephritis, hemolytic anemia, hypocomplementemia and anti-Sm antibody, and inversely correlated with CRP, while HLA-DR<sup>+</sup>Treg was low in nephritis. In patients without nephritis, the proportions of naïve CD8<sup>+</sup> T cells, activated B cells, transitional B cells and  $\gamma\delta$  T cells were significantly lower and CD8<sup>+</sup>Tcm was higher in late-onset SLE. In a healthy population (mean age 41.2 years, 26% over 50 years), none of the above cells were associated with age except naïve CD8<sup>+</sup> T cells. [Conclusions] Late-onset SLE has fewer nephritis and different clinical features compared with early-onset SLE. There may be peripheral blood immune cell subsets characteristic of late-onset SLE that cannot be explained by clinical features and aging.

## ICW6-4

### Clinical features of cerebral vasculitis in patients with systemic lupus erythematosus: a case series study

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Conflict of interest: None

[Objective] Neuropsychiatric SLE refers to the neurological and psychiatric disorders complicated with SLE and can be challenging to diagnose. Magnetic resonance (MR) vessel wall imaging (VWI) of the brain has been used to diagnose cerebral vasculitis (CV). Although CV in patients with SLE classified into focal manifestation has been reported to be rare, their evaluation by VWI has yet been reported. The aim of this study was to investigate the clinical characteristics of CV in patients with SLE. [Methods] This case series study comprised 32 SLE patients with subjective symptoms including fever, headache, vertigo, dysarthria, paralysis, and psychiatric symptoms who underwent VWI at our department from July 2018 to July 2021. The diagnosis of CV was defined as the detection of a concentric enhancement of the vessel wall and atherosclerosis with a non-concentric enhancement was excluded. The clinical/laboratory manifestations and MRI/MRA findings of the SLE patients with CV were collected and analyzed. A follow-up VWI was performed within 6 months after treatment in 4 patients. [Results] A total of 32 patients with SLE underwent VWI, including 29 females (91%), were enrolled. The median age at enrolled was 33 years old (range: 16-62). Of 32 patients, 8 patients were diagnosed with CV (25%) by VWI. The subjective symptoms included fever 3 (38%), headache 3 (38%), vertigo 2 (25%), dysarthria 2 (25%), paralysis 1 (13%), and psychiatric symptoms 4 (50%). Laboratory data showed median CRP level was 0.7 (interquartile range: IQR 0.3-2.5) mg/L, median complement titers 31.5 (IQR 27.6-34.4) and anti-DNA antibody titers 10.3 (IQR 4.9-42.2) index. The MRI/MRA findings included infarctions 4 (50%), microhemorrhage 3 (38%) and arterial stenosis 2 (25%). Follow-up VWI of the 4 patients showed improvement of the vessel wall enhancement. [Conclusions] Our study revealed the clinical characteristics of CV in SLE.

## ICW6-5

### Immunophenotypes predicting flare of systemic lupus erythematosus (SLE) - using data from LOOPS/FLOW registry -

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Conflict of interest: None

[Objective] This study investigated the relationship between the clinical findings and immunophenotypes of SLE involved in flare after remission by assessing a large SLE cohort (LOOPS registry) and comprehensive immunophenotyping (FLOW study). [Methods] We retrospectively assessed SLE patients with high disease activity who were admitted to our hospital between November 2012 and December 2018 and achieved remission in response to remission induction therapy. We followed flare of the patients for 3 years after remission induction. A BILAG index of one A or that of two B was the criterion for flare. Immunophenotype analysis of peripheral blood was performed according to the NIH/FOCIS protocol at the time of remission induction and 6 months later; the primary endpoint was immunophenotype findings related to flare. [Results] Overall, we assessed 103 patients, 15 (14.5%) of whom experienced flare within 3 years (average: 21.6 months). The patients in the flare and non-flare groups were not significantly different in terms of age, sex, duration of illness or disease activity. Although there was no significant between-group difference in the immunophenotype at the time of remission induction, the percentages of plasmablasts (CD19<sup>+</sup>CD20<sup>+</sup>CD27<sup>+</sup>CD38<sup>+</sup>), activated Th1 cells (CD3<sup>+</sup>CD4<sup>+</sup>CXCR3<sup>+</sup>CCR6<sup>+</sup>CD38<sup>+</sup>HLA-DR<sup>+</sup>), activated CD8<sup>+</sup> T cells (CD3<sup>+</sup>CD38<sup>+</sup>CD38<sup>+</sup>HLA-DR<sup>+</sup>), and dendritic cells (CD3<sup>+</sup>CD14<sup>+</sup>CD19<sup>+</sup>CD20<sup>+</sup>HLA-DR<sup>+</sup>) were significantly higher and the ratio of naïve CD4<sup>+</sup> T cells (CD3<sup>+</sup>CD4<sup>+</sup>CD45RA<sup>+</sup>CCR7<sup>+</sup>) significantly lower in the flare group than in the non-flare group 6 months after remission induction. Multiple logistic regression analysis identified plasmablasts (odds ratio 3.71,  $p=0.001$ ) and naïve CD4<sup>+</sup> T cells (odds ratio 0.55,  $p=0.015$ ) after 6 months as factors related to flare. [Conclusions] Plasmablast expansion and abnormal CD4<sup>+</sup> T cell differentiation in peripheral blood after remission induction appear to be related to the risk of flare.

## ICW6-6

**Depression is Associated with Frailty in Systemic Lupus Erythematosus Patients: Multicenter Retrospective analysis using Systemic Lupus Erythematosus International Collaborating Clinics-Frailty Index**  
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Conflict of interest: None

**Objectives:** Systemic Lupus Erythematosus International Collaborating Clinics-Frailty Index (SLICC-FI) is a novel health measure in systemic lupus erythematosus (SLE) and was reported to have impact on outcomes including mortality. The objective of the study was to identify modifiable factors including depression and evaluate the association with frailty in SLE. **Methods:** SLE patients who fulfilled 1997 American College of Rheumatology (ACR) classification criteria were enrolled from five tertiary hospitals in Korea and the participants filled out questionnaires at outpatient clinic. Electronic medical records were reviewed for laboratory results, disease activity at enrollment and medications. The SLICC/ACR damage index score and SLICC-FI was calculated based on questionnaires and medical records. To assess the severity of depression, patient health questionnaire-9 (PHQ-9) was used. Logistic regression analysis was used to evaluate the factors associated with frailty in SLE patients. **Results:** In total, 247 patients were recruited. Mean (standard deviation, SD) age of the cohort was 50.5 (1.6) and 91.9% of the cohort was female. According to SLICC-FI, 36 (14.6%) patients were classified as frail (SLICC-FI > 0.21) and others were classified as non-frail (SLICC-FI ≤ 0.21), which include least fit (0.10 < SLICC-FI ≤ 0.21), relatively less fit (0.03 < SLICC-FI ≤ 0.10) and robust (SLICC-FI ≤ 0.03) patients. In multivariable logistic regression analysis, age (1.09), ESR (1.03), SLE-DAI-2K (1.18), PHQ-9 score (1.27) and SLICC/ACR damage index (3.22) were associated with frailty (odds ratio in parenthesis). Mild depression (PHQ-9 score ≥ 5) was observed in 97.2% of frail patients and 54.5% of non-frail patients. Severe depression (PHQ-9 ≥ 20) was observed in 22.2% of frail patients and 1.4% of non-frail patients. **Conclusion:** Early detection of depression and social support may improve outcomes of frail-

ty in SLE patients

## ICW7-1

### **Efficacy and safety of abatacept in rheumatoid arthritis patients with prior malignancy**

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Conflict of interest: None

[Objective] To evaluate the efficacy and safety of abatacept (ABT) in rheumatoid arthritis (RA) patients with prior malignancy in clinical practice. [Methods] Patients who received ABT for RA at our department from October 2010 to May 2021 were included in the study. Patient background, prior malignancy at starting ABT, disease activity from starting ABT up to 60 months, continuation rate of ABT, and safety including onset or relapse of malignancy during ABT use were retrospectively collected from electronic medical records. The patients were divided into two groups according to the absence or presence of prior malignancy, and the collected parameters were compared between the groups. [Results] A total of 258 patients were included, of which 55 had prior malignancy at the time of starting ABT. The rate of MTX use was significantly lower in the patients with prior malignancy (30.9 vs. 52.7%,  $p = 0.0041$ ), although there were no significant differences in other patient backgrounds between the two groups. There was no significant difference in the rate of biologic and JAK inhibitor naïve patients between patients without or with prior malignancy (72.4 vs. 74.5%). The disease activity improved significantly at three months after starting ABT, and DAS28-CRP remission was maintained after that. There was no significant difference in disease activity between the groups from starting ABT to 60 months after. There were no significant differences for the duration, continuation rates for 1-year and 5-year of ABT between patients without or with prior malignancy ( $3.5 \pm 3.0$  vs.  $3.5 \pm 2.6$  years, 82.7 vs. 81.4%, and 60.9 vs. 58.8%, respectively). There was no significant difference for the incidence of relapse or new onset of malignancy at five years after starting ABT between patients without or with prior malignancy (6.8% vs. 4.7%). [Conclusions] In our clinical practice, ABT showed similar efficacy and safety in patients with prior malignancy as in patients without prior malignancy.

## ICW7-2

### **Impact of rheumatoid arthritis on degenerative lumbar spine surgery outcomes**

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Conflict of interest: None

[Objective] Degenerative lumbar disease in rheumatoid arthritis (RA) patients remains a major challenge. Well-controlled comparisons between RA patients and their non-RA counterparts have not yet been reported. The objective of the present study was to compare postoperative outcomes of lumbar spine surgery between RA and non-RA patients using propensity score matching. [Methods] Patients who underwent primary posterior spine surgery for degenerative lumbar disease in our prospective multicenter study group between 2017 and 2020 were enrolled. Demographic data including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, diabetes mellitus, smoking, steroid usage, number of spinal levels involved, and preoperative patient-reported outcome (PRO) scores (numerical rating scale [NRS] for back pain and leg pain, Short Form-12 physical component summary [PCS], EuroQOL 5-dimension [EQ-5D], and Oswestry Disability Index [ODI]) were used to calculate a propensity score for RA diagnosis. One-to-one matching was performed and 1-year and 2-year postoperative outcomes were compared between groups. [Results] Among the 4567 patients included, 90 had RA (2.0%), who were more likely to be female, with lower BMI, higher ASA grade and lower current smoking rate than non-RA patients. Preoperative NRS scores for leg pain, PCS, EQ-5D, and ODI were worse in RA patients. Propensity score matching generated 61 pairs of RA and non-RA patients, and RA patients reported worse 1-year post-



operative PCS (28.4 vs. 37.2,  $p=0.008$ ) and EQ-5D (0.640 vs. 0.738,  $p=0.03$ ), although these differences were not significant between RA and non-RA patients not on steroids. Two-year postoperative outcomes did not differ between the two groups. [Conclusions] RA patients showed worse 1-year postoperative outcomes after posterior surgery for the degenerative lumbar disease, while steroid-independent RA cases showed equivalent outcomes to non-RA patients.

### ICW7-3

#### Perinatal clinical course of female patients with rheumatoid arthritis treated with bDMARDs

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Conflict of interest: None

[Objective] To clarify whether bDMARDs should be continued or discontinued when a patient becomes pregnant. [Methods] A single-center retrospective analysis of female patients with rheumatoid arthritis who wish to conceive or after pregnancy diagnosis between 2002 and 2018 was conducted. Pregnancy outcomes, disease activity and treatment before pregnancy, at conception, in each trimester, at 1, 3, 6, and 12 months postpartum were collected. [Results] Pregnancies were established in 74 patients with 96 pregnancies, 71 patients with 85 live births, and 7 patients with 11 miscarriages. The median (interquartile range) age at delivery was 36.0 (33.6-38.9) years, birth weight 2760 (2544-3008) g, 13 NICU admissions, 7 preterm births. There were no significant differences in pregnancy outcomes according to whether or not bDMARDs were used during pregnancy, or when they were used. Of the 85 cases with live births, 54 received bDMARDs at the time of conception, 18 continued bDMARDs (Continuation group) and 38 discontinued. Of the 38 cases, 13 remained stable throughout pregnancy (Flare- group) and 25 experienced disease flare (Flare+ group), and of these, 17 restarted bDMARDs. The achievement rate of low disease activity in the third trimester resulted in 75% by therapy intensification in the Flare+ group, which was not significantly different from the Continuation group or Flare- groups. By 12 months postpartum, all the three groups had a high rate of disease worsening: 71% in the Continuation group, 73% in the Flare- group, and 83% in the Flare+ group. The median time to worsening was 87, 95, and 35 days, respectively, and was significantly earlier in the Flare+ group (log-rank test  $p=0.12$ , Peto-Peto-Wilcoxon test,  $p=0.031$ ). [Conclusions] Regardless of whether bDMARDs are continued or discontinued, patients experience worsening after childbirth in a high rate. In particular, patients who had flares during pregnancy need to be closely monitored and their treatment reassessed.

### ICW7-4

#### Validation of RABBIT risk score in Japanese patients with rheumatoid arthritis treated with first bDMARDs - results from the IORRA cohort data

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Conflict of interest: Yes

[Objective] Predicting the risk of developing serious infections in patients with rheumatoid arthritis (RA) starting first biological disease modifying antirheumatic drugs (bDMARDs) is important for their appropriate use. The RABBIT risk score, a one-year prediction model for serious in-

fection in patients with RA, is easily calculated by age, complications, Health Assessment Questionnaire score, previous infection, and types of DMARDs. Validation analyses have been reported that the area under the receiver operating characteristic curve (AUROC) for serious infection was 0.69-0.86. However, it has not been validated using data from Japanese patients with RA, especially those treated with first bDMARDs. We herein assessed the prediction ability of the RABBIT risk score for serious infection in Japanese patients with RA treated with first bDMARDs. [Methods] Among RA patients aged 18 years or older who participated in the IORRA cohort study, those who were treated with their first bDMARDs were enrolled. Participants with missing data to calculate the RABBIT risk score were excluded. The prediction ability was analyzed by the AUROC. Serious infection was defined as hospitalized infection or infection requiring intravenous antibiotics, which were validated by their medical records. [Results] Data of 1055 bDMARDs users were extracted, with median age of 55 years (interquartile range [IQR] 43-65). The number of patients starting TNF inhibitors, IL-6 inhibitors and abatacept were 795 (75.3%), 183 (17.3%) and 77 (7.3%), respectively. We identified 18 serious infections, and the most frequent cause was bacterial pneumonia ( $n=7$ , 38.9%). The median RABBIT risk score was 1.8% (IQR 1.3%-3.0%), which was significantly higher in the serious infection group versus the others (3.7% vs 1.8%,  $p=0.008$ ). The AUROC for serious infection was 0.68 (95% CI 0.51-0.81). [Conclusions] We validated the prediction ability of RABBIT risk score in Japanese patients with RA treated with first bDMARDs.

### ICW7-5

#### Identification of prognostic factors for the progression of interstitial lung disease in rheumatoid arthritis patients treated with JAK inhibitors

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Conflict of interest: None

[Objective] Antirheumatic drugs with various mechanisms of action are used for rheumatoid arthritis (RA), but treatment options are often limited in the setting of concomitant interstitial lung disease (RA-ILD). Although little attention has been paid to the efficacy and safety of Janus kinase (JAK) inhibitors for RA-ILD, baricitinib is now recognized as a treatment option for COVID-19 pneumonia. The aim of this study is to observe the changes in CT findings in RA-ILD treated with JAK inhibitors. [Methods] Patients with RA-ILD who introduced tofacitinib or baricitinib between January 2017 and December 2020 and have gotten baseline and follow-up chest CT were included. The CT images were evaluated independently by two respiratory physicians blinded to clinical data for each patient. Each site was scored for inflammation and fibrosis and calculated as CT score. Factors associated with worsening of CT score after 1 year were extracted by multivariable analysis. [Results] Thirty-five patients were enrolled, of whom 29 and 6 were treated with tofacitinib and baricitinib, respectively. Methotrexate (MTX) was concomitantly used for 40%. Comparing the change in high-resolution CT before and after JAK inhibitor treatment for 1 year, 23 patients had a  $\Delta$ CT score  $< 1$  (improvement or invariance), while 12 patients had a  $\Delta$ CT score  $\geq 1$  (worsening). Logistic regression analysis with  $\Delta$ CT score as the objective variable showed that the concomitant MTX was an independent factor influencing the results (odds ratio: 0.09, 95% confidence interval: 0.009-0.881,  $p$ -value: 0.039). In the MTX group, the DAS improvement rate was higher, suggesting that concomitant MTX may improve the CT findings of interstitial lung disease by acting on the inflammatory pathology in the lung. [Conclusions] The results of this study suggest that the combination of JAK inhibitors and MTX may inhibit the progression of ILD in RA patients by enhancing the anti-inflammatory effect.

## ICW7-6

### Utility of right atrium area size to diagnosis of pulmonary artery hypertension with connective tissue diseases

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Conflict of interest: Yes

[Objective] We previously demonstrated the utility of right atrium area size (RAAs) as the predicting factor of survival in patients with pulmonary artery hypertension with connective tissue diseases (CTD-PAH). We screened RAAs to clarify the utility to diagnose CTD-PAH. [Methods] CTD patients undergoing right heart catheterization (RHC) in our institute from 2020 until 2021 were enrolled. Echocardiography data were analyzed by logistic regression analysis. [Results] Twenty patients including 8 systemic sclerosis (SSc) and 9 systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD) patients were enrolled. Age was 59.9±14.9 (mean±SD) years old and tricuspid regurgitation velocity (TRV) was 3.1±0.3 m/s by echocardiography. Among 15 CTD patients (75%) diagnosed with pulmonary hypertension (PH) by RHC, 9 patients (45%) were diagnosed with pulmonary artery hypertension (PAH) and 4 patients (20%) were diagnosed with PH with left heart disease. In the analysis of our CTD registry, the incident rate of PAH in overall SSc patients was 2.1% (95%CI: 1.1%-5.8%) and overall SLE or MCTD patients was 0.4% (95%CI: 0.1%-1.7%). RAAs was the predicting factor for diagnosis of PAH (OR 1.15, 95%CI: 0.73-1.94,  $p=0.032$ ) and the left atrium area size did not predict diagnosis of PH with left heart disease (OR 0.56, 95%CI: 0.16-1.12,  $p=0.109$ ). [Conclusions] In addition to previously known predicting factor of PH such as TRV, RAAs measured by echocardiography could be useful to detect and treat CTD-PAH early in its disease course.

## ICW8-1

### Comparison of the drug retention and reasons for discontinuation of Tumor Necrosis Factor Inhibitors, Interleukin-6 Inhibitors, and Janus Kinase Inhibitors in Japanese patients with Elderly-onset Rheumatoid Arthritis-the ANSWER cohort study

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Conflict of interest: None

Objective: This multi-center, retrospective study aimed to clarify retention rates and reasons for discontinuation of either Tumor Necrosis Factor inhibitors (TNFi), Interleukin-6 Inhibitors (IL-6i), or Janus Kinase Inhibitors (JAKi) in patients with elderly-onset rheumatoid arthritis (EORA). Methods: Patients with rheumatoid arthritis (RA) enrolled in a Japanese multicenter observational registry between 2011 and 2021 were included. EORA was defined as RA with onset at 60 or over. To adjust confounding by indication for treatment with TNFi, IL-6i or JAKi, a propensity score based on multiple baseline characteristics variables was used to compare the drug retention and causes for discontinuation between TNFi, IL-6i, and JAKi. Adjusted cumulative incidence of drug discontinuation for each rea-

son was compared between the three groups using the Fine-Gray model. Results: Among a total of 10,488 patients in the registry, 746 TNFi, 360 IL-6i, and 126 JAKi initiators with EORA were identified. Age, the proportion of females, seropositivity, and baseline disease activity at the time of drug initiation were similar between the groups. After adjusting for differences in baseline characteristics between the groups, overall drug discontinuation was significantly lower in the IL-6i and JAKi as compared to the TNFi (HR=0.64, 95%CI=0.52-0.80,  $p<0.01$ ) (HR=0.71, 95%CI=0.51-0.99,  $p=0.04$ ). The adjusted cumulative incidence of discontinuation due to lack of effectiveness was lower with the IL-6i (HR=0.43, 95%CI=0.30-0.61,  $p<0.01$ ) and the JAKi (HR=0.55, 95%CI=0.35-0.88,  $p=0.01$ ) while those due to adverse events (HR=0.84, 95%CI=0.64-1.43,  $p=0.28$ ) (HR=0.22, 95%CI=0.37-1.25,  $p=0.28$ ) were similar. Conclusions: In EORA patients initiating a TNFi, IL-6i or JAKi, significantly higher drug retention was observed with IL-6i and JAKi. Discontinuation due to lack of effectiveness was significantly less frequent in IL-6i and JAKi while discontinuations due to adverse event were similar.

## ICW8-2

### Prediction of disease flare by biomarkers after discontinuing biologics in patients with rheumatoid arthritis achieving stringent remission

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Conflict of interest: None

[Objective] To elucidate the disease-flare process in rheumatoid arthritis (RA) after discontinuing biological disease-modifying antirheumatic drugs (bDMARDs), we focused on RA-flare prediction after achieving stringent remission criteria. [Methods] Patients with RA who maintained a simplified disease activity index  $\leq 3.3$  for  $\geq 3$  months during November 2014-January 2018 in our institute were eligible. The primary endpoint was flare (disease activity score 28-erythrocyte sedimentation rate  $\geq 3.2$  with increase from baseline  $> 0.6$ ) within 2 years after bDMARD discontinuation. Comprehensive clinical assessments, ultrasonographic evaluation of 40 joints, and blood sampling for 12 biomarkers were performed every 2-3 months for 2 years unless patients experienced flare. Flare-positive and flare-negative patients were compared using univariate and Kaplan-Meier analyses. [Results] Thirty-six patients (80.6% female, median disease duration, 5.2 years; median treatment period with discontinued bDMARD, 2 years; median remission duration, 18 months) were enrolled. Twenty patients (55.6%) experienced RA flare 43-651 (median, 115) days after the first skipped date of bDMARDs. Two patients who withdrew without disease flare were excluded from the comparison. Clinical evaluations did not show significant between-group differences; Kaplan-Meier analysis showed that higher baseline soluble tumor necrosis factor receptor 1 (sTNFR1) concentration impacted subsequent disease flare ( $p = 0.0041$ ), and indeed, sTNFR1 level showed a significant increase from the baseline upon disease flare. Furthermore, higher baseline interleukin (IL)-2 concentration was exclusively beneficial to patients with lower sTNFR1 ( $p = 0.0058$ ), resulting in remission maintenance in 83.3% of patients with lower sTNFR1 and higher IL-2. [Conclusions] We demonstrated the usefulness of combined biomarker evaluation for predicting sustained remission after bDMARD discontinuation in RA.

## ICW8-3

### Post-disease control by discontinuation of tofacitinib in patients with rheumatoid arthritis; a multicenter, prospective, randomized study (XANADU study)

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Conflict of interest: None

[Objective] JAK inhibitors (JAKi) are similarly effective to biologics in rheumatoid arthritis (RA). However, concerns remain in terms of the long-term safety and economic burden. Therefore, a treatment holiday should be considered. However, the withdrawal strategy for JAKi has not been investigated. [Methods] XANADU study was conducted as a multicenter, prospective, randomized study. RA patients who had an inadequate response to methotrexate (MTX-IR) and started tofacitinib (TOF) were randomly divided into two groups; MTX-free and TOF-free. Either drug was withdrawn if patients achieved CDAI remission at week 52. The primary endpoint was the proportion of patients who remained TOF-free or MTX-free and maintained below low disease activity (LDA) at week 104. [Results] A total of 113 patients (56 in TOF-free and 57 in MTX-free) participated. Among the 48 patients (42.4%) that achieved remission at 52 weeks, 10 patients (41.6%) in TOF-free and 13 patients (65.0%) in MTX-free were in sustained LDA at week 104. Namely, 17.8% of the RA patients in high disease activity treated with TOF and MTX were able to maintain below LDA following TOF withdrawal and 22.8% following MTX withdraw at week 104. Patients below LDA and who remained TOF-free at week 104 had a smaller number of prior-biologics (OR 0.40 95%CI 0.17-0.94,  $p=0.03$ ). In fact, 37.5% (sensitivity 0.60, specificity 0.78) of the bio-naïve patients were able to remain TOF-free at week 104 and this trend was not observed in the MTX-free group. Of those who flared re-started the discontinued treatment, 13/14 patients in the TOF-free group and 5/7 patients in the MTX-free group achieved LDA. [Conclusions] Approximately 18% of MTX-IR RA patients with high disease activity treated with TOF and MTX were able to discontinue TOF and remain below LDA at week 104 and this trend was stronger with bio-naïve patients. These results indicate that a “treatment holiday” could be one of the realistic goals in MTX-IR RA patients.

## ICW8-4

### The association of large joint involvement at the start of biologic agents or JAK inhibitors with drug continuity rate and disease activity in rheumatoid arthritis patients - ANSWER cohort study

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Conflict of interest: None

[Objective] To investigate whether large joint involvement (LJI) affects drug continuity rates and disease activity in rheumatoid arthritis (RA) patients on biological DMARDs (bDMARDs) or JAK inhibitors (JAKi). [Methods] Patients with RA in a Japanese multicenter observational registry between 2011 and 2021 were included. The enrolled patients had a mean age of 61 years and a mean disease duration of 102 months. We defined large joints as shoulder, elbow, hip, knee, and ankle joints according to the ACR/EULAR 2010 classification criteria. The treatment courses (TCs) were divided into two groups according to LJI at the initiation of bDMARDs and JAKi, and the drug continuity rates were compared among two groups using log-rank test and Cox proportional hazards models.

Changes in CDAI between baseline and 12 months were compared using the t-test and linear regression models. Multiple regression was used to control for potentially confounding factors of age, sex, disease duration, ACPA, RF, and other csDMARDs. [Results] Among total 7602 TCs, 1940 TCs from 1640 patients were included after excluding patients with no joint involvement or missing values (LJI group: 1306, small joint involvement (SJI) group: 634). Drug continuation rates were similar in both groups (HR: 0.91, 95%CI: 0.77-1.07,  $P=0.26$ ). LJI group had significantly lower changes in CDAI at 12 months (Difference of CDAI changes at 12 months between the two groups: 5.0, 95%CI: 3.7-6.0,  $p<0.001$ ). Subgroup analyses based on the type of bDMARDs/JAKi or age showed 6 similar results. [Conclusions] The patients with LJI had a better response to bDMARDs/JAKi than one with SJI in terms of CDAI. This suggests RA with LJI may have different pathogenesis from RA with SJI.

## ICW9-1

### Drug retention of biologics or JAK inhibitors in patients with difficult-to-treat rheumatoid arthritis: Results from the ANSWER cohort

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Conflict of interest: Yes

[Objective] Difficult-to-treat rheumatoid arthritis (D2T RA) is defined as RA in which disease activity is uncontrolled despite the use of two or more biologics or Janus kinase inhibitors (JAKi) with different mechanisms of action (MOA). To explore the optimal treatment strategy for D2T RA, we evaluated the drug retention, efficacy, and reasons for discontinuation of biologics or JAKi used for patients with D2T RA in a longitudinal multicenter cohort. [Methods] RA patients with clinical disease activity index (CDAI)  $>10$  despite the use of at least two biologics or JAKi with different MOA and further treated with biologics or JAKi were included. The drug retention rates of biologics (TNFi, IL-6Ri, and CTLA4-Ig) or JAKi were estimated at 12 months using the Kaplan-Meier method and adjusted for potential confounders (age, sex, disease duration, concomitant MTX and PSL use, and the number of switched biologics or JAKi) using Cox proportional hazards models. [Results] A total of 251 treatment courses (TCs) from 167 patients were included (TNFi: 97 TCs, IL-6Ri: 67 TCs, CTLA4-Ig: 27 TCs, JAKi: 60 TCs). Baseline characteristics showed no difference in age, sex, disease duration, ACPA positivity, CDAI, and concomitant MTX and PSL use between the four groups. Drug retention excluding non-toxic reasons and remission was significantly higher in patients treated with JAKi or IL-6Ri than in patients treated with TNFi or CTLA4-Ig ( $P=0.00172$ ). Multivariate analysis using Cox proportional hazards models demonstrated that discontinuation of the drug was associated with the use of TNFi or CTLA4-Ig (HR: 3.29, 95%CI: 1.15-9.42,  $P=0.027$ ) and concomitant PSL use (HR: 1.14, 95%CI: 1.04-1.26,  $P=0.0084$ ). In terms of disease activity evaluated with CDAI, no difference was observed between the four groups at 3 months ( $P=0.90$ ), at 6 months ( $P=0.77$ ), and at 12 months ( $P=0.75$ ). [Conclusions] In patients with D2T RA, JAKi or IL-6Ri may have treatment advantages compared with TNFi or CTLA4-Ig.



## ICW9-2

### Study of the characteristics of patients with rheumatoid arthritis showing an inadequate response to Janus kinase inhibitors and suitable treatment options: From the FIRST Registry

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Conflict of interest: None

[Objectives] Janus kinase inhibitors (JAKis) are effective in patients with rheumatoid arthritis (RA); however, some patients with RA show an inadequate response to JAKis (JAKi-IR). This study aimed to determine the clinical characteristics of JAKi-IR patients with RA and identify suitable molecular-targeted drugs for such patients. [Methods] The subjects were 368 patients with RA who were administered JAKis (tofacitinib, 183 patients; baricitinib, 163; peficitinib, 8; and upadacitinib, 14). The clinical characteristics of JAKi-IR patients were analyzed. The efficacy and safety of switched molecular-targeted drugs were analyzed six months after switching treatment to identify suitable molecular-targeted drugs in JAKi-IR patients. [Results] Overall, 75 (20.4%) patients were JAKi-IR one year after the introduction of JAKi. The factors associated with JAKi-IR were identified a history of biologic use ( $p=0.04$ ) and low IgG levels ( $p=0.03$ ) by multivariable logistic regression analysis. Out of 68 JAKi-IR patients who switched to another molecular-targeted drugs (TNF $\alpha$  inhibitor [TNFi], 15; IL-6 receptor inhibitor [IL-6Ri], 19; abatacept [ABA], 7; JAKi, 27), 12 (17.7%) patients achieved CDAI remission. There was no significant difference in the patient characteristics at the time of switching treatment and in the retention rates among the four groups. The proportion of patients who achieved remission was significantly higher in the group that switched to a different JAKi (37%) than in the other drug groups (TNFi, 0%; IL-6Ri, 0%; ABA, 29%;  $p<0.01$ ). The factors associated with remission in JAKi-IR patients were identified only switching to a different JAKi ( $p<0.01$ ) by logistic regression analysis. [Conclusion] Patients with RA who have a history of biologic use and low IgG levels may show an inadequate response to JAKis. Besides, it might be appropriate to select a different JAKi to improve disease activity in JAKi-IR patients with RA.

## ICW9-3

### Risk estimation of difficult-to-treat (D2T) RA: FIRST registry

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Conflict of interest: None

(Objective) The EULAR Task Force established recommendations addressing the unmet needs in the management of difficult-to-treat RA (D2TRA). The aim of this study was to clarify predictive factors for D2TRA and establish a strategy to prevent D2TRA. (Methods) We investigated the incidence of D2TRA, according to the EULAR definition. Data of RA patients who were administered the first b/ts DMARDs after August 2013 were collected from the FIRST registry. We also investigated the risk factors for D2TRA development based on patient background and the use of first product-class of b/ts DMARDs. (Results) In the FIRST registry (2946 patients were registered 4317 times), 1438 patients were administered the first b/ts DMARDs after August 2013. Of these, 1183 patients (mean follow-up 34.7 months) were included in the current analysis. Among them, 151 patients (12.8%) developed D2TRA after 25.3 months of follow-up. High BMI (odds ratio [95% CI]: 1.07 [1.02-1.11]), high HAQ (odds ratio [95% CI]: 1.37 [1.03-1.82]), and high pain VAS (odds ratio [95% CI]: 1.02 [1.00-1.03]) at the initiation of the first b/ts DMARDs were predictors of D2TRA development. A risk estimation model based on multivariable logistic regression estimated that 21.5% of patients were at a risk of developing D2TRA; 27.6% of at-risk patients and 8.8% of the remaining patients developed D2TRA (odds ratio [95% CI] 3.97 [2.78-5.67]). Different rates of D2TRA development were associated with different product classes ( $p<0.01$ )-TNF inhibitors (TNFi): 14.5%; IL-6 receptor inhibitors (IL6Ri): 8.2%; CTLA4Ig: 16.2%; and JAK inhibitors

(JAKi): 6.6%. After adjustment of patient background by the IPTW method, 19.5% of TNFi, 8.9% of IL6Ri, 18.8% of CTLA4Ig, and 6.3% of JAKi users developed D2TRA ( $p<0.01$ ). (Conclusions) IL6Ri and JAKi suppressed D2TRA development. We suggest that IL6Ri or JAKi be considered as first-line b/ts DMARDs in patients with high BMI, HAQ, and pain VAS.

## ICW9-4

### Clinical features of difficult-to-treat rheumatoid arthritis: A multicenter RA ultrasound prospective observational cohort study in Japan

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Conflict of interest: None

[Objective] The concept of difficult-to-treat rheumatoid arthritis (D2T RA) has emerged as the unmet need in recent years. We have investigated the clinical characteristics and the contributing factors toward the outcome in patients with D2T RA in the real world setting using a multicenter RA ultrasound prospective observational cohort study. [Methods] We enrolled 371 RA patients who received biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) therapy. We evaluated the therapeutic efficacy by the patients' clinical disease activity scores and musculoskeletal ultrasound (MSUS) scores every 3 months. We defined a D2T RA as a patient with (1) failure of  $\geq 2$  b/tsDMARDs (with different mode of action) and (2) at least moderate disease activity (DAS28-ESR $>3.2$  or CDAI $>10$ ) or inability to taper glucocorticoid treatment ( $\geq 7.5$  mg/day prednisone) at baseline. First, we compared characteristics between D2T RA and non-D2T RA. Second, we attempted to identify any variables that were independently contributing factors of the good outcome defined as the achievement of low disease activity (LDA, CDAI  $\leq 10$ ) with the continuation of b/tsDMARDs. [Results] Among 371 patients with RA, 57 (15.4%) were D2T RA. Disease duration, the positivity of rheumatoid factor, a complication of interstitial pneumonia were significantly higher in D2T RA compared with non-D2T RA. Clinical remission (CDAI  $\leq 2.8$ ) rates at 12 months were significantly lower in D2T RA (8.8 vs 38.2%,  $p<0.0001$ ). In D2T RA, 14 (38.6%) patients have achieved a good outcome. Multivariate logistic regression analysis showed that EGA (odds ratio [OR] 0.94, 95% confidence interval [CI] 0.89-0.99,  $p=0.024$ ), total GS score (OR 0.93, 95%CI 0.87-0.99) and using CTLA-4Ig (OR 103, 95%CI 4.52-2364,  $p=0.0037$ ) were independent contributors of a good outcome. [Conclusions] In patients with D2T RA, low EGA, low total GS score at baseline and treatment with CTLA-4Ig were associated with a good outcome.

## ICW9-5

### The implication of persistent pain in patients with rheumatoid arthritis albeit in DAS28-remission: data from the KOBIO registry

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Conflict of interest: None

[Objective] Patient-reported symptoms such as pain and fatigue may persist despite remission in rheumatoid arthritis (RA). We thereby assessed the prevalence of pain in patients after achieving remission according to the Disease Activity Score (DAS28)-erythrocyte sedimentation rate (ESR), and analyzed the demographic and clinical characteristics of these patients with persistent pain. [Methods] Data from 1891 patients with RA registered in the KOBIO (from Dec 2012 to Sep 2020) were obtained. DAS28-remission was defined as DAS28-ESR  $< 2.6$ . Pain Visual Ana-

logue Scale (VAS) was evaluated. The intensity of pain was classified as severe (VAS  $\geq 7$  out of 10), moderate (VAS  $\geq 4$  and  $< 7$ ), and mild (VAS  $< 4$ ). The association between baseline clinical characteristics and pain VAS after 1-year treatment with biologics or Jak inhibitors (JAKi) were assessed using a multivariate logistic regression model. [Results] Our analysis showed that 52.6% of patients complained of severe pain (VAS) at the time point starting biologics or JAKi. After using biologics or JAKi, the proportion of patients who achieved DAS28-remission in the first year was 36.0% (n = 680). However, 21.5% (n = 146) of patients in remission still complained of moderate to severe pain: this population had higher frequency of married status, erosions in feet and comorbidities of endocrine, renal, and psychiatric disorders than patients with lower degree of pain. In the multiple regression analysis, longer disease duration (odds ratio [OR] 1.01, 95% confidence interval [CI] 1.00-1.05), high RAPID3 (OR 1.59, 95% CI 1.44-1.76) and low tender joint count (OR 0.64, 95% CI 0.52-0.80) at baseline were independently associated with moderate to severe pain despite achieving remission. [Conclusions] Displeasing pain is yet a lingering problem in a good deal of patients even in clinical remission. New treatment guidelines would need to address this and include strategies to better alleviate pain in patients with RA.

## ICW10-1

### Estimation of short-term prognostic factors in hospitalized patients with herpes zoster, and the incidence of cerebro-cardiovascular events and the possible risk factors after hospitalization: a descriptive study using a national administrative inpatient database in Japan

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Conflict of interest: None

[Objectives] Herpes zoster (HZ) has a relatively high incidence and severity in patients with underlying diseases including connective tissue diseases (CTD). Also, there is an increased risk of the incidence of cerebro-cardiovascular events after HZ. The purpose of this study was to investigate short-term prognostic factors and risk factors of cerebro-cardiovascular events associated with HZ in hospitalized HZ cases. [Methods] We enrolled HZ cases who received antiviral for 7 days or more and started treatment within 7 days after admission between April 2016 and March 2018. Records were extracted from a Japanese nationwide inpatient database. [Results] Total number of cases was 29054 (female n=15202). Median age (years) 71.0, types of HZ; central nervous system (n=9034), disseminated (n=3051), ophthalmicus (n=1069) and like. There were 301 deaths and 385 post-hospitalization onsets of cerebro-cardiovascular events. A total of 17973 cases had some underlying diseases including 1492 CTD cases. 30 days survival rate were 97.0%. A multivariable Cox regression analysis (HR, [95%CI]) demonstrated that over 75 years old: HR 2.18 [1.55-3.05], liver cirrhosis and hepatic failure: HR 5.93 [2.16-16.27], chronic kidney disease: HR 1.82 [1.24-2.68], heart failure (HF): HR 1.65, [1.22-2.24] and old cerebrovascular disease: HR 1.92 [1.10-3.34] were associated with poor prognosis. A multivariable logistic regression analysis (OR, [95%CI]) demonstrated that over 75 years old: OR 1.70 [1.29-2.24], diabetes: OR 1.50 [1.19-1.89], dyslipidemia: OR 1.95 [1.51-2.51], hyperuricemia: OR 1.63 [1.18-2.27], hypertension: OR 1.76 [1.40-2.20], HF: OR 1.84, [1.32-2.55] and glucocorticoid (GC) use: OR 1.59 [1.25-2.01] were associated with increased risk of cerebro-cardiovascular event. [Conclusions] CTD was not an obvious poor prognostic factor in hospitalized HZ cases. In addition to general coronary risk factors, GC might be a possible risk for the onset of cerebro-cardiovascular events after HZ.

## ICW10-2

### The effect of hydroxychloroquine on infectious diseases in patients with systemic lupus erythematosus: a preliminary retrospective cohort study from the LUNA registry

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Conflict of interest: None

[Objective] Infections are a major cause of mortality for patients with systemic lupus erythematosus (SLE). Although previous reports have shown the protective effect of hydroxychloroquine (HCQ) against infections, there is no such evidence in the Japanese population. Here we investigated the protective effect of HCQ on infection in Japanese SLE patients. [Methods] The patients who were registered in the multicenter SLE registry "LUNA" were included in the study. We collected the data of treatment, disease activity, and clinical and serological variables and used the generalized estimating equation to analyze the protective effect of HCQ against infections. The endpoint was the onset of severe infection, defined as an infection requiring hospitalization. [Results] Nine hundred twenty-five patients (median age 45 (IQR 35-57) years; female 88.1%) were included and 1,592 visits in total were monitored in the study. At enrollment, 267 had been prescribed HCQ while 656 had not. The observation period was 1 to 5 years. All infections were reported 110 times, with the most common infections being pulmonary infections (29.1%), followed by infections in the urinary tract (27.3%), skin and soft tissue (15.5%). The glucocorticoid dose (regression coefficient 2.08 [95% confidence interval 1.41-3.06],  $p = 2.0 \times 10^{-4}$ ), the presence of immunosuppressive drugs (1.68 [1.05-2.68],  $p = 0.029$ ), and the age at registration (1.04 [1.02-1.06]) were positively associated with the severe infections. Although the use of HCQ tended to reduce the incidence of severe infections, we could not find statistical significance (0.63 [0.33-1.23],  $p = 0.18$ ). [Conclusions] In this study, we could not prove the protective effect of HCQ against infection in patients with SLE. We plan to analyze it in a larger population in the future study.

## ICW10-3

### Safety profile of the adjuvanted recombinant zoster vaccine: Zoster-J is a single center's experience with rheumatoid arthritis patients

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Conflict of interest: None

[Objective] We investigated prospectively the impact of the adjuvanted recombinant zoster vaccine (RZV) in RA patients taking DMARDs and measured the incidence of disease flare and adverse reaction. [Methods] Inclusion criteria was RA patients aged 50 years and older who want to receive the RZV. The RZV is two-dose series, with doses given 2 to 6 months apart. We evaluated a disease activity before and after vaccination. A flare was defined as new/switching or increased dose of DMARDs due to worsening disease activity. Adverse reactions were collected for 30 days after each vaccination and graded on a scale from mild to severe. [Results] 28 patients (28 patients received 1 dose, 24 patients received 2 doses) were

included: 71% female, mean age 68 years, mean RA duration 12.8 years, mean CDAI:  $9.5 \pm 7.7$ . 7 patients (25%) reported a past history of herpes zoster (HZ) and 27 patients (96%) had varicella zoster virus (VZV)-IgG  $\geq 4.0$ . Treatments were JAKi used with 26 patients (74%), bDMARDs with 6 patients, MTX with 14 patients (50%, mean 9.1 mg) and GCs with 11 patients (31%, mean 9.9 mg). We measured 7.1% ( $n=2/28$ ) flares occurring after the first RZV. One patient increased dose of MTX due to worsening of CDAI (3.1→5.0), a second patient switched JAKi due to worsening of CDAI (3.8→22.3). 24 patients didn't flare after the second RZV. None of the patients didn't receive the second RZV because of flare or adverse events. Of the 23 patients, local reactions were reported 91%, most of the reactions were mild to moderate in median over 4 days. General reactions were reported 65% in median over 4 days. One case of HZ taking JAKi and GCs was reported as occurring 6 weeks after the first RZV. [Conclusions] All flares responded to treatments. The local reactions of ZOE-50/70 studies were 81% however Zoster-J was 91% and the general reactions were same at 65%. These data indicate that the possibility of safe usage of this vaccine for RA patients with mild to moderate disease activity.

## ICW10-4

### Immunological response to anti-SARS-CoV-2 mRNA vaccines in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Long-term vaccine-induced protection is crucial for controlling the COVID-19 pandemic. Since very few data are available regarding anti-SARS-CoV-2 vaccination against rheumatic arthritis (RA) patients, whether disease-modifying anti-rheumatic drug (DMARD) treatment should be continued through vaccination is not clarified yet. We aimed to evaluate the humoral and cellular immune responses by anti-SARS-CoV-2 mRNA vaccination in RA patients on DMARDs. [Methods] A prospective, observational study of RA patients on DMARDs and healthy controls who planned to receive two doses of the mRNA-1273 vaccine (Moderna) or the BNT162b2 vaccine (Pfizer-BioNTech), has been initiated from June 2021 and had follow-up period of 6 months, at four hospitals in Japan. Serum samples and peripheral blood monocytes (PB-MCs) were collected at baseline, 3 weeks after the first vaccination, and 5 months after the second vaccination. Quantitative antibody testing was performed using the Roche Elecsys Anti-SARS-CoV-2 spike subunit 1 assay that measures antibodies to SARS-CoV-2 spike protein 1 and to SARS-CoV-2 nucleoprotein. PBMCs were analyzed using flow cytometry to detect proportions of B cells, Th1, Th17, Treg, and Tfh cells. A questionnaire was given for subjects on each visit to ask prior respiratory infection and history of close contact with COVID-19 patients. [Results] A total of 50 Japanese patients with low disease activity of RA on DMARDs and 30 healthy controls were recruited. 20 patients were on csDMARDs only, 17 patients were on anti-cytokine directed biologics in monotherapy or combination therapy, 8 patients were on abatacept, and 5 patients were on JAK inhibitors in monotherapy or combination therapy. Our study will demonstrate the beginning and the persistence of the humoral and cellular immune responses against anti-SARS-CoV-2 vaccines in RA patients on DMARDs.

## ICW10-5

### Salazosulfapyridine as prophylaxis for pneumocystis pneumonia in patients with rheumatoid arthritis: A retrospective propensity score-matched cohort study

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Conflict of interest: None

Background Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii* and a potentially fatal infection for immunosuppressed individuals, including patients with rheumatoid arthritis (RA). Recently, some retrospective studies have indicated the preventive effect of salazosulfapyridine (SASP), a conventional synthetic disease modifying anti-rheumatic drug (csDMARD), on the development of PCP. Given the cross-sectional nature of them, the findings remain to be verified by other methods. Objectives This study aimed to investigate the potential of SASP as primary prophylaxis for PCP in RA patients. Methods We retrospectively reviewed medical records in RA patients who started to receive csDMARDs, biological DMARDs or targeted synthetic DMARDs from 2006 to 2020 in our hospital. Patients were classified into two groups according to the use of SASP. The incidence of PCP was assessed in the two groups. Diagnosis of PCP was based on the presence of clinical features, characteristic radiographic findings, elevated serum  $\beta$ -D-glucan levels and Polymerase Chain Reaction as well as Grocott staining in the cytopathology. We performed a 1:1 propensity score (PS) matching using nearest neighbor matching to minimize baseline imbalance and reviewed efficacy outcome in the post-matched population. Results This study included 580 patients with 114 in the SASP group. 16 PCP cases occurred during a total of 580.5 person-years. Univariable Cox-proportional hazards regression analysis in the PS-matched population ( $n=97$  in both groups) revealed that the use of SASP significantly reduced the 1-year incidence of PCP (Hazard Ratio (HR) 0.09; 95% confidence interval (CI) 0.00-0.79,  $p=0.03$ ). The result was confirmed by multivariable analysis (adjusted HR 0.06; 95% CI 0.00-0.58,  $p=0.01$ ). Conclusion The current propensity score-matched cohort study verifies the prophylactic effect of SASP against PCP. The beneficial off-target effect of this traditional DMARD may have an impact in the treatment of RA.

## ICW10-6

### Efficacy and safety of molecular-targeted treatment in combination with antibacterial therapy for rheumatoid arthritis associated with pulmonary non-tuberculous mycobacterial disease-FIRST registry

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Conflict of interest: None

[Objective] The prevalence of pulmonary non-tuberculous mycobacterial disease (PNTM) in rheumatoid arthritis (RA) is high, and the introduction of biologic and targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) may be a factor in the development and progression of PNTM. In this study, we performed computed tomography (CT) scan before the introduction of b/tsDMARD to accurately diagnose PNTM associated with RA and investigated the efficacy and safety of the b/tsDMARD in combination with NTM therapy. [Methods] Among the 3832 patients with RA whose chest CT was performed before the introduction of b/tsDMARD, 28 patients who were suspected of having pulmonary lesions based on CT and diagnosed PNTM were included in this study. In these patients, b/tsDMARD was introduced along with NTM treatment (PNTM group). The primary endpoint was the b/tsDMARD continuation rate of the PNTM and non-PNTM groups at 24 months post-introduction. [Results] There were no significant differences between the PNTM and non-PNTM groups in the b/tsDMARD continuation rate at 24 months (PNTM: non-PNTM group = 53.6%: 64.9%,  $p=0.39$ ). The effect of PNTM complications on the b/tsDMARD continuation rate was adjusted for sex, age, BMI, ACPA positivity rate, history of using b/tsDMARD, and of using TNF inhibitors, and was analyzed using the Cox proportional hazard model; PNTM complications did not affect the continuation rate (hazard ratio, 1.34; 95% CI, 0.80-2.24,  $p=0.26$ ). No significant difference in RA disease activity was noted between the two groups at 24 months (PNTM: non-PNTM group = CDAI 7.7 (IQR 4.20-15.8) vs 5.7 (IQR 1.60-13.4),



p=0.15). PNTM relapse was not observed in the 25 patients who continued NTM treatment, but it was observed in one of the three patients who did not. [Conclusions] PNTM in patients with RA, as well as RA disease activity itself, can be controlled without relapse of PNTM, by continuation of molecular-targeted treatment with concomitant NTM treatment.

## ICW11-1

### Development and practical application of scoring system for the Sharp/van der Heijde score using convolutional neural network

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Conflict of interest: None

**Objective:** To construct scoring system for the Sharp/van der Heijde score (SHS) and explore applications for research settings. **Methods:** First, we constructed U-net base model to identify the coordinates of each joint to extract images for each joint. Then, the model extracted 35,640 joint images from 2,376 hand radiographs with SHS. Next, to score SHS, we constructed an Efficient-net based scoring system that incorporates transfer learning, self-Attention, deep-mutual learning, and additional information on dislocations, ankylosis, collapse, and erosions from Single Shot MultiBox Detector. To assess effects of ACPA and treatments of RA on joint destruction, we divided the 1,393 radiographs within 8 years from onset of RA by the year they were taken (Y1: -2002, Y2: 2003-2010, Y3: 2011-) and examined difference of SHS and ulnar dislocation angle (UDA) between patients with and without ACPA within each calendar period. Y1 corresponds to pre-bDMARD era, Y2 to early bDMARD era, and Y3 to post-approval of 16 mg/week of MTX in Japan. **Results:** U-net was tested to predict 6215 joint coordinates using images resized to 224x224. The average pixel distance between the predicted and correct coordinates was 1.4 pixels. 100% of the predicted coordinates were within 10 pixels of the correct coordinates. The correlation coefficients of SHS between the system and the specialists were 0.815 for erosion and 0.846 for JSN. Our model outperformed the inter-rater reliability of JSN scores by specialists reported previously. JSN scores of Y1 and Y2, and erosion scores of Y1 showed significant differences between ACPA positive and negative patients, but no difference was observed in UDA (Y1~Y3), JSN scores of Y3 and erosion scores of Y2 and Y3 between the two groups. **Conclusion:** We constructed a high-performance scoring system. Our analysis suggested that UDA may progress due to factors other than ACPA.

## ICW11-2

### Identification of new predictors of joint destruction using machine learning in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

**Objective:** To identify new predictors of joint destruction by analyzing hand radiographs using machine learning. **Methods:** First, we constructed a convolutional neural network (CNN) to calculate three indices: Sharp/van der Heijde score (SHS), carpal height ratio (CHR), and ulnar deviation angle (UDA). Next, we calculated three indices using the CNN for the hand radiographs of patients taken at multiple time points. (Y-1: -2002, Y-2: 2003-2010, Y-3: 2011-) (N=460). Finally, to predict the progression of joint destruction, we defined the objective variable as the difference in SHS between years (Y-N~Y-M) ( $\Delta$ SHSY-N: Y-M) > imaging interval (years) x2. The explanatory variables were selected automatically from the clinical factors (ACPA, RF, sex, age of onset), CHR, UDA, and the erosion (16 joints) and JSN (15 joints) scores evaluated in SHS in the reference year (Y-M) using Boruta method, which created fake variables, trained a random forest model (RFM), and compared the feature impor-

tance of fake and original variables. We constructed RFM with and without Boruta for  $\Delta$ SHSY3: Y2 with 5-fold cross validation, and tested the best AUC model with  $\Delta$ SHSY2: Y1. **Results:** The correlation coefficients of SHS between the CNN model and the specialists were 0.815 for bone erosion and 0.846 for joint space narrowing. Boruta selected, ACPA, RF, age of onset, CHR, UDA, the erosion score of trapezium, and JSN scores between trapezium and scaphoid and between scaphoid and capitate. The AUC of RFM without Boruta for  $\Delta$ SHSY-3: Y-2 was 58.6, and for  $\Delta$ SHSY-2: Y-1, was 62.5 and the AUC of RFM with Boruta for  $\Delta$ SHSY-3: Y-2 was 61.2, and for  $\Delta$ SHSY-2: Y-1, was 67.5. **Conclusion:** We constructed a high-performance CNN to predict  $\Delta$ SHS and showed possible contribution of CHR, UDA, and the erosion score of trapezium, the JSN scores between trapezium and scaphoid and between scaphoid to predicting progression of joint destruction.

## ICW11-3

### Femoral cortical thickness in patients with rheumatoid arthritis and correlation with disease activity score 28

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Conflict of interest: None

[Objection] It is well known that patients with RA have bone insufficiency. However, little is known about cortical bone thickness in patients with RA. This study aimed to evaluate the femoral cortical thickness and compare them with healthy controls (HC). [Subjects and Methods] Forty-eight RA patients who underwent TKA or THA due to destructive joints were registered. The average age at the surgery was 67 years, average RA duration was 14 years, BMI was 23.8 kg/m<sup>2</sup>, and DAS28 before surgery was 2.18. The DICOM data from preoperative computed tomography of the whole lower limb were used. The femoral cortical thicknesses were equally divided into 3 regions, such as proximal, central, and distal diaphysis areas and classified as anterior, posterior, medial, and lateral parts. These divisions were measured using Stradwin® software. Data were standardized by body length. A correlation analysis between standardized cortical thickness and each parameter related to RA was performed. In addition, the statistical difference in femoral cortical thickness was analyzed between RA and HC. Statistical significance was determined at p-value <0.05. [Result] In the RA group, femoral cortical thicknesses in proximal diaphysis-posterior (PP), proximal diaphysis-medial (PM), central diaphysis-anterior (CA), and central diaphysis-medial (CM) areas were negatively correlated with DAS28 (PP, r=-0.218, p=0.035; PM, r=-0.206, p=0.047; CA, r=-0.206, p=0.011; and CM, r=-0.251, p=0.015). The average femoral cortical thicknesses of distal diaphysis-anterior (DA) and distal diaphysis-medial (DM) areas in the RA group showed a significant decrease compared to the HC group (DA; 3.14 mm in the RA group vs. 4.42 mm in the HC group, and DM; 3.35 mm versus 4.60 mm, both p<0.001). [Conclusion] In the RA group with destructive knee and hip, femoral cortical thickness became thin and had higher disease activity. Femoral cortical thicknesses in DA and DM areas were significantly thin in RA patients.

## ICW11-4

### Estimating deep remission using concordance of clinical and imaging remission using ultrasonography in rheumatoid arthritis receiving different biologic agents

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Conflict of interest: None

[Objective] To clarify the deep remission through the concordances clinical and US imaging remission among RA by different mechanism of bDMARDs. [Methods] We enrolled 57 RA patients in clinical remission defined as Disease Activity Score in 28 joints (DAS28) < 2.6 receiving treatment with a biologic agent including TNF- $\alpha$  antagonists (TNFa; n=31) and IL-6 receptor blocker (IL6Rb; n=26). All patients were per-

formed US examination of 44 joints (based on DAS44) and physicians and US evaluations were reciprocally blinded. US images of gray scale (GS) and power Doppler (PD) were evaluated by semi-quantitative scoring 0-3. Definition of US imaging remission was no PD signal in any assessed joint. [Results] Baseline characteristics including median age, disease duration and clinical remission duration and proportion of SDAI, CDAI and Boolean-based remission were similar in both patient with TNFa and IL-6Rb. The concordance of clinical and US imaging remission was significantly higher in TNFa (TNFa 74.3% vs IL6Rb 31.7%,  $p=0.01$ ), although the proportion of CDAI and of Boolean remission in IL6Rb group was 92.3% (24/26) and 68.4% (17/26), respectively. The residual US synovitis scores of GS and PD in 44 joints were significantly higher in IL6Rb group (GS (44); TNFa  $1.2 \pm 2.0$  vs IL6Rb  $4.7 \pm 4.5$ ,  $p < 0.01$ , PD (44); TNFa  $0.9 \pm 1.5$  vs IL6Rb  $3.2 \pm 3.5$ ,  $p < 0.01$ ). US PD synovitis scores in IL6Rb correlated with HAQ score (Rs 0.55,  $p < 0.01$ ). Receiver operating characteristic curve found the DAS28 of 1.94 in TNFa (AUC; 0.66, Sensitivity 62%, Specificity 70%) and DAS28 of 1.30 in IL6Rb (AUC; 0.60, Sensitivity 81%, Specificity 70%) discriminated the both clinical and US imaging remission, respectively. [Conclusions] Our results showed that the significant discordance of clinical and US imaging remission in RA patients receiving TNFa and IL-6b. We suggest that each estimated DAS28 target according to US imaging remission may helpful to consider deep clinical remission in RA using biologic agents.

## ICW11-5

### Baseline ESR level predicts long-term inhibition of radiographic progression by tocilizumab: the KURAMA cohort

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Conflict of interest: None

[Objective] Tocilizumab (TCZ) is endorsed as one of the biological disease-modifying anti-rheumatic drugs (bDMARDs) for RA patients who are not controlled by conventional synthetic DMARDs. The short-term effect of TCZ on radiographic progression has been reported; however, reports on its long-term effect are scarce. In this study, we aimed to evaluate the long-term inhibitory effect of TCZ on joint destruction in patients who had been treated with TCZ for at least 2 years. [Methods] RA patients who had been treated with TCZ for more than 2 years and for whom X-rays were available in the Kyoto University were included. Radiographic progression was evaluated with van der Heijde modified Total Sharp Score (mTSS) by two rheumatologists at TCZ introduction and after more than 2 years. Multivariate logistic regression analysis was used to identify factors associated with structural remission defined as the mean annual change in mTSS  $\leq 0.5$ . [Results] Of the 59 patients included in this study (median age: 62 years, female: 81.4%, median disease duration: 7 years, ACPA-positivity: 83.1%, median CDAI at TCZ introduction: 13.30, median duration of TCZ: 3.13 years), 34 patients (57.6%) fulfilled the definition of structural remission. Patients who achieved structural remission had significantly lower baseline levels of ESR (36.81 mm/h vs 61.28 mm/h,  $P=0.004$ ) and tended to have lower baseline CRP levels (1.69 mg/dL vs 4.02 mg/dL,  $P=0.052$ ) than those who did not. Multivariate logistic regression analysis demonstrated that baseline ESR level was significantly associated with structural remission (odds ratio: 0.97, 95%CI: 0.948-0.999,  $P=0.044$ ). Receiver operating characteristic curve analysis yielded the cut-off value of ESR as 35 mm/h (AUC: 0.73, 95%CI: 0.58-0.89,  $P=0.0085$ ). [Conclusions] Our study results demonstrated that baseline ESR level is a critical determinant for long-term inhibitory effect of TCZ on joint destruction.

## ICW11-6

### Dynamic functional connectivity associated with response to biologics in rheumatoid arthritis and spondyloarthritis

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Conflict of interest: None

[Objective] Dynamic functional connectivity (dFC) analysis is a method to investigate dynamic changes of the brain activity using resting-state functional magnetic resonance imaging (rs-fMRI). Our previous studies showed the association between specific FC and pain in inflammatory arthritis (IA) including rheumatoid arthritis (RA) and spondyloarthritis (SpA), but did not consider the dynamics of FC fluctuation over time. In this study, we explored the significance of dynamics of FC by comparing dFC and the response to biologics in patients with IA. [Methods] We analyzed the retrospective ( $n=33$ : RA 22, SpA 11) and prospective dataset ( $n=31$ : RA 19, SpA 12) of IA patients on biologics who underwent rs-fMRI before biologics treatment. The dFC was calculated as time-varying FCs in short-time scales, and their patterns were classified using cluster analysis. Treatment response was evaluated with the American College of Rheumatology 20 (ACR20)/Assessment of Spondyloarthritis International Society response criteria 20 (ASAS20) and patient's global assessment (PGA) at 3 months after treatment. The correlation between occurrence probability of each dFC pattern and clinical indices was analyzed. [Results] In retrospective dataset, four patterns of dFC were identified (pattern1-4). The occurrence probability of pattern 3 was significantly higher in the group of ACR20/ASAS20 responder than that in non-responder ( $p < 0.05$ ) and significantly correlated with the improvement rate of patient global assessment (PGA) ( $R=0.3$   $P=0.032$ ). These results were validated in the prospective dataset. The dFC pattern 3 represented higher functional corticocortical correlations, including subcortical regions, compared to other patterns. [Conclusions] We identified a specific dFC pattern associated with response to biologics and found its correlation with PGA in patient with IA. Assessment of dFC may provide an objective evaluation of patient-reported outcomes such as PGA in future.

## ICW12-1

### Disease-specific characteristics of immune cells in BALF and blood from connective tissue disease-associated interstitial lung disease patients analyzed by single-cell RNA sequencing

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Conflict of interest: None

[Objective] Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a serious complication of various autoimmune diseases. Its mechanisms are also variable. We try to clarify the pathological difference of CTD-ILD complicated by different autoimmune diseases. [Methods] From September 2019 to December 2020, we collected bronchoalveolar lavage fluid (BALF) through bronchoscopy and peripheral blood from 5 rheumatoid arthritis (RA), 4 dermatomyositis (DM), 4 Sjogren's syndrome (SS), 2 systemic sclerosis (SSc) patients who complicated interstitial lung disease, and 7 idiopathic pulmonary fibrosis (IPF) patients as controls. We applied Seq-Well, a robust, portable, and cost-efficient platform for massively parallel single-cell RNA sequencing to analyze immune cells in BALF and blood. We compare the distribution of immune cells and differential gene expressions in BALF and blood for each disease. [Results] We found that cells in BALF and blood had a characteristic pattern for each disease. In BALF, we found more neutrophils in RA patients, while T cells increased in DM patients and B and T cells in SS patients. Alveolar macrophages (AMs) were major cell types in all diseases except SS patients. Therefore, we further classified AMs into more

detailed subsets based on gene expression patterns and compared them between each disease. In SSc patients, we found that there was an increase in AMs that highly expressed C1q-related genes and genes related to cell division and proliferation. In RA patients, AMs, which highly express genes related to inflammatory cytokines, increased. In blood, neutrophils increased in RA patients, and B and T cells increased in DM, SS, and SSc patients. [Conclusions] In CTD-ILD, we found differences in the distribution of immune cells and gene expression patterns among diseases, which may reflect the pathology of each disease. These differences will lead to the optimal diagnosis of CTD-ILD patients and precision medicine.

## ICW12-2

### **NLRP3 inflammasome activation mechanism of Cold-inducible RNA-binding protein (CIRP) in innate immune cells**

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Conflict of interest: None

[Objective] IL-1 $\beta$  production is dependent on inflammasome activation, which requires a priming signal, followed by an activating signal. Cold-inducible RNA-binding protein (CIRP) belongs to a cold-shock proteins family upregulated in various stress condition such as hypothermia, irradiation, and hypoxia. Recently, extracellular CIRP has been identified as danger-associated proteins. Monosodium urate (MSU) acts as activation signal of NLRP3 inflammasome activation. The aim of this study is to clarify the role of CIRP in MSU-mediated IL-1 $\beta$  secretion using human neutrophils. [Methods] Human neutrophils were stimulated with MSU and CIRP. IL-1 $\beta$  or caspase-1 (p20) production in cellular supernatants were analyzed by enzyme-linked immunosorbent assay (ELISA). The cellular lysates were visualized by immunoblotting using anti-cleaved IL-1 $\beta$  or anti-cleaved caspase-1 antibodies. [Results] CIRP or MSU stimulation alone did not result in the efficient IL-1 $\beta$  secretion from human neutrophils. However, CIRP-primed neutrophils stimulated with MSU induce IL-1 $\beta$  secretion in a dose-dependent manner. The expression of cleaved IL-1 $\beta$  (p17) and cleaved caspase-1 were observed in CIRP-primed neutrophils stimulated with MSU. Additionally, CIRP stimulation induced the protein expression of pro-IL-1 $\beta$ . The expression of cleaved IL-1 $\beta$  (p17) was inhibited by the pretreatment of MCC 950, which is a specific inhibitor for NLRP3 inflammasome. [Conclusions] CIRP can be an important priming stimulus for MSU-mediated IL-1 $\beta$  production in human neutrophils. We propose that CIRP acts as a proinflammatory stimulant that activates NLRP3 inflammasome and pro-IL-1 $\beta$  processing in response to uric acid in innate immune cells.

## ICW12-3

### **Large-scale immune cell-type-specific gene expression atlas revealed critical transcriptome architecture underlying the disease establishment and exacerbation of systemic lupus erythematosus**

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Conflict of interest: Yes

[Objective] Systemic lupus erythematosus (SLE) is a complex autoimmune disease with unknown etiology involving multiple immune cells and diverse clinical phenotypes. Cell-type-specific transcriptome analysis

using patients with multiple clinical statuses has a promise to elucidate its pathogenesis. [Methods] We purified 27 immune cell types from 136 SLE patients with diverse clinical presentations and 89 healthy volunteers and investigated their RNA-sequencing data. [Results] We first profiled two distinct cell-type-specific transcriptomic signatures: disease-state and disease-activity signatures associated with case-control and case-case contrast, respectively. After confirming the high replicability of both signatures in independent cohorts, we identified different cell-type-specific biological processes driving these signatures: e.g., upregulated *E2F* transcriptional activity in Th1, CD8<sup>+</sup> memory T-lineage, and NK cells and dynamic increase of *IL21* and *CXCL13* in Th1 cells in an active phase of SLE. Moreover, we elaborated the clinical utility of disease-activity signatures as biomarkers for clinical phenotypes and therapeutic response: (i) activity signatures from myeloid-lineage cells were specific to severe organ involvements (e.g., lupus nephritis and neurological manifestations) and (ii) belimumab and mycophenolate mofetil suppressed activity signatures of B cell-lineage cells and plasmablast, respectively, especially in good responders. However, in-depth integrative analyses with genetics findings (GWAS and eQTL results), we observed that current SLE GWAS risk alleles based on case-control study design were predominantly enriched around disease-state signatures and could not reflect the disease-activity signatures. [Conclusions] Our study identified comprehensive gene signatures reflecting the establishment and exacerbation of SLE, which would be an essential basis for future genomic and genetic studies.

## ICW12-4

### **TIGIT agonistic signaling selectively and efficiently suppresses T follicular helper cells and subsequent B cell differentiation and antibody production**

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Conflict of interest: Yes

[Objective] T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) is selectively expressed in T cells and plays a critical role in T cell homeostasis. We previously showed that TIGIT expression on CD4<sup>+</sup> T cells is elevated in some autoimmune diseases and correlated with disease activity. However, the precise functional properties of TIGIT signaling to T cell subsets has not been elucidated. [Methods] Measurement of TIGIT expression and isolation of T cell subsets from peripheral blood of healthy individuals was done with a flow cytometer and cell sorter, respectively. Functional assay was performed using newly developed anti-human TIGIT agonistic monoclonal antibodies (mAbs). [Results] In 15 healthy individuals, the proportion of TIGIT surface expression was significantly higher in CD45RA<sup>+</sup> CXCR5<sup>+</sup> T follicular helper (Tfh) cells and CXCR5<sup>+</sup> T PD1<sup>high</sup> peripheral helper cells, at an average 69.1% and 61.5%, compared with 16.3% in total CD4<sup>+</sup> T cells. In addition, TIGIT expression in the Tfh subset was significantly enhanced after 4 days culture with stimulation by anti-CD3/CD28 antibody, while that in non-Tfh cells and naive T cells remained unchanged even after stimulation. Next, when we treated Tfh and non-Tfh cells with anti-TIGIT agonistic mAbs (or isotype control) under stimulation, agonistic intervention of TIGIT signaling had stronger suppressive activity in Tfh cells than non-Tfh cells (90.3% vs 40.1%,  $p=0.0025$ ). To confirm the functional effect on B-cell differentiation and IgG production, Tfh and CD27<sup>+</sup> memory B cells were purified and co-cultured for 7 days with the mAbs (or isotype control). TIGIT signaling decreased differentiation to plasma cells (44.8%,  $p=0.04$ ) and IgG production (69.8%,  $p=0.02$ ) compared with the isotype. [Conclusions] Targeting the TIGIT signal may become a useful option in correcting T cell-dependent B cell abnormality in autoimmune disease.

## ICW12-5

### **Recruitment of Treg cells by using irrelevant antigen is not enough to suppress T cell response to unknown antigens**

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Conflict of interest: None

[Objective] Effective recruitment and stimulation of Treg cells would be an crucial factor to obtain a higher performance of Treg cell therapy. Utilization of some introduced antigens for this purpose sounds like a suitable solution to suppress an unwanted inflammation. However, it remained unresolved whether both suppressive function and recruitment function to the target site work together. [Methods] (1): Recruitment-antigen specific Tregs (R-Treg) were transferred into syngeneic mice intravenously together with naive CD4 T cells specific for recruitment-Ag, CD4 T cells for target-Ag, and DCs that had been pulsed with both recruitment-Ag and target-Ag (DC-RT). Harvested lymphocytes were analyzed on day 3 to determine the antigen specificity of the suppression. (2) DC-RT were separated from the culture between the DC-RT and R-Treg, and were analyzed for their ability to stimulate effector T cells specific for recruitment-Ag or for target-Ag. [Results] (1): R-Treg did not suppress T cell response to target-Ag but suppressed recruitment-Ag T cell response. (2): Suppression formed on DC-RT was antigen specific. A suppression of T cell response to the target-Ag was only observed when T-Treg were used for the culture with DC-RT. [Conclusions] Utilizing irrelevant-Ag to recruit Tregs to the inflammation site where target DCs are located is not an effective way to suppress pathogenic T cells responses to the causative, target antigens that are sometimes unknown in autoimmune diseases.

## ICW12-6

### Transcriptome-wide association study of immune-related traits using a large-scale immune cell gene-expression database

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Conflict of interest: Yes

[Background] Although genome-wide association studies (GWAS) have clarified thousands of disease-associated genetic polymorphisms, their functions are largely unknown, harboring our deeper understanding of the disease pathogenesis. Transcriptome-wide association study (TWAS) is known as a method to prioritize causal genes by integrating the results of GWAS and the expression quantitative trait loci (eQTL) analyses. TWAS can bridge the genetic variants to genes, for which we can interpret the function. To gain meaningful insights about the disease pathogenesis from TWAS, using eQTL datasets of disease relevant cell types is crucial. Here, we utilized the eQTL data of dozens of immune cells from Immune Cell Gene Expression Atlas from the University of Tokyo (ImmuNexUT), and performed TWAS with GWAS of immune-mediated diseases. [Methods] TWAS consists of two steps: making gene expression prediction models from eQTL dataset and applying it to GWAS results. For the former step, we compared and fine-tuned existing state-of-the-art methods and tested their performance with the independent dataset. Then we applied the model to GWAS data of immune-mediated diseases. [Results] Our model enabled us to predict the gene expression of immune cells from the genotype data with high accuracy (approximate median  $r=0.3$  in the independent dataset). By applying this model to rheumatoid arthritis GWAS, we detected candidate gene sets related to disease onset. These genes included previously underrecognized genes as well as reported genes. Notably, some of these associations were observed only in a specific immune cell type or lineage, indicating the cell type specific functions of disease-associated variants. [Conclusions] Here we reported the construction of immune cell type specific TWAS model in an unprecedented scale. Our approach has a potential to elucidate the subset-specific effects of disease-associated variants and the causal genes of a wide variety of immune-mediated diseases.

## ICW13-1

### Clinical and laboratory features of patients with primary Sjögren's syndrome with and without drug allergy

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Conflict of interest: None

[Objective] A high prevalence of allergic disorders was found in patients with primary Sjögren's syndrome (pSS). Nevertheless, it was not clear what is a risk factor for drug allergy in patients with pSS. Drug allergy may lead to delayed treatment and unnecessary clinical tests. The aim was to investigate the risk factors for drug allergy in the pSS patients. [Methods] We retrospectively examined consecutive patients diagnosed with pSS in our hospital from 2010 to 2020. The patients with pSS met the criteria of the 1999 revised Japanese Ministry of Health criteria. Drug allergy was defined as rash, angioedema or anaphylaxis after drug ingestion. The analysis was performed on risk factors for drug allergy by univariate and multivariate analysis. [Results] There were 77 pSS patients with drug allergy and 215 without drug allergy. The mean ages of pSS patients with and without drug allergy were 56.0 and 57.8 years old, respectively. Females were 96.1% and 93.5%, respectively. The pSS patients with drug allergy had higher levels of IgG ( $2028 \pm 1409$  mg/dL,  $1726 \pm 587$  mg/dL:  $p = 0.01$ ), higher levels of eosinophils ( $220 \pm 247/\mu\text{L}$ ,  $126 \pm 112/\mu\text{L}$ :  $p < 0.01$ ), and higher positivity rate of anti-SSA antibody (89.6%, 79.2%:  $p = 0.06$ ) than those without drug allergy. We found that higher levels of IgG and eosinophils, and positivity of anti-SSA antibody significantly affected drug allergy by univariate analysis ( $p < 0.05$ ). By multivariate analysis among IgG, eosinophils, anti-SSA antibody, sex and age, only higher levels of eosinophils, and positivity of anti-SSA antibody had significantly affected drug allergy ( $p < 0.05$ ). [Conclusions] Among patients with pSS, the risk factors for drug allergy were higher levels of eosinophils and positivity of anti-SSA antibody.

## ICW13-2

### Effect of smoking on serum IgG4 during health checkups in Nagasaki Island Study (NaIS)

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Conflict of interest: None

[Objective] We attempted to verify the accuracy of the magnetic bead panel assay (MBA), which can evaluate IgG4 levels with only a few ml of serum compared to the nephelometric immunoassay (NIA), which is conventionally used to measure IgG4. We also examined the relationship between IgG4 measured by the MBA and background information of healthy subjects (HS) in NaIS to identify variables that correlate with serum IgG4. [Methods] We collected 947 HS-samples in Kanazawa University, using IgG4 levels were measured by both MBA (IgG4-MBA, Merck, Germany) and NIA (IgG4-NIA, Binging Site, UK) methods, and the correlation between the two methods was verified using Spearman's rank correlation coefficient. The cutoff value of MBA corresponding to the cutoff of NIA (135 mg/ml) was determined. Serum IgG4 of 3240 samples of Nagasaki Island Study (NaIS) were measured by MBA, stratified between the two groups using the aforementioned cutoff values, and compared with background information. Serum IgG1, total IgG, and IgE were measured using MBA in 200 serum IgG4-positive subjects and 300 subjects randomly selected from 3200 negative subjects. [Results] IgG4-MBA correlated well with IgG4-NIA ( $r=0.94$ ,  $p\text{-value} < 0.0001$ ) and 1,463,550 ng/mL of IgG4-MBA corresponded to 135 mg/dl, the normal cut-off value for IgG4 by NIA. In the analysis of NaIS samples, the overall IgG4 positivity rate was 6.3%. Multivariable analysis by age, gender, smoking and alcohol con-

sumption showed that gender and smoking were significantly associated with serum IgG4 positivity (gender: odds ratio = 1.75, 95%CI = 1.15-2.65,  $p = 0.0086$ , smoking: odds ratio = 1.70, 95%CI = 1.12-2.54,  $p = 0.012$ ). [Conclusions] We concluded that MBA is a good method to measure serum IgG4 in health checkups. Our data showed that male and smoking are independent factors associated with serum IgG4 positivity.

### ICW13-3

#### **Malignancy complication can make distinct clinical features of IgG4-related disease**

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Conflict of interest: None

[Objective] The aim of this study is to investigate the clinical relevant of presence of malignancy in patients with IgG4-related disease (IgG4-RD). [Methods] We reviewed all consecutive patients with IgG4-related disease in Keio University Hospital between 2010 and 2021 and retrospectively collected clinical data from their medical records. We divided patients into two groups according to the presence of malignancy and compared their clinical characteristics. We defined the presence of malignancy as those diagnosed within two years before and after the diagnosis of IgG4-RD. [Results] A total of 134 patients with IgG4-RD were enrolled. The mean age at diagnosis was 61.1 years old, and 51.5% were male. Among them, 17 (12.7%) were complicated with malignancy. The types of malignancies were as follows; gastric cancer ( $n=3$ , 17.6%), bladder cancer ( $n=2$ , 11.8%), and others ( $n=12$ , 70.6%). Malignancy preceded in 6 (35.3%), IgG4-RD preceded in 8 (47.1%) and concurrent diagnosis in 3 (17.6%). The proportion of male and smoking history, and age at diagnosis of IgG4-RD were significantly higher in the malignant group (76.5 vs 47.9%,  $p=0.037$ ; 76.5% vs 46.2%,  $p=0.035$ ; 69.6 vs 59.8 years,  $p=0.007$ , respectively). Proportion of patients with allergic history was significantly lower in the malignancy group (17.6 vs 52.6%,  $p=0.009$ ). There was no difference between the two groups in the number and types of affected organs, baseline serum IgG4 levels, and the relapse rate of IgG4-RD. [Conclusions] IgG4-RD complicated with malignancy may be a distinct clinical phenotype of IgG4-RD.

### ICW13-4

#### **Artificial Neural Networks Approaches to Predict Myocardial Fibrosis in Primary Sjögren Syndrome Patients without Cardiac Symptoms**

Marina Hamaguchi, Hitomi Haraoka, Shinya Asatani, Masahiro Nishihara, Yutaka Tanikawa, Shoei Yoshizawa, Hiroshi Tsuzuki, Yosuke Nagasawa, Kaita Sugiyama, Masako Tsukamoto, Kumiko Akiya, Noboru Kitamura, Masami Takei, Hideki Nakamura

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Conflict of interest: None

[Objective] A recent meta-analysis showed that the probability of heart failure (HF) was higher in primary Sjögren syndrome (pSS) patients. Myocardial abnormalities antedating onset of HF can be early assessed by Cardiac magnetic resonance imaging (CMR). Global longitudinal strain (GLS), using non-contrast feature tracking CMR (FT-CMR) relates to the extent of myocardial fibrosis corresponding to late gadolinium enhancement (LGE). As artificial neural networks (ANNs) are considered as an established method to analyse large datasets, this study aimed to predict the onset of myocardial fibrosis assessed by FT-CMR and LGE in pSS utilizing ANNs models. [Methods] We conducted a cross-sectional study of pSS patients, who underwent CMR, without cardiac symptoms. We used a random forest classifier to predict myocardial abnormalities in two indices (LGE, GLS). This is an algorithm that uses multiple decision trees for classification, which were finally reduced to 10 (e.g., age, duration, Raynaud phenomenon, BMI, Framingham score, ESR, rheumatoid factor, IgG, HbA1c, and NT-proBNP) by feature selection based on the trained model. [Results] We evaluated 52 patients with pSS (100% women; mean age,  $59.5 \pm 9.0$  years) and 20 controls (100% women; mean age,  $55.7 \pm 4.5$  years). All subjects underwent FT-CMR, and 52 patients underwent LGE. The pSS group had significantly lower GLS ( $p = 0.015$ ). Abnormal

LGE was seen in 10/52 (19%). A created mathematical model enabled to predict abnormal GLS and LGE with an area under the curve value of 0.72 and 0.79, respectively. The accuracy, specificity, positive predictive value, and negative predictive value for prediction of abnormal GLS and LGE were 88%, 40%, 100%, 100%, 86% and 67%, 30%, 88%, 56%, 70%, respectively. [Conclusions] This mathematical model, which potentially identifies pSS patients with myocardial fibrosis using laboratory values and clinical items, could be employed in clinical settings as a prediction tool.

### ICW13-5

#### **The Survival and Prognosis Prediction Model of Interstitial Lung Disease Associated with Primary Sjögren's syndrome**

Ziwei Liu<sup>1</sup>, Mengtao Li<sup>1</sup>, Rong Zhang<sup>2</sup>, Jing Xue<sup>3</sup>, Wei Wei<sup>4</sup>, Xinwang Duan<sup>5</sup>, Yi Zheng<sup>6</sup>, Jing Tian<sup>7</sup>, Yanjie Hao<sup>8</sup>, Qian Wang<sup>1</sup>, Dong Xu<sup>1</sup>, Jiuliang Zhao<sup>1</sup>, Jvhong Shi<sup>1</sup>, Yanhong Wang<sup>1</sup>, Yan Zhao<sup>1</sup>, Xiaofeng Zeng<sup>1</sup>

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Conflict of interest: None

[Objective] Interstitial lung disease (ILD) is a severe complication of primary Sjögren's syndrome (pSS). We aimed to investigate the long-term survival, and to develop a multidimensional prognosis prediction model for pSS-ILD. [Methods] A multi-center, retrospective cohort of patients with pSS-ILD was enrolled. All patient performed chest high resolution CT and pulmonary function test. The CT scans were collectively reviewed by experienced radiologists. The primary end point was all-cause death. Lasso regression was used to screen candidate variables according to the accessibility, stability and literature knowledge of the factors. Multiple Cox regression and nomogram were used to develop and present the risk prediction model. The model was tested for accuracy and robustness by concordance-index, calibration curve and Brier score. [Results] A total of 188 patients with pSS-ILD were enrolled from 11 centers in China, including 33 patients died during follow-up ( $4.01 \pm 1.71$  years). Among all patients, 90.4% were female. The most common radiology pattern was non-specific interstitial pneumonia (43.4%). The 1-, 3-, and 5-year survival rates were 94.1%, 85.0%, and 82.7%, respectively. The final prediction model included five clinical variables (gender, history of smoking, crackles sign, CRP, and DLCO%). A 5-year survival probability-predictive nomogram was established. The model was validated by concordance-index (0.740), calibration curve and Brier score (0.018). [Conclusions] This study presented the robust long-term survival of pSS-ILD in a multi-center cohort. We developed a prognosis prediction model using routine clinical assessments. This model may effectively predict the survival rates and be useful for physicians to make individual treatment and follow-up strategies.

### ICW14-1

#### **Crucial involvement of macrophage infiltration regulated by chemokine receptors, CCR2 and CCR5, in glomerular endocapillary hypercellularity in lupus nephritis**

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Conflict of interest: None

[Objective] Lupus nephritis (LN) comprises various glomerular lesions, including endocapillary hypercellularity with macrophage infiltration. However, the involvement of macrophage-tropic chemokine receptors in the pathogenesis of these glomerular lesions has not been clear. [Methods] MRL/lpr mouse-derived monoclonal IgG3 antibody-producing hybridomas, 2B11.3 and B1, were injected into BALB/c mice (WT) to induce endocapillary hypercellularity and wire-loop lesions, respectively. The expression of chemokine and chemokine receptors was analyzed by qRT-PCR and immunofluorescence. The roles of chemokine receptors in these lesions were evaluated using chemokine receptor-deficient mice or a

selective CCR5 antagonist, maraviroc. [Results] 2B11.3 caused glomerular endocapillary hypercellularity with a significant number of CD68-positive macrophages. Further, enhanced expression of CCL2, CCL3, CCR2, CCR5, and CX3CR1 was observed in the renal cortex, compared to B1 injection, which induced wire-loop lesions. In 2B11.3-injected mice, CD68-positive glomerular macrophages expressed CCL2, CCL3, CCR2, CCR5, and CX3CR1, while glomerular endothelial cells expressed CCL2, CCL3, and CX3CL1. In human LN, CD68-positive glomerular macrophages expressed CCR5 and CCL3, consistently. When 2B11.3 was injected, CCR2<sup>-/-</sup> and CCR5<sup>-/-</sup>, but not CX3CR1<sup>-/-</sup>, mice exhibited reduced endocapillary hypercellularity, attenuated glomerular macrophage infiltration, and improved serum blood urea nitrogen (BUN) levels. Only CCR2<sup>-/-</sup> mice developed wire-loop lesions. B1 injection caused wire-loop lesions in these chemokine receptor-deficient mice to a similar extent as WT. Maraviroc treatment reduced 2B11.3-induced endocapillary hypercellularity and improved serum BUN levels. [Conclusions] CCR2 and CCR5 regulate glomerular macrophage infiltration and contribute to endocapillary hypercellularity in LN. CCR5 inhibition can be a specific therapy for endocapillary hypercellularity without inducing wire-loop lesions.

## ICW14-2

### Hypoxia Promotes the Expression of ADAM9 by Tubular Epithelial Cells which Enhances TGF- $\beta$ 1 Activation and Promotes Tissue Fibrosis in Lupus Nephritis

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Conflict of interest: None

[Objective] Enhanced expression of transforming growth factor-beta (TGF- $\beta$ ) in the kidneys of patients with lupus nephritis (LN) can lead to progressive fibrosis, resulting in end-organ damage (J Immunol. 180, 1903-1912. 2008). We previously reported that a disintegrin and metalloproteinases 9 (ADAM9) enhances Th17 cell differentiation and autoimmunity by activating TGF- $\beta$ 1 (PNAS. 118, 2021). We hypothesized that ADAM9 in the kidney may accelerate fibrogenesis by activating TGF- $\beta$ 1. [Methods] We assessed the expression of ADAM9 in kidneys from MRL/lpr mice and control MPJ mice and determined the expression levels of ADAM9 in kidney cells. We conducted *in vitro* experiments using tubular epithelial cells (TEC) isolated from B6 mice and explored the mechanisms responsible for the upregulation of ADAM9 in tubular epithelial cells (TEC) and the subsequent activation of TGF- $\beta$ 1 by ADAM9 expressed in TEC. To assess the role of ADAM9 in the development of tubular-intestinal fibrosis in LN, we generated MRL/lpr. *Adam9*<sup>-/-</sup> mice and compared the intensity of renal fibrosis between *Adam9* sufficient and deficient MRL/lpr mice. [Results] We identified ADAM9 to be highly expressed in tubules from MRL/lpr mice. The transcription factor hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ) was found to promote the transcription of ADAM9 in TEC. TEC from *Adam9*-deficient mice exposed to the hypoxia inducer dimethylglycine (DMOG) failed to cleave the latency-associated peptide to produce bioactive TGF- $\beta$ 1 from latent TGF- $\beta$ 1. Co-culture of TEC from *Adam9*-deficient mice and fibroblasts with DMOG and latent TGF- $\beta$ 1 showed decreased production of type I collagen and alpha smooth muscle actin by fibroblasts. *Adam9*-deficient MRL/lpr mice showed mitigated tubular-intestinal fibrosis. [Conclusions] Our findings have revealed that hypoxia promotes the expression of ADAM9 by TEC which is responsible for the development of interstitial fibrosis in LN by promoting the generation of bioactive TGF- $\beta$ 1 for fibroblast.

## ICW14-3

### High levels of proteins, cell counts and IL-6 concentrations in cerebrospinal fluid are associated with damage accrual in patients with neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

[Objective] The aim of this study was to identify factors associated with damage accrual in patients with neuropsychiatric systemic lupus erythematosus (NPSLE). [Methods] We reviewed all patients with SLE who had attended our hospital between 2010 to 2020 retrospectively and analyzed clinical characteristics associated with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index (SDI) progression after the onset of NPSLE. [Results] 461 patients with SLE were reviewed. Among them, 37 (8.0%) were diagnosed with NPSLE. Thirty-five patients were included in the analysis after excluding two patients with insufficient information. Sixteen (45.7%) patients were new-onset and 19 were relapsed. At NPSLE onset, the mean age was 33.9 years, the mean SLEDAI 21.8, the mean observation period 10.0 years. The most frequent disease types according to the 1999 ACR classification were lupus headache in 10 patients, followed by seizure disorders in 8 patients and cerebrovascular disease in 7 patients. Nine patients (25%) had neuropsychiatric damage progression with SDI. Neuropsychiatric damage progression was not associated with SLEDAI-2K at NPSLE onset or positivity of anti-cardiolipin antibodies. In 21 patients who underwent cerebrospinal fluid (CSF) examination, CSF IL-6 was also associated with neuropsychiatric damage progression ( $p=0.032$ ). Also, high levels of CSF protein ( $p=0.030$ ), cell counts ( $p=0.007$ ), and IL-6 ( $p=0.032$ ) were associated with over all SDI progression. [Conclusions] CSF IL-6 concentrations are associated with neuropsychiatric damage progression, and high CSF protein, cell counts and IL-6 at onset in patients with NPSLE can predict damage accrual.

## ICW14-4

### Characterization and pathogenicity of CD8<sup>+</sup> T cells in patients with systemic lupus erythematosus - LOOPS/FLOW registry -

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Conflict of interest: None

[Objective] The pathological involvement of CD8<sup>+</sup> T cells in SLE remains unclear. We investigated the relationship between CD8<sup>+</sup> T cells and the clinical manifestations based on a large SLE cohort (LOOPS registry) and comprehensive immunophenotyping (FLOW study). [Methods] The study consisted of 211 SLE patients (mean age, 42.3 years; female ratio, 89%; mean disease duration, 112.8 months) who were first admitted to the hospital and enrolled in the LOOPS registry between November 2012 and December 2018 and 62 age-sex matched healthy controls (HC). Based on peripheral blood comprehensive immunophenotyping according to the NIH/FOCIS protocol, CD8<sup>+</sup> T cells were classified into naïve (CD45RA<sup>+</sup>CCR7<sup>+</sup>), central memory (CM) (CD45RA<sup>+</sup>CCR7<sup>+</sup>), effector memory (EM) (CD45RA<sup>+</sup>CCR7<sup>-</sup>), and EMRA (CD45RA<sup>+</sup>CCR7<sup>-</sup>) cells for cluster analysis. [Results] (1) The number of CD8<sup>+</sup> T cells in peripheral blood is increased in SLE compared with HC ( $p<0.001$ ). (2) Activated CD8<sup>+</sup> T cells correlated with anti-ds-DNA antibodies ( $r=0.497$ ,  $p<0.001$ ) and CH50 ( $r=-0.420$ ,  $p<0.001$ ), and significantly increased in patients with active lupus nephritis (renal BILAG  $\geq$  B) ( $p=0.004$ ). (3) SLE patients are classified into three subpopulations by cluster analysis of CD8<sup>+</sup> T cells: Group 1; low CD8<sup>+</sup> T cells, Group 2; high naïve, and Group 3; high EM/EMRA. Group 3 has high ds-DNA antibodies, hypocomplementemia and high disease activity SLE with BILAG A  $\geq$  1 or B  $\geq$  2 items ( $p<0.001$ ). In addition, activated cytotoxic T cells (aTc1 cells: CXCR3<sup>+</sup>CCR6<sup>+</sup>CD38<sup>+</sup>HLA-DR<sup>+</sup>) are markedly increased in this group. The aTc1 is significantly correlated with plasmablast (CD19<sup>+</sup>CD20<sup>+</sup>CD27<sup>+</sup>CD38<sup>high</sup>) ( $r=0.409$ ,  $p<0.001$ ), activated Th1 (CD4<sup>+</sup>CXCR3<sup>+</sup>CCR6<sup>+</sup>CD38<sup>+</sup>HLA-DR<sup>+</sup>) ( $r=0.811$ ,  $p<0.001$ ), Tfh (CD4<sup>+</sup>CXCR5<sup>+</sup>ICOS<sup>+</sup>) ( $r=0.290$ ,  $p<0.001$ ). [Conclusions] Activated CD8<sup>+</sup> T cells are increased in correlation with disease activity of SLE. In particular, Tc1 cells may be implicated in the pathogenesis of SLE through the possible association with Th1/Tfh/plasmablast axis.



## ICW14-5

### Increased IL-21 receptor expression level via glycolysis in B cells and its potential as a trigger for exacerbation of disease activity in SLE

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Conflict of interest: None

**Objectives;** B cells play an important role in SLE. Some triggers may induce exacerbations and flare-ups via B cell activation. However, its mechanism is unclear. Recently, immunometabolism attract much attention. In this study, we examined the initial activation mechanism of B cells in SLE from the viewpoint of immunometabolism. **Methods:** CD19<sup>+</sup> cells or naïveCD27<sup>+</sup>CD19<sup>+</sup> cells were isolated from peripheral blood of healthy controls (HCs) and SLE patients, and cultured with/without stimuli to evaluate cellular metabolism (flux analyzer), expression of cytokine receptors and transcription factors by PCR or flow cytometry. **Results;** (1) Stimulation of CD19<sup>+</sup> cells with BCR cross-linking, sCD40L and CpG rapidly increased extracellular acidification rate (ECAR), which indicates glycolysis, but not oxidative phosphorylation. (2) sCD40L and CpG stimulation increased mRNA expression of IL-2R, IL-21R and IFNGR1 at 6 h and protein level at 24 h. IL-21R and IFNGR1 expression levels were higher in naïve B cells. (3) IL-21 and IFN- $\gamma$  were added after 24 hours of sCD40L and CpG stimulation. The expression levels of IRF4 and PRDM1, transcriptional factors for B cell differentiation, were induced by IL-21 stimulation. (4) IL-21R expression induced by sCD40L and CpG was suppressed by glycolysis inhibitors such as 2-DG (hexokinase 2 inhibitor) and Hepatelicid acid (GAPDH inhibitor), but not other metabolic pathway inhibitors or glycolysis inhibitors. (5) The expression levels of glycolytic enzymes, GLUT1, p-S6, and p-mTOR in naïve B cells of SLE patients were increased compared to those of HCs. The serum level of IL-21 in SLE patients was also increased. (6) The expression levels of p-S6 and p-mTOR were positively correlated with SLEDAI in SLE patients. **Conclusion;** These results suggest that enhanced glycolysis is initially induced in naïve B cells, and IL-21 stimulation is trigger for exacerbation of disease activity in SLE. This mechanism may be promising therapeutic target for SLE.

## ICW14-6

### CD38 promotes Ca<sup>2+</sup> flux and suppresses interleukin-2 production by promoting the expression of GM2 on the surface membrane of SLE T cells

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Conflict of interest: None

[Objective] Lipid microdomains of cell membrane enriched with gangliosides, are increased and involved in abnormal T cell signaling in SLE. However, how lipid components were altered in SLE is unknown. Here, we hypothesized that CD38 is responsible for altering lipid profile of cell membrane and modified CD4 T cell functions in SLE. [Methods] CD4 T cells were isolated from healthy and patients with SLE. CD38 knocked-out Jurkat cells was generated by CRISPR/Cas9. Lipidomics, RNA-seq and ATAC-seq were performed to compare CD38-deficient and CD38-sufficient cells. B4GALNT1, gangliosides, cytokines and calcium flux were measured by flow cytometry. Intracellular organs of CD4 T cells were examined by electron microscopy. [Results] CD38 was significantly upregulated in CD4 T cells in patients with SLE compared to healthy subjects. In lipidomics, CD38-sufficient Jurkat cells showed marked difference in the profile of alpha-series of monosialogangliosides, from GM3 to GM2 and GD1a compared to CD38-deficient cells. B4GALNT1, GM2 synthase, was upregulated in CD4CD38<sup>+</sup> T cells in SLE, CD38/Sirtuin1 dependent. GM2-dominance in CD4CD38<sup>+</sup> T cells caused marked intracellular

calcium flux, while less cytokine production including IL-2 compared to CD4CD38<sup>-</sup> cells in SLE. RNA-seq showed enriched gene differences related to endoplasmic reticulum (ER) stress in CD38-sufficient cells compared to CD38-deficient. Consistently, one of ER stress markers, XBP1s, was markedly upregulated and enlarged ER were detected due to ER stress in CD4CD38<sup>+</sup> T cells compared to CD4CD38<sup>-</sup> T cells in SLE. Finally, inhibition of calcium signaling by IP3 receptor inhibitor decreased XBP1s and restored IL-2 production. [Conclusions] This study demonstrates that CD38 controls calcium homeostasis in CD4<sup>+</sup> T cells by controlling cell membrane lipid composition that results in suppressed IL-2 production. CD38 inhibition with biologics or small drugs should be expected to benefit patients with SLE.

## ICW15-1

### Assessment of type 1 interferon signature in undifferentiated inflammatory diseases

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Conflict of interest: None

[Objective] Upregulation of type I interferon (IFN) signaling is increasingly recognized in various autoimmune and autoinflammatory diseases and is a potential biomarker to identify IFN-driven inflammatory diseases. But it is not clear to what extent type I IFN is involved in the pathogenesis of patients with undifferentiated inflammatory diseases. This study aimed to measure the type I IFN signature of patients with undifferentiated inflammatory diseases and assess the clinical characteristics of those with high IFN signature. [Methods] Type I IFN signature was measured using whole blood cells. Clinical and biological data were collected retrospectively, and intensive genetic analysis was conducted in undiagnosed patients with high IFN signature. [Results] 113 samples from 94 patients with inflammatory diseases, including 37 undiagnosed cases were measured. 19 out of these 37 patients showed upregulation of IFN signaling. 10 of them showed clinical features commonly found among the type I interferonopathies. Especially, skin manifestations of 8 patients were macroscopically and histologically similar with those of proteasome associated autoinflammatory syndrome. Genetic analysis identified novel mutations of *PSMB8* in one patient, and rare variants of unknown significance in genes linking to type I IFN signaling in four patients. JAK inhibitor was effective in the treatment of a patient with *PSMB8* mutations. It was also remarkable that patients with clinically quiescent idiopathic pulmonary hemosiderosis and A20 haploinsufficiency showed enhanced IFN signaling. [Conclusions] We found upregulated type I IFN signaling in patients with clinically and genetically undifferentiated inflammatory diseases, A20 haploinsufficiency and idiopathic pulmonary hemosiderosis, which indicated association of type I IFN with the pathogenesis of these diseases. Type I IFN signature was useful for narrowing down candidate genes in genetic analysis.

## ICW15-2

### Butyric acid suppresses migration of Monocyte derive Dendritic Cell by inhibiting Actin polymerization via mDia1 inhibition

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Conflict of interest: None

[Objective] Butyric acid improves chronic inflammation such as inflammatory bowel disease and arthritis. Dendritic cells activate locally inflamed, migrate to regional lymph nodes, and activate naïve T cells. In this study, we investigated the effect of butyric acid on the migration ability of monocyte-derived dendritic cells. [Methods] Human CD14<sup>+</sup> cells were purified by positive selection from PBMC using CD14 magnetic beads. Cells were cultured in the presence of GM-CSF and IL-4 for 5 days.

After culturing for 5 days, cells were matured with LPS for 24 hours. Butyric acid was administered at different dose or period. We investigate surface antigen by flow cytometry (FACS VERSE), migration assay (Boyden chamber), and Western blot analysis on monocyte derived Dendritic cells (moDC). Actin was stained Alexa Fluor 488 conjugated phalloidin. [Results] Butyric acid decreased the CCR7 expression in dendritic cells, leading to suppress the migration of moDC toward CCL21 and fetal bovine serum (FBS). In addition, moDCs cultured with butyric acid had a small cell morphology, a round shape and poor formation of dendrites and pseudopodia. Actin plays an important role in pseudopodia formation for migration. From the above, it was suggested that butyric acid acts on the cytoskeleton of moDC. Actin staining of moDC revealed butyrate suppressed actin polymerization in a dose dependent manner. Next, we performed the analysis of signaling of moDC. Western blot analysis confirmed that butyrate decreased the protein expression of mDial1. mDial1 was reported to accelerate actin nucleation and elongation. Our result confirmed that butyric acid inhibited moDC migration and actin polymerization via mDial1 inhibition. [Conclusions] Butyric acid suppresses migration of moDC by inhibiting Actin polymerization via mDial1 inhibition.

### ICW15-3

#### **Annexin A1 (AnxA1) suppresses inflammatory bone resorption though activation of PPAR-g signaling pathway**

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Conflict of interest: None

[Objective] Inflammatory environment facilitates the hyperactivity of osteoclasts leading to bone loss. In the current study, we investigate the therapeutic effects of N-terminal AnxA1 (Ac2-26) on bone loss and osteoclast activities initiated by TNF- $\alpha$  or RANKL. [Methods] Murine calvarial osteolysis model induced by consecutive injections of RANKL or TNF- $\alpha$  for 4 days was used for in vivo evaluation, and the changes in calvariae were analyzed by  $\mu$ CT and histopathology. Osteoclast assay was performed with human monocytes, and transcriptional profiling was analyzed by RNAseq. [Results] Ac2-26 treatment significantly reduced osteolysis induced by local administration of TNF- $\alpha$  and RANKL. On the other hand, RNA-seq analysis revealed that AnxA1 inhibited osteoclast differentiation via suppressing NF- $\kappa$ B signaling and activation of PPAR-g signaling pathway. Macrophages stimulated by AnxA1 exhibited a significant increase in expression of PPAR-g after 3 hrs. These results demonstrated the importance of AnxA1-PPAR-g axis in regulating bone resorption in related diseases, including rheumatoid arthritis and osteoporosis. [Conclusions] Our data suggest that AnxA1 is a clinically-translatable therapeutic agent for management diseases typified by inflammatory bone loss.

### ICW15-4

#### **Regnase-1 regulates pulmonary arterial hypertension**

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Conflict of interest: None

[Objective] Pulmonary arterial hypertension (PAH) is a severe complication of connective tissue diseases. PAH is characterized by remodeling of the pulmonary vessels that result in right heart failure and premature death. The mechanisms of PAH are poorly understood, though there is increasing evidence that inflammation plays a pivotal role in the pathogenesis of PAH. We focused on Regnase-1, an RNase that destabilizes a set of inflammatory genes, and is critical for the regulation of inflammation. [Methods] We generated two mouse strains (CD11c-Cre and LysM-Cre/Regnase-1 flox mice) to evaluate the role of Regnase-1 in myeloid cells, examined the histopathology and right ventricular systolic pressure. [Results] These mice spontaneously developed severe PAH with vascular occlusion and plexiform-like lesions. This histopathology mimics the characters of human PAH. Since alveolar macrophage (AM $\Phi$ ) is the common

cell type lacking Regnase-1 in these 2 mouse strains, it was hypothesized that AM $\Phi$  are responsible for the development of PAH. We analyzed secretory factors in AM $\Phi$  regulated by Regnase-1 via transcriptome analysis and isolated a set of factors responsible for the thickening of pulmonary arteries. We applied the data to NicheNet, a computational method that predicts ligand-target links by combining transcriptome data of AM $\Phi$  and pulmonary arteries. The analysis identified a set of ligand-target networks potentially operating between Regnase-1-lacking macrophages and pulmonary arteries. [Conclusions] Regnase-1 in AM $\Phi$  regulates multiple factors involved in the pathogenesis of PAH by a post-transcriptional regulatory mechanism.

### ICW15-5

#### **Canonical TGF-beta signaling via SMAD3 and SMAD4 suppresses Th1 and Th17 differentiation in psoriasis**

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Conflict of interest: None

[Objective] Transforming growth factor (TGF)- $\beta$  is abundantly expressed and activated in the psoriatic lesions. Canonical TGF- $\beta$  signaling pathway is mediated through TGF- $\beta$ -specific receptor-regulated SMADs: SMAD2 and SMAD3 and the common SMAD: SMAD4. However, signaling mechanisms how SMAD-mediated TGF- $\beta$  signaling regulates pathogenic T cell responses in psoriasis remain largely unknown. [Objective] We sought to determine the mechanisms how canonical TGF- $\beta$  signaling pathway regulates the pathogenicity of effector T cell subsets in psoriasis. [Methods] We generated T cell-specific SMAD4-deleted mice using Cre-loxP system (*Cd4Cre; Smad4<sup>fl/fl</sup>, +/-*). They were treated with 5% imiquimod (IMQ) cream for 6 days on ear and shaved back. The clinical course is assessed using the Psoriasis Activity and Severity Index (PASI) scale, histology and immunophenotyping. [Results] IMQ-induced psoriasis was significantly exacerbated in *Cd4Cre; Smad4<sup>fl/fl</sup>* mice compared with the *Cd4Cre; Smad4<sup>+/-</sup>* littermates. Th1 and Th17 cells significantly increased in the draining lymph nodes and skin lesions of IMQ-treated *Cd4Cre; Smad4<sup>fl/fl</sup>* mice. SMAD3 and SMAD4 repressed T-bet and IFN- $\gamma$  in CD4<sup>+</sup> T cells. In contrast with linker phosphorylated SMAD2, we found that SMAD3 and SMAD4 rather suppressed Th17 differentiation by direct repression of IL-17A and Ror $\gamma$ t as well as by indirect suppression of STAT3 signaling via upregulating the negative regulators of STAT3 activation. [Conclusions] SMAD3 and SMAD4 suppresses differentiation of pathogenic Th1 and Th17 in murine psoriasis model, suggesting that enhancing SMAD3/4 signaling in the skin lesion could be a therapeutic strategy for psoriasis.

### ICW15-6

#### **Semaphorin 7A plays a critical role in the growth of allergic nasal polyps by inducing eosinophil extracellular traps**

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Conflict of interest: None

[Objective] Semaphorin family molecules play key roles in autoimmune inflammatory diseases. We recently reported semaphorin-mediated signaling is involved in the infiltration of eosinophils into allergic nasal polyps (Tsuda T, Nishide M, et al, *J Allergy Clin Immunol.* 2020). In this study, we further investigated the role of semaphorins in eosinophil activation and cell death, which affect the growth of nasal polyps in Eosinophilic chronic rhinosinusitis (ECRS). [Methods] Nasal tissues of patients with ECRS who underwent surgery at Osaka University Hospital were used for RNA-Seq, qPCR, and immunostaining assay. Human eosinophils were isolated by using the magnetic beads separation method (Miltenyi Biotec). Isolated eosinophils were pre-treated with Platelet Activating Factor (PAF);

2  $\mu$ M) for 30 minutes and incubated for 120 minutes, followed by nucleic acid staining using SYTOX Green (Thermo Fisher Scientific). In some experiments, recombinant SEMA7A-Fc proteins were pre-coated overnight on the surface of culture well plates. Galectin-10 and dsDNA levels in the cell culture supernatants were measured by ELISA. [Results] RNA-Seq analysis revealed the expression of *sema7a* is up-regulated in the nasal tissue of ECRS patients in comparison with that of non-ECRS patients. The qPCR data showed *sema7a* is expressed significantly higher in the nasal polyp tissue than in other nasal tissues. SEMA7A was strongly stained in the nasal epithelium by immunohistochemistry. SEMA7A activates eosinophils through the SEMA7A-Integrin $\beta$ 1-ERK signaling pathway and induces a unique type of cell death, eosinophil extracellular traps formation. Consistently, the levels of Galectin-10 and dsDNA in the culture supernatant were significantly increased. [Conclusions] Nasal epithelial cell surface SEMA7A stimulates eosinophils through the SEMA7A-Integrin $\beta$ 1-ERK pathway. SEMA7A promotes eosinophil extracellular traps formation and contributes to the exacerbation of nasal polyps (Manuscript in preparation).

## ICW16-1

### Development and validation study of algorithm for classification of patients into polymyalgia rheumatica and seronegative elderly onset rheumatoid arthritis using musculoskeletal ultrasonography

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Conflict of interest: None

[Objective] The main purpose of this study was to develop and validate an algorithm for the classification of patients into polymyalgia rheumatica (PMR) and elderly onset rheumatoid arthritis (EORA) using musculoskeletal ultrasonography (MSUS) findings. [Methods] At first, we enrolled newly diagnosed 35 patients with PMR (n=18) and EORA (n=17) from ongoing cohort study. We evaluated the following findings; (1) the 2010 EULAR/ACR Classification Criteria for RA (CCRA) and the 2012 EULAR/ACR Provisional Classification Criteria for PMR, (2) physical findings and (3) MSUS findings with medical records review in differentiating between PMR and EORA. The sensitivity and specificity of these findings were calculated. Then, we developed an algorithm and applied to validating patients (total n=57) from our two hospitals. [Results] The sensitivity of MSUS was the highest (94.7% for PMR, 94.1% for EORA) and the specificity of the classification criteria was the highest (75.9% for PMR, 95.5% for EORA), so the algorithm was constructed based on a combination of these two findings. We validated a total of 92 cases according to our algorithm its accuracy assessed by positive predictive value (PPV). Using 'RA diagnosis per rheumatologists' as the gold standard, the PPVs were ranged 66.7-100%. [Conclusions] Although classification criteria for PMR and EORA already existed, there is still no consensus on the distinction between PMR and EORA. We found the distribution of MSUS findings and CCRA may help to classify PMR and EORA. Therefore, MSUS should be performed to distinguish between PMR and EORA at an early stage as much as possible. We need to create a more accurate algorithm to distinguish EORA from PMR.

## ICW16-2

### Agonistic stimulation of Glucagon-like peptide-1 receptor ameliorates experimental polymyositis through inhibiting muscle fiber necroptosis

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Conflict of interest: None

[Objective] Since current treatments for PM are insufficient to recover muscle weakness, novel therapy that improves muscle strength as well as suppresses inflammation is awaited. Glucagon-like peptide-1 receptor (GLP-1R) agonists have pleiotropic actions including suppressing inflammation and muscle atrophy, in addition to anti-diabetic effect. We have previously shown that injured muscle fibers in PM undergo FASLG-mediated necroptosis, a regulated cell death accompanied with release of in-

flammatory mediators such as HMGB1. We also found that the inhibition of necroptosis or HMGB1 ameliorated C protein-induced myositis (CIM), a murine model of PM. We aimed in this study to examine the role of GLP-1R in PM and the effect of a GLP-1R agonist on PM models in vivo and in vitro. [Methods] Muscle specimens of PM and CIM were examined for GLP-1R expression. The effect of PF1801, a GLP-1R agonist, on CIM was evaluated. As an in vitro model of PM, C2C12-derived myotubes were treated with FASLG to induce necroptosis. The serum level of HMGB1 in CIM was measured by ELISA. The expression of AMP-activated protein kinase (AMPK) and PGAM5 was assessed with western blotting in vitro. The level of reactive oxygen species (ROS) was analyzed with CellROX assay and the expression of antioxidant molecules was analyzed with quantitative real-time PCR in vitro. [Results] GLP-1R was expressed on the inflamed muscle fibers of PM and CIM. PF1801 suppressed muscle weakness, muscle weight loss, and muscle inflammation in CIM. PF1801 decreased the serum level of HMGB1 in CIM. In vitro, PF1801 inhibited myotube necroptosis in AMPK dependent manner. PF1801 activated AMPK and decreased the level of PGAM5, which was crucial for myotube necroptosis. Furthermore, PF1801 upregulated the expression of antioxidant molecules and suppressed FASLG-induced ROS accumulation in the myotubes. [Conclusions] GLP-1R agonist could be a novel therapy for PM that recovers muscle weakness and suppresses inflammation.

## ICW16-3

### Association of preoperative muscle composition of the lower extremity with gait function after total knee arthroplasty

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Conflict of interest: None

[Objective] Limitations of gait function persist in some patients with knee osteoarthritis after total knee arthroplasty (TKA). This study aimed to identify preoperative muscle composition variables of the operated limb associated with postoperative gait function. [Methods] Longitudinal data from 45 patients who underwent unilateral primary TKA were retrospectively analyzed. Timed Up-and-Go test (TUG) and gait speed were measured preoperatively and at 3 and 6 months postoperatively. Preoperative muscle composition in the glutei medius and minimus, the quadriceps, the hamstrings, and combination of the hamstrings and quadriceps were evaluated by computed tomography. The area ratio of the individual muscle composition to the total muscle was calculated. The factors associated with TUG and gait speed were identified using stepwise regression analysis. [Results] Shorter TUG and faster gait speed at each time point correlated with higher lean muscle mass area of the total hamstrings, higher area ratio of lean muscle mass to the total hamstrings or to combination of the hamstrings and quadriceps, and lower area ratio of low density lean tissue or intramuscular adipose tissue to the total hamstrings. Shorter TUG at each time point also correlated with higher combined area of lean muscle mass of the hamstrings and quadriceps. Faster gait speed at each time point additionally correlated with lower area ratio of intramuscular fat to the total hamstrings and lower area ratio of lean tissue mass or intramuscular adipose tissue to combination of the hamstrings and quadriceps. Regression analysis using the significant muscle composition variables revealed that the area ratio of lean muscle mass to the total hamstrings was the only predictor of TUG and gait speed after TKA. [Conclusions] Preoperative area ratio of ipsilateral lean muscle mass to the total hamstrings could predict gait function after TKA.

## ICW16-4

### Musculoskeletal ambulation disability symptom complex as a risk factor of incident bone fragility fracture

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Conflict of interest: None

Objective Influence of presenting musculoskeletal ambulation disability symptom complex (MADS) on occurrence of bone fragility fracture (BFF) was investigated with retrospective cohort study. Methods A total of 931 subjects joined in the study. Subjects were selected as bone fragility



risk positive in the FRAX questionnaire. Their assumed risk factors were harvested from the medical records and X-ray pictures. They were followed up at least 8 years consecutively, and occurrence of incident BFF was set as primary endpoint. Each assumed risk factor including MADS was evaluated using Cox regression analysis. Subjects were divided into two groups according to presence of MADS (G-MADS and G-noMADS). Adjusted hazard ratio between the two groups was evaluated using Cox regression analysis. The statistical procedures were performed before and after propensity score matching (PSM) procedures in order to make parallel with assumed risk factors. Results Statistically significant risk factors within 5% were prevalent vertebral body fracture, disuse, MADS, cognitive disorder, hypertension, contracture, Parkinsonism, being female sex, hyperlipidemia, insomnia, T-score in the femoral neck  $\leq -2.3$ , chronic kidney disease  $\geq$  Grade 3a, chronic obstructive pulmonary diseases, glucocorticoid steroid administrated, and osteoarthritis in order of the adjusted hazard ratios (from highest to lowest). Adjusted hazard ratios between G-MADS and G-noMADS were 2.70 and 1.83 for before and after PSM, respectively. Conclusions MADS demonstrated as significant risk factor of BFF occurrence. In treating osteoporosis, fall risk should be aware of as well as bone fragility risk.

## ICW16-5

### Predicting factor for poor prognosis in amyopathic dermatomyositis patients

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Conflict of interest: None

[Objectives] To investigate predicting factor for survival prognosis in patients with amyopathic dermatomyositis (ADM). [Methods] ADM patients admitted in Kitasato University Hospital from 2013 to 2020 for induction therapy were retrospectively analyzed. Overall survival and predicting factor were analyzed by Kaplan-Meier curve and cox proportional hazards model. Induction of the high-flow oxygen therapy (HFT) including mechanical ventilation was defined events and HFT free-survival was analyzed. [Result] Twenty three patients (19 females) were enrolled, age was 57.0 years (IQR 47.0, 67.0 years). ADM-associated interstitial lung disease (ILD) was diagnosed in 22 patients (95.7%) and 17 patients (73.9%) were anti-MDA5 antibody (Ab) positive. Serum KL-6 and ferritin were  $822.0 \pm 574.5$  (mean  $\pm$  SD) U/ml and  $399.7 \pm 575.6$  ng/ml, respectively. The interval from diagnosis to treatment was 27.0 days (IQR 14.0, 66.0 days). Sixteen patients (69.6%) were on triple therapy with glucocorticoid, intravenous cyclophosphamide and calcineurin inhibitor. There were 4 ILD-related death and 6 HFT induced patients. All ILD-related death patients were pre-treated with HFT. Two HFT patients that survived, had secondarily delivered continuous home oxygen therapy. Multi-variate cox proportional hazards model, followed by the univariate analyses revealed the serum albumin (Alb) level at the time of diagnosis as the significant predicting factor of death (HR 0.82, 95% CI 0.68-0.96,  $p=0.01$ ). Likewise, age and serum Alb level were the significant predicting factors for introducing HFT (HR 1.07, 95% CI 1.01-1.16,  $p=0.031$  and HR 0.82, 95% CI 0.70-0.94,  $p=0.002$ ). Ferritin at diagnosis and anti MDA5 Ab titer did not show any significance as the predictor neither for death nor HFT. [Conclusion] Our results demonstrated that serum Alb level at the time of diagnosis or the age at onset may be the possible predictive factors for survival prognosis in patients with ADM.

## ICW16-6

### Antigen-specificity of the antibodies produced in the disease lesion of patients with antisynthetase syndrome

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Conflict of interest: None

[Objective] Antisynthetase syndrome (ASS) is an idiopathic inflam-

matory myopathy with a high prevalence of interstitial lung disease (ILD), and is characterized by serum anti-aminoacyl transfer RNA synthetase antibody (anti-ARS antibody). Recently, Jo-1 specific T cells were found in bronchoalveolar fluid (BALF) of anti-Jo-1 antibody positive patients, however, humoral immunity of the lung lesion is not well understood. [Methods] We recruited ASS patients with lung involvement, sorted the antibody-secreting cells (ASC) from their BALF, read the sequence of antibody of each cell, and produced them as monoclonal antibodies *in vitro*. One patient was performed salivary gland biopsy, and we also produced antibodies from ASCs in salivary gland. The reactivity of them were examined by antigen-binding beads assay. [Results] We generated 119 and 81 antibodies from 3 serum anti-Jo-1 antibody-positive and 3 anti-EJ antibody-positive patients, respectively. Whereas the proportion of anti-Jo-1 antibody in the lung lesion ranged from 2-18%, which was similar to the proportion of autoantibody in lung lesions of rheumatoid arthritis, sjögren's syndrome, and mixed connective tissue disease, anti-EJ antibodies were highly enriched in the lung lesion, ranging from 33-57%. Notably, more than half of the ASC in the salivary glands of anti-EJ antibody-positive patients also produced anti-EJ antibodies. These antibodies recognize various portions of the antigen, suggesting that they are selected in an antigen-driven manner. In addition, anti-Ro52 antibodies, which was reported to be related with ILD, were detected in 16% of the ASC. [Conclusions] Our comprehensive strategy for antigen specificity analysis at single cell level revealed that anti-ARS and anti-Ro52 antibodies were produced in lung lesion. In particular, anti-EJ antibodies showed higher antigen specificity than other autoantibodies, and it was also suggested that anti-EJ antibody-producing lesion may be formed outside the lung.

## ICW17-1

### Investigation of oral microbiome in rheumatoid arthritis regarding to ACPA and HLA DRB1\*SE: Nagasaki Island Study

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Conflict of interest: None

[Objective] ACPA production is prior to the onset of rheumatoid arthritis (RA), and oral mucosa is considered to be one of the important tissues. A gene-environment interaction between oral dysbiosis and HLA-DRB1\*shared epitope (SE) provides a high risk of ACPA-positive RA. However, the interaction of HLA-DRB1\*SE, ACPA and oral microbiota (oral MB) of RA patients remains to be elucidated. We investigated that the difference of oral microbiota among RA patients and healthy subjects (HS) regarding to ACPA and HLA-DRB1\*SE. [Methods] Both of blood and salivary samples were obtained from 1422 subjects from 2016 to 2018 in NaIS. We analyzed 1196 subjects. ACPA positive HS were 22, RA subjects were 33 (11 ACPA positive subjects and 22 ACPA negative subjects) and ACPA negative HS were 1141. ACPA was measured by ELISA, and HLA genotyping was quantified by next-generation sequencing. The operational taxonomic unit analysis was performed. The richness of microbial diversity within subject ( $\alpha$ -diversity) was scaled via Shannon entropy. The dissimilarity between microbial community composition was calculated using Bray-Curtis distance as a scale, and differences between groups (b-diversity) were tested by permutational multivariate analysis of variance. In addition, UniFrac distance calculated in consideration of the distance on the phylogenetic tree were performed. [Results] Alpha-diversity stratified by RA and ACPA positivity showed no significance between four groups. Beta-diversity showed five clusters which stratified by RA and ACPA positivity. In one of the two clusters of ACPA-positive HS, *Prevotellaceae* was predominant and another cluster, *Prevotellaceae* and *Pasteurellaceae* were predominant. [Conclusions] *Prevotellaceae* and *Pasteurellaceae* were detected in ACPA-positive HS for the first time. These bacteria may play an important role in the development of RA. Our study suggested that oral MB may reflect the immunological status of ACPA-positive RA.

## ICW17-2

### Synovial phenotyping in Japanese RA patients using ultrasound-guided needle biopsy

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Conflict of interest: None

[Objective] In parallel with the recent development of biologic agents and kinase inhibitors that has advanced the treatment of rheumatoid arthritis (RA), there is an urgent need to stratify patients by expected therapeutic responsiveness. This study is aimed to establish a basis for precision medicine in Japanese RA patients through synovial phenotyping at the single cell level using ultrasound-guided synovial needle biopsy. [Methods] US-guided synovial needle biopsies were performed in 15 RA patients. The proportion of 5 immune cell subsets (CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, B cells, NK cells, monocytes) and mesenchymal cells were analyzed by flow cytometry (FCM). CD45<sup>+</sup> live cells and CD45<sup>-</sup> live cells were sorted from the cell suspension, and single-cell RNA sequencing (scRNA-seq) was performed using the 10x chromium system. [Results] Twelve of the 15 patients were positive for at least one of rheumatoid factor or anti-CCP antibody. All patients had clinically active synovitis (Clinical Disease Activity Index; >22 [n = 8], >10 to ≤22 [n = 6] and >2.8 to ≤10 [n = 1]). Four patients were treatment-naïve, 6 patients were conventional synthetic disease-modifying antirheumatic drugs inadequate responder (csDMARDs-IR), and 5 patients were biological DMARDs-IR. Based on the composition of immune cells in FCM data, hierarchical cluster analysis revealed 3 distinct synovial subtypes: “CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells dominant”, “CD4<sup>+</sup> T cells dominant” and “monocytes dominant”. There were no significant differences in autoantibody titer, disease activity or treatment at biopsy. Of the 7 patients who received interleukin-6 receptor inhibitors after biopsy, “monocytes dominant” type tended to be more responsive to treatment than other types. [Conclusion] Synovial phenotyping using US-guided needle biopsies has the potential to be useful in predicting treatment responsiveness. Integrating the unbiased transcriptional profiling with scRNA-seq would reveal elaborate landscapes.

## ICW17-3

### Assessment of Disease Phenotype Using Combined Evaluation with Inflammatory Cytokines and Immune-checkpoint Molecules in RA Patients

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Conflict of interest: None

<Objective> T cell immunoglobulin and mucin-domain containing-3 (TIM-3) is an immune-checkpoint molecule involved in inhibitory signaling. Galectin-9 (Gal-9) mediated ligation of TIM-3 induces the amelioration of autoimmune diseases. TIM-3 is expressed in synovial osteoclasts and be involved in the rheumatoid bone destruction. The aim of this study was to investigate the relationship between inflammatory cytokines or immune-checkpoint molecules in RA phenotypes. <Methods> Serum levels of IL-6, TNF- $\alpha$ , soluble TIM-3 (sTIM-3) and Gal-9 were determined by ELISA. Patients were stratified into two groups based on ACPA titers. Serum levels of cytokines or immune-checkpoint molecules were evaluated between RA patients with low-medium ACPA titers (<200 U/mL) and high ACPA titers ( $\geq$ 200 U/mL). <Results> Elevated serum levels of inflammatory cytokines were correlated with DAS28-ESR in RA patients. Although serum levels of sTIM-3 were elevated in RA patients, significant correla-

tions between sTIM-3 and cytokines were observed exclusively in RA patients with low-medium ACPA titers (<200 U/mL) (IL-6;  $r = 0.30$ ,  $p = 0.005$ . TNF- $\alpha$ ;  $r = 0.31$ ,  $p = 0.0034$ ). Serum levels of IL-6 and TNF- $\alpha$  levels were significantly correlated with elevated Gal-9 levels regardless of ACPA status. A significant correlation between IL-6 and Gal-9 was observed in RA patients without advanced joint damage ( $r = 0.44$ ,  $p = 0.005$ ). Conversely, a significant correlation between TNF- $\alpha$  and Gal-9 was observed in RA patients with advanced joint damage ( $r = 0.33$ ,  $p = 0.001$ ). <Conclusions> Our data indicated that there are positive correlations between circulating inflammatory cytokines and checkpoint molecules in RA patients and these interactions can be modulated by ACPA status or joint damage stage. The combination of inflammatory cytokines and checkpoint molecules may be useful for predicting the immune phenotype and further personalized treatment of RA.

## ICW17-4

### Contribution of PRIME cells to treatment response and long-term outcomes of biologics treatment in rheumatoid arthritis

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Conflict of interest: Yes

[Objective] Preinflammatory mesenchymal (PRIME) cells were recently identified as a subset of fibroblasts in the peripheral blood mononuclear cells (PBMCs) of rheumatoid arthritis (RA) patients. PRIME cells were reported to increase before disease flares, but their effect on response to RA treatment and long-term outcomes is still unknown. This study aims to investigate a correlation between treatment outcomes of the RA and the proportion of PRIME cells in PBMCs before and after biologics initiation. [Methods] Blood was drawn and PBMCs were isolated before and 3 months after biologics initiation from 79 patients with RA from 2013 to 2015, and total mRNA was sequenced (bulk RNA-seq). CIBERSORTx was used to deconvolute bulk RNA-seq data and the fractions of cell types in the PBMCs were imputed. Correlation between CIBERSORTx-inferred PRIME cell counts and clinical data after biologics initiation was analyzed. [Results] Patients followed for more than three years (n=48) were analyzed. The average follow-up period was 6.71 years. CIBERSORTx-inferred PRIME cell fractions in PBMCs were decreased by 0.247% compared before and after biologics induction (before: 6.88%, after: 6.63%). PRIME cell fraction was significantly correlated with DAS28-ESR improvement at 3, 6, and 12 months ( $p < 0.05$  in all comparisons), and the treatment-failure group showed significantly lower PRIME cells (7.37% vs 5.70%,  $p = 0.0061$ ). PRIME cell fraction before biologics initiation was a good predictor of treatment response when setting a threshold of PRIME cell fraction at 7% (sensitivity 41.2%, specificity 88.9%, AUC=0.684). In a long-term observation, PRIME cell fraction was not correlated with the number of RA flares and disease activity at the last visit. [Conclusions] The percentage of PRIME cells in PBMCs before initiation of biologics might be a good predictor of treatment response to biologics. PRIME cell fraction was not related to long-term outcomes in RA patients with biologics therapy.

## ICW17-5

### Synovial tissue heterogeneity and predominant inflammatory signals in rheumatoid arthritis

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Conflict of interest: None

[Objective] Recent advances in single-cell RNA sequencing technology have improved our understanding of the immunological landscape of rheumatoid arthritis (RA) through subdividing immune cells (e.g., T cells, B cells, and monocytes) and mesenchymal cells. We aimed to stratify the RA synovium from Japanese patients by immune cell compositions, and gain insight into the inflammatory drivers depending on the synovial phenotype. [Methods] Synovial tissues were obtained from RA patients (n = 41) undergoing joint replacement surgery. The cell-type compositions were computationally estimated from bulk tissue RNA sequencing data by deconvolution approach with single-cell expression reference (CellR package). Gene set enrichment (GSE) analysis was performed to evaluate variation of inflammatory signaling activity (GSVA package). [Results] Hierarchical clustering of cellular composition data revealed 5 distinct synovial subtypes, and 4 of them tended to be associated with clinically high clinical disease activity (HDA). These 4 HDA clusters included 2 clusters characterized by abundant autoimmune-associated B cells (ABC) and interferon (IFN)- $\gamma$  producing CD8<sup>+</sup> T cells (ABC type), 1 cluster enriched with peripheral helper T cells (Tph) and naïve and memory B cells (Tph type), and 1 cluster enriched with activated macrophages and IFN- $\gamma$  producing CD8<sup>+</sup> T cells (macrophage type). By integrating GSE data, IFN signaling was suspected to be activated in macrophage type. In ABC type, enhanced these two pathways were observed. *IL6* expression in one of the ABC type was higher than that in Tph type and macrophage type. [Conclusion] This study revealed the cellular diversity of RA synovium in Japanese patients, and suggested link with predominant inflammatory signals. Synovial phenotyping in individual patients has the potential to be useful for precision medicine, including prediction of treatment responsiveness.

## ICW17-6

### Effect of specific inhibition of CaMK4 in T cells on arthritis: Role of CaMK4 in the pathogenesis of rheumatoid arthritis

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Conflict of interest: None

[Objective] T cells play an important role in the development and progression of rheumatoid arthritis (RA). Activation of calcium/calmodulin-dependent protein kinase IV (CaMK4) plays an important role in the development of autoimmune responses. The aim of this study is to clarify the significance of CaMK4 expressed on T cells in the development and progression of RA. [Methods] To determine whether CaMK4 expressed by T cells is responsible for the development of collagen-induced arthritis (CIA), we deleted genetically CaMK4 in T cells by crossing *Camk4*<sup>fllox/fllox</sup> mice with *Lck-Cre* mice to generate conditional knockout (CKO) *Lck-Cre*. *Camk4*<sup>fllox/fllox</sup> mice. To treat mice with established CIA, KN-93 (total 10  $\mu$ g/week) loaded nanolipogels (nlg) tagged with each biotinylated CD4, CD8, or isotype control antibodies were administered by intraperitoneal injections on day 14, 21, and 28 after the immunization. [Results] Clinical arthritis scores at 33 days post-immunization were significantly lower in CKO mice (p = 0.0010). Consistent with this result, the pathological score of pannus was also significantly lower in CKO mice (p = 0.042). No significant difference was observed in IFN $\gamma$ -producing cells in T cells of splenocytes between the two groups, whereas the percentage of IL-17-producing cells was significantly lower in CKO mice (p = 0.0007). In addition, we found that DBA/1J mice treated with CD4-nlg-KN-93 developed sig-

nificantly less disease than when they were treated with KN-93-loaded nlgs preparations tagged with CD8 or isotype control antibodies. Histological analysis of the joints revealed that mice treated with CD4-nlg-KN-93 had suppressed pannus scores and interestingly, and the effect of CD4-targeted delivery was better than systemic administration of KN-93. [Conclusions] CaMK4 expressed on T cells is an important target molecule in the pathogenesis of RA, and CaMK4 inhibition may be a new approach to regulate the development of arthritis by controlling T cells.

## ICW18-1

### Digital gangrene in Chinese systemic sclerosis patients: a case-control study

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Conflict of interest: None

[Objective] Digital gangrene, as an infrequent presentation of ischemic microvascular involvement, leads to degradation of quality of life and poses therapeutic challenges, but little is known about its pathogenesis. This study aims to investigate the characteristics, risk factors and outcomes of digital gangrenes. [Methods] A retrospective case-control study was performed from February 2003 to April 2021. Forty-three SSc patients with digital gangrenes admitted to Peking Union Medical College Hospital were included. 146 age and sex-matched controls were selected from SSc patients without gangrene during the same period. Microvascular manifestations were documented and other clinical features were compared between cases and controls. Multivariate logistic regression analysis was used to determine risk factors. [Results] While more than 80% RPs and DUs occurred in autumn and winter, 22/43 (51.2%) of gangrenes happened in spring and summer. 8/43 (18.6%) cases complicated with macrovascular stenosis, which are prone to have gangrenes in multiple sites (87.5% vs 42.9%, p=0.023). The proportion of elevated ESR (54.8% vs 34.9%, p=0.020) and levels of high-sensitive C reactive protein (median 7.2 mg/L vs 1.8 mg/L, p=0.045) was much higher in SSc individuals than in controls. In the multivariable logistic regression analysis, digital contracture (OR 3.642, 95%CI 1.131-11.728, P=0.030), positive anti-centromere antibody (OR 3.803, 95%CI 1.426-10.144, p=0.008) and elevated ESR (OR 3.044, 95%CI 1.272, 7.097, p=0.012) were identified as independent risk factors for gangrenes. Most (79.0%) cases were treated with combination of immunosuppressive and vasodilating therapy, but four cases receiving only glucocorticoid and immunosuppressive agent also got remised in the follow-up. [Conclusions] Digital contraction, positive anti-centromere antibody and increased ESR were independent risk factors for digital gangrenes in SSc. Vasculitis may contribute to the progression of digital gangrenes.

## ICW18-2

### Autoantibodies to the Survival of Motor Neuron (SMN) complex as a novel marker for pulmonary arterial hypertension and internal lung disease in patients with mixed connective tissue disease (MCTD)

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Conflict of interest: None

[Objective] Mutation or deletion of survival of motor neuron 1 (SMN1) causes a hereditary neuromuscular disease, spinal muscular atrophy. In eukaryotic cells, SMN complex (SMN + Gemin 2-7) plays a key role in the assembly of snRNPs (U1RNP, Sm). Isolated anti-SMN complex antibodies (Abs) were uncommon and reported in idiopathic inflammatory myopathies (IIM)/systemic sclerosis (SSc) overlap syndrome, however, anti-SMN complex Abs often coexisted with anti-U1RNP Abs. The aim of this study was to evaluate the clinical significance of anti-SMN complex Abs in patients with mixed connective tissue disease (MCTD). [Methods] Fifty-two patients with newly diagnosed and untreated MCTD were enrolled between April 2014 and June 2021. Serum anti-SMN complex Abs and other autoantibodies were screened by immunoprecipitation of



<sup>35</sup>S-methionine-labeled cell extracts and enzyme-linked immunosorbent assay. Associations between anti-SMN complex Abs and clinical characteristics were analyzed. [Results] Anti-SMN complex Abs were detected in 35% (18/52) of patients. Anti-SMN complex Abs positive patients had higher prevalence of pulmonary arterial hypertension (PAH; 56% vs. 9%,  $p < 0.001$ , odds ratio: OR 12.9) and interstitial lung disease (ILD; 89% vs. 47%,  $p = 0.006$ , OR 9.0) vs negative patients. All patients with anti-SMN complex Abs had PAH or ILD. Nailfold microvascular abnormalities, which had strong association with PAH, were more common in patients with anti-SMN complex Abs positive vs negative patients (73% vs. 27%,  $p = 0.002$ ). Furthermore, when MCTD patients were classified based on the combination of their clinical features of SLE, SSc, and IIM, the prevalence of anti-SMN complex Abs was the highest in a subset with clinical features of SLE + SSc + IIM (71%: 10/14, vs. a subset with only SLE + SSc features, 25%: 8/32,  $p = 0.002$ ). [Conclusions] Anti-SMN complex Abs appear to be a new biomarker for PAH and ILD in MCTD and also associated with “typical MCTD” that has feature of SLE, SSc and IIM.

### ICW18-3

#### **Nailfold microvascular abnormalities predict pulmonary arterial hypertension and can be improved by immunosuppressant treatment in patients with mixed connective tissue disease (MCTD)**

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Conflict of interest: None

[Object] Mixed connective tissue disease (MCTD) manifests with microvascular damage and overlapping clinical features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIM). The aim of this study is to investigate the clinical importance of microvasculopathy in patients with MCTD using nailfold videocapillaroscopy (NVC). [Methods] Forty-six patients with newly diagnosed and untreated MCTD, enrolled between April 2014 and May 2021, participated in this prospective study. Clinical features and NVC findings were assessed before and after 1-year immunosuppressive therapy, with age- and sex-matched patients with SLE ( $n=40$ ), SSc ( $n=70$ ), and IIM ( $n=50$ ) as controls. [Results] All MCTD patients presented Raynaud's phenomenon and were positive for anti-U1 RNP antibodies. Among them, 89% (41/46) had sclerodactyly, 59% (27/46) had interstitial lung disease (ILD), and 24% (11/46) had pulmonary arterial hypertension (PAH). The prevalence of NVC abnormalities in MCTD was 41.3%, which was significantly lower than SSc (89%) but higher than SLE (10%). In addition, when we divided MCTD patients into two groups by presence or absence of NVC abnormalities, the prevalence of sclerodactyly or ILD were comparable. However, we found that a higher prevalence of PAH in patients with NVC abnormalities ( $P < 0.001$ ). Namely, NVC abnormalities were observed in all MCTD patients with PAH, but were seen in only 23% of those without PAH. Moreover, NVC changes were significantly improved and disappeared in half of the MCTD patients after 1-year intensive immunosuppressive therapy in contrast to SSc patients who did not show any NVC changes after similar treatments. [Conclusions] MCTD differed from SLE, SSc, and IIM in terms of the prevalence and the responsiveness of NVC abnormalities to the immunosuppressive therapy. Detection of NVC abnormalities in MCTD could contribute to predicting PAH and help us to understand further aspects of the pathogenesis of MCTD.

### ICW18-4

#### **Krebs von den Lunge-6 as a quantitative biomarker for the extent of systemic sclerosis associated interstitial lung disease**

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Conflict of interest: None

[Objective] Software-based quantitative chest computed tomography (qCT) has been utilized to evaluate the activity and severity of chronic

lung diseases such as pulmonary fibrosis and emphysema. It has recently been applied in the management of systemic sclerosis associated interstitial lung disease (SSc-ILD) as well, particularly in the assessment of response to tocilizumab (Roofeh D, et al. *Arthritis Rheumatol.* 2021). However, it is still impractical to perform qCT in daily clinical practice. This study aimed to approximate qCT with conventional clinical parameters. [Methods] A total of 85 patients with SSc attending Hokkaido University Hospital between 2010 and 2021 were included. Pulmonary function test, right heart catheterization and serum biomarkers were evaluated. Chest high-resolution CT was analyzed using a software (Synapse Vincent Ver.3.0, Fujifilm) to represent abnormal lung volume (ALV). [Results] The mean age of the enrolled patients was 64 years [range 52-70]. The median value of ALV was 25.4% (interquartile range, 9.6-57.1). In univariable linear regression analysis, serum levels of Krebs von den Lunge-6 (KL-6) ( $\beta$  coefficient = 0.65,  $p < 0.001$ ), forced vital capacity ( $\beta$  coefficient = -0.24,  $p = 0.004$ ) and diffusing capacity of lung for carbon monoxide ( $\beta$  coefficient = -0.40,  $p < 0.001$ ) had a significant correlation with ALV. In multivariable linear regression analysis, KL-6 had the strongest correlation ( $\beta$  coefficient = 0.40,  $p < 0.001$ ). Receiver operating characteristics curve analysis revealed that KL-6 showed excellent predictive performance for the existence of moderate to severe ILD, an ALV of  $\geq 20\%$  (area under the curve = 0.92). The optimal cut off value of KL-6 for an ALV of  $\geq 20\%$  was 376 U/mL (sensitivity = 0.96, specificity = 0.75). [Conclusions] Serum KL-6 levels have a significant correlation with ALV evaluated by qCT. KL-6, although not a novel biomarker, may efficiently predict the existence of moderate to severe ILD in patients with SSc.

### ICW18-5

#### **Efficacy and safety of Nintedanib (NTD) for interstitial pneumonia with progressive fibrosis (PF-ILD) associated with systemic sclerosis (SSc)**

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Conflict of interest: None

[Objective] The efficacy of NTD on PF-ILD in patients with SSc was demonstrated in clinical trials. However, its efficacy in cases receiving diverse therapies is still unknown. The purpose of this study is to clarify the efficacy and safety of NTD in patients with SSc in clinical practice. [Method] 18 patients with SSc taking NTD more than 1 year and who met the criteria of PF-ILD and assessed organ damages by using a clinical pathway were enrolled. The changes in pulmonary function tests, blood tests were obtained within 24 months before, at the start of, and 1 year after NTD introduction. [Result] The mean age before starting NTD was 62.1 years, disease duration was 31.8 months. Before starting (mean 9 months before), mean %VC, %FVC, %DLco, and KL-6 were 86.4%, 90.3%, 72.1%, and 552.5 U/ml, respectively. Whereas at starting NTD, mean %VC, %FVC, %DLco, and KL-6 were 74.6%, 86.0%, 68.9%, and 954.5 U/ml. Significant deterioration in %VC and %DLco were observed ( $p = 0.03$ , 0.05). When to start taking NTD, 16 patients had concomitant therapy (GC;  $n=11$ , TAC;  $n=3$ , CsA;  $n=1$ , TCZ;  $n=1$ , IVCY;  $n=7$ ). The continuation rate of NTD after 1 year was 66.7%, adverse events occurring in 72.2%, gastrointestinal symptoms were the most common (55.6%). 5 patients discontinued and 12 patients continued NTD for 1 year. 1 year after, mean %VC, %FVC, %DLco were 82.4%, 84.8%, and 64.8%, respectively, showing no significant decrease compared to the start of NTD ( $p = 0.77$ , 0.37, 0.08). The annual %FVC reduction was suppressed compared to before (pre-NTD: post-NTD = -4.3%: -1.2%). 7 cases (58.3%) in which the %FVC reduction was unchanged or decreased by less than 5%. These patients were characterized by more severe mRSS and lower CRP at the start of NTD compared to worsening group. [Conclusion] NTD slows the decrease of %FVC even with concomitant therapy, and it is effective in patients with severe skin sclerosis and poor inflammatory findings. Continuous administration by symptomatic treatment is important.

## ICW18-6

### Establishment of systemic sclerosis associated pulmonary arterial hypertension specific endothelial cells through iPSCs and their functional and molecular analyses

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Conflict of interest: Yes

[Objective] Pulmonary arterial hypertension associated with systemic sclerosis (SSc-PAH) is of particularly clinical significance since its outcomes remain unfavorable despite modern PAH therapies. Previous reports have indicated the abnormality of endothelial cells (ECs) in SSc-PAH, but details have yet to be shown. We aimed to investigate the pathogenesis of SSc-PAH using disease-specific induced pluripotent stem cells (iPSCs). [Methods] iPSCs were established from a SSc-PAH patient and a healthy donor. ECs were differentiated from iPSCs. Vasculogenesis and cell proliferation were evaluated by the tube formation assay and the BrdU assay, respectively. RNA-sequencing (RNA-seq) was performed to pick up differentially expressed genes (DEGs). Knockdown experiment was performed using siRNA and human umbilical vein endothelial cells (HUVECs). Endothelial to mesenchymal transition (EndoMT), another possible hallmark of SSc-PAH, was evaluated by immunofluorescence staining of alpha SMA and vimentin. [Results] The cellular uptake of BrdU was increased ( $0.49 \pm 0.05$  vs  $0.30 \pm 0.01$  abs,  $p < 0.05$ ,  $n = 3$ ) while the tube formation was impaired ( $31.2 \pm 2.0$  vs  $47.0 \pm 1.3$  mm,  $p < 0.01$ ,  $n = 3$ ) in SSc-PAH ECs compared to healthy ECs. RNA-seq revealed some DEGs and enriched Gene Ontology terms, including blood vessel development and vascular endothelial growth factor-activated receptor activity. According to the previous reports regarding vascular disease or fibrotic disorders, GeneX, one of the downregulated genes in SSc-PAH ECs, was picked up. siRNA-mediated knockdown of GeneX in HUVECs resulted in increased uptake of BrdU ( $0.70 \pm 0.05$  vs  $0.46 \pm 0.01$  abs,  $p < 0.001$ ,  $n = 6$ ) and increased expression of EndoMT markers compared to HUVECs treated with control siRNA. [Conclusions] We detected abnormalities in ECs of SSc-PAH, derived from iPSCs, such as impaired vasculogenesis and facilitated cell proliferation. Downregulation of GeneX may be related to impaired vasculogenesis. GeneX might also be involved in EndoMT.

## ICW19-2

### The efficacy of Classical Indian Yoga in the treatment of Fibromyalgia: A Randomized Controlled Trial

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Conflict of interest: None

**Purpose:** - Fibromyalgia (FM) is a complex musculoskeletal disorder treated with multidisciplinary therapies. - Classical Indian Yoga is an ancient life style healing technique which has an integrated mind-body approach to enhance both physical and mental health. **Methods:** - One year, single-blind, randomized trial of Classical Indian Yoga (50 patients) versus attention control group (stretching and wellness education) of 50 patients for Fibromyalgia. - The classical Indian Yoga involved 60-minute group sessions thrice-weekly. - The primary outcome measure was change in the FM Impact Questionnaire (FIQ) score at 2 years. - Secondary outcome measures were tender point count, sleep quality (PSQI), 10-minute walk, timed chair stand, grip strength, depression and quality of life. - These outcome measures were repeated at 2 years to test durability of response. Both groups were compared using an intent-to-treat analysis. **Results:** - Mean age of 100 patients was 55 years (SD 11), disease duration 10 years (SD 7) and BMI  $30 \text{ kg/m}^2$  (SD 8). - 80 patients were females. - Patients baseline expectations of benefit from an exercise intervention were similar: Classical Yoga = 4.1 and the controls = 4.3. - After 1 year patients in the classical Yoga group had a significantly greater improvement in FIQ score: between-group change -20, 95% CI (-24.0 to -8.8);  $P = 0.0005$ . - The Yoga group patients also had significant improvement in secondary outcome measures: reduction in pain scale (VAS), improved patient global assessment, physical function, depression, and health status. - After 2 years patients compliant with the classical Yoga had sustained and durable benefits in FIQ score quality of sleep and quality of life. The

two groups did not differ in medication usage. No adverse events were noted. **Conclusion:** Classical Indian Yoga appears to be highly effective in the management of FM having a positive impact on physical, psychological and social aspects of FM in this medium term analysis.

## ICW19-3

### The Use of complementary and alternative medicine by Rheumatoid arthritis patients in a university hospital clinic in India

Vikas Trivedi  
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Conflict of interest: None

**Background:** There is a paucity of data regarding the use of and attitudes toward complementary and alternative medicine (CAM) among rheumatoid arthritis (RA) patients in Asia, especially India where these practices are highly prevalent. This study was performed to evaluate the pattern of utilization of CAM, related demographic and clinical factors, and attitudes among Indian RA patients. We focused on the CAM systems utilizing oral drugs and acupuncture. **Methods:** We conducted a survey of patients in rheumatology clinics affiliated with a university hospital. 250 patients suffering from rheumatoid arthritis (RA), satisfying American College of Rheumatology (ACR) criteria were interviewed for the modalities of therapy and drugs used. All patients have been diagnosed with RA more than 5 years back. We analysed prescriptions of both conventional and CAM practitioners. Direct questionnaires regarding CAM were avoided. Fifty two percent (130 patients) had used CAM drugs and 60% of them had used more than two modalities. **Results:** Ayurveda, homeopathy, Persian medicine and acupuncture were the four common CAM utilized by the patients in that order. About 80 percent patients using CAM believed conventional medicine has no cure for RA and adverse reactions were rare in CAM. These factors predominantly influenced their decision to use CAM. Family income, urban and rural living did not influence usage of CAM. The use of CAM significantly increased as the duration of disease increased. (detailed results will be presented) **Conclusion:** The knowledge of CAM is essential to avoid drug interactions, recognise their reactions and also appreciate their risks and benefits. 'Alternative treatments' play an important role as self prescribed therapy in rheumatoid arthritis and their use should not be ignored nor underestimated. A scientific scrutiny to these practices and utilizing them carefully, if beneficial is needed.

## ICW19-4

### Thrombocytopenia in Primary Antiphospholipid Syndrome: Significance in Clinical Implications and Prognosis

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Conflict of interest: Yes

[Objective] Thrombocytopenia as a frequently seen clinical manifestation in patients with Antiphospholipid syndrome (APS) could be an independent predictor of recurrent thrombotic, obstetrical events and severe extra-criteria events. [Methods] This is a prospective study enrolling 218 consecutive patients diagnosed with primary APS (PAPS) between 2010 to 2021. A platelet count less than  $100 \times 10^9/\text{L}$  is defined as thrombocytopenia. [Results] Our cohort included 74 patients with thrombocytopenia and 144 with continuous normal platelet count. Comparison of baseline characteristics indicated that patients with thrombocytopenia had more extra-criteria manifestations (mainly hemolytic anemia) [20 (27.03%) vs 17 (11.81%),  $p = 0.007$ ] than those with continuous normal platelet count. Hypocomplementemia tend to appear among patients with thrombocytopenia [19 (25.68%) vs 16 (11.11%),  $p = 0.0099$ ]. The aCL-IgG/IgM, anti- $\beta_2$ -glycoprotein I (GPI) and lupus anticoagulant (LA) were more frequently found in patients with thrombocytopenia. In survival analysis, thrombotic, obstetrical and severe extra-criteria survival rate was significantly poorer among patients with thrombocytopenia. In multivariate Cox regression, thrombocytopenia was independent risk factor for all endpoint events including thrombotic event, pregnancy morbidity and severe-extra criteria event [HR (95%CI) 2.93 (95%CI 1.31, 6.56),  $p = 0.009$ ; 8.00 (2.43, 26.37),  $p = 0.0006$ ; 16.84 (2.07, 136.73),  $p = 0.008$  respectively]. 12 (16.22%) pa-

tients with thrombocytopenia appeared to be no response (NR) to the received treatment. Their minimum PLT count was significantly lower than the non-NR group [22.5 (14.25, 36.25) vs 68.5 (26.25, 99),  $p=0.0112$ ]. The complement level and antibody profiles between them were not statistically different. [Conclusions] Thrombocytopenia could be a predictor to early identify PAPS patients at high risk of developing thrombotic events, pathological gestation and severe extra-criteria events.

## ICW19-5

### Higher level of complement 4 as a risk factor for hydroxychloroquine-induced skin reaction

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Conflict of interest: None

[Objective] Hydroxychloroquine (HCQ) is one of the key drugs of systemic lupus erythematosus (SLE), which is recommended to be administered for those with any organ involvements. However, the possibilities of the adverse reactions sometimes interrupt the prompt administration in the clinical setting. Thus, the aim of this study is to identify the risk factors associated with the reactions. [Methods] This study was conducted as a retrospective single center cohort. The patients who were diagnosed as having SLE and started to treat with HCQ during July 2015 and April 2021 were selected. Any adverse reactions which require dose reduction or cessation of HCQ until six months after the HCQ initiation were confirmed. The risk factors associated with the HCQ intolerance were identified using multivariable logistic analyses. The cut-off levels of risk factors were determined by receiver operating characteristic (ROC) curve. [Results] A total of 124 patients with SLE were registered. The mean age was 42.6 years old, with a female ratio of 90.0%. The patients who were treated with glucocorticoids (GCs) and immunosuppressants (ISs) were 88.7% and 56.5%, respectively. The HCQ intolerance was observed in 27 patients (21.8%): skin reaction in 7 (5.6%) (morbilliform eruption in 6, alopecia in 1), diarrhea in 14 (11.3%). The multivariable analyses, adjusted for HCQ dose, GC dose and use of ISs, showed that higher levels of Complement (C) 4 (Odds ratio (OR) 1.1,  $p=0.01$ ) and CH50 (OR 1.1,  $p=0.05$ ) at baseline were predictive for the risk of HCQ intolerance and higher C4 levels were most predictive for that of skin reaction (OR 1.1,  $p=0.06$ ). In ROC curve analysis, the sensitivity and specificity of C4 levels indicating the HCQ intolerance were 85.7% and 50.6%, respectively with a cut-off level of 13.0 mg/dL. [Conclusions] In summary, our results revealed that baseline complement levels are positively associated with HCQ intolerance, especially C4 levels with HCQ-induced skin reaction.

## ICW19-6

### Clinical characteristics of immunoglobulin A vasculitis associated with Mediterranean fever gene mutation in Japanese patients

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Conflict of interest: None

[Objective] Immunoglobulin A vasculitis (IgAV) is the most common vasculitis of childhood. However, its etiology remains unknown. In the Mediterranean region, 10% of patients with IgAV harbor homozygous and compound heterozygous mutations in the Mediterranean fever (*MEFV*) gene. Thus, such mutations may be involved in the development of IgAV. Herein, we present a Japanese patient with IgAV harboring *MEFV* gene mutation. Further, a comprehensive literature analysis was performed to validate the clinical characteristics of Japanese patients with IgAV harboring *MEFV* mutation. [Methods] A 5-year-old girl presented with IgAV. She experienced prolonged abdominal pain, which was steroid-resistant. When treatment with colchicine was started, her abdominal pain disappeared immediately. The serum interleukin-18 levels of the patient and other patients with IgAV and FMF were evaluated using enzyme-linked immunosorbent assay. Moreover, all exons of the *MEFV* gene were analyzed using the direct sequence method. A comprehensive search of Japanese patients with IgAV harboring *MEFV* gene mutations in PubMed, Ichushi-Web, and Medical Online was conducted. [Results] The serum interleukin-18 level of the patient was higher than that of other patients with IgAV and was

similar to that of patients with FMF harboring M694I mutation. In addition, the patient presented with E148Q/M694I mutation. In previous studies, only four patients presented with IgAV harboring *MEFV* gene mutation in Japan. [Conclusions] *MEFV* gene mutations can be masked if the symptoms of IgAV are prolonged or if patients are refractory to treatment. Moreover, the prevalence of IgAV associated with *MEFV* gene mutation is low in Japan.

## ICW20-1

### Differential class effect of b/ts DMARDs on bone metabolism; from FIRST registry

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Conflict of interest: None

[Objective] To elucidate the class effect of b/ts DMARDs on bone metabolism. [Methods] RA patients who receive the first b/ts DMARDs without antiosteoporosis, glucocorticoids, and no history of fracture from FIRST registry were included. Hip and radial bone mineral density (BMD), serum bone ALP (BAP), and urinary NTx (uNTx) were measured. [Results] 494 patients (TNFi 260, IL6Ri 103, CTLA4Ig 87, JAKi 44) were included. Overall, BMD decreased at 6M (change in BMD g/cm<sup>3</sup>,  $p$  vs. pretreatment. [Hip] -0.012,  $p<0.01$ , [Radius] -0.008,  $p<0.01$ ). Both hip and radial BMD decreased in TNFi and IL6Ri groups, while both was preserved in CTLA4Ig group. JAKi group showed the preserved hip BMD at 6M ([Hip] TNFi -0.010,  $p<0.01$ ; IL6Ri -0.022,  $p<0.01$ ; CTLA4Ig -0.008,  $p=0.30$ ; JAKi -0.007,  $p=0.24$ , [Radius] TNFi -0.004,  $p<0.01$ ; IL6Ri -0.009,  $p<0.01$ ; CTLA4Ig -0.005,  $p=0.08$ ; JAKi -0.007,  $p=0.01$ ). To elucidate the class effect of b/ts DMARDs on bone metabolism, patient's background characteristics were adjusted by IPTW. Decrease in hip and radial BMD in TNFi and IL6Ri groups was reproduced, whereas both was preserved in JAKi group. CTLA4Ig group showed the preserved radial BMD ([Hip] TNFi -0.011,  $p<0.01$ ; IL6Ri -0.020,  $p<0.01$ ; CTLA4Ig -0.016,  $p=0.02$ ; JAKi -0.004,  $p=0.26$ , [Radius] TNFi -0.005,  $p<0.01$ ; IL6Ri -0.012,  $p<0.01$ ; CTLA4Ig -0.000,  $p=0.95$ ; JAKi -0.005,  $p=0.64$ ). To further analyze the class effect of b/ts DMARDs, bone metabolism markers were analyzed after IPTW adjustment. JAKi group, compared to the others, significantly increased BAP and decreased uNTx at week 2, which suggests that JAKi preserve BMD by promoting bone formation, and suppressing bone resorption. TNFi and JAKi demonstrated earlier RA disease control than the others. Further IPTW adjustment revealed preserved hip BMD in JAKi group, which suggests that JAKi preserve hip BMD independent of its RA disease control. [Conclusions] JAKi may arise a favor bone metabolism in RA.

## ICW20-2

### Number of Prior Molecular Targeted Agents and the Efficacy of Janus Kinase Inhibitors in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] To investigate the relationship between the number of prior molecular targeted agents (biologics and Janus kinase inhibitors (JAK-inibs)) and the efficacy of JAK-inibs in patients with rheumatoid arthritis (RA). [Methods] RA patients who had initiated JAK-inibs at our hospital by February 2021 were retrospectively analyzed. Patients previously treated with  $\leq 1$  molecular targeted agents (group O,  $N=47$ ) or  $\geq 2$  molecular targeted agents (group T,  $N=32$ ) were matched by propensity scores for gender, concomitant therapy, and Simplified Disease Activity Index (SDAI). Disease activity at 6 months was investigated. [Results] Twenty-six patients for each group were selected following propensity score matching. Disease duration was significantly longer in group T (12.6 [9.4-



23.6] years) than in group O (7.4 [0.7-20.7] years) ( $p=0.035$ ). The baseline SDAI in group O and group T was 19.69 [12.33-27.71] and 21.35 [10.17-26.98] ( $p=0.76$ ), which decreased to 10.45 [3.40-14.73] and 15.67 [10.33-20.55] at 1 month ( $p=0.029$ ). However, SDAI at 3 months was 9.88 [4.77-17.04] and 9.83 [5.88-15.28] ( $p=0.74$ ), at 6 months was 6.38 [1.77-15.39] and 8.68 [5.68-15.83] ( $p=0.26$ ). SDAI low disease activity (LDA) rate in group O and group T was 23.1% and 26.9% ( $p=1.00$ ) at baseline, 53.9% and 30.8% ( $p=0.16$ ) at 1 month, 61.5% and 57.7% ( $p=1.00$ ) at 3 months, and 65.4% and 61.5% ( $p=1.00$ ) at 6 months, respectively. [Conclusions] There was no difference in SDAI LDA rate throughout the observation period irrespective of the number of previous treatments with molecular targeted agents. However, patients with a lower number of previous molecular targeted agents responded rapidly with significantly lower SDAI at 1 month. The impact of the agents used just before initiating JAKinibs is an important issue that needs to be investigated in the future. The limitations of this study are that not all factors were matched and the number of patients was small due to the use of propensity score matching.

## ICW20-3

### Comparing efficacy and safety of Janus kinase inhibitors and IL-6 receptor antibodies in patients with rheumatoid arthritis using propensity score-based inverse probability of treatment weighting and growth mixture modeling: from the FIRST registry

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Conflict of interest: None

[Objectives] The safety of Janus kinase inhibitors (JAKis) concerns remains, unlike biologics. This study aimed to determine differences in efficacy and safety between JAKis and anti-interleukin-6 receptor antibodies (IL-6Ri) in patients with rheumatoid arthritis (RA). [Methods] The efficacy and safety of JAKis ( $n=304$ , tofacitinib/baricitinib/peficitinib/upadacitinib=156/138/7/3) was compared with IL-6Ri ( $n=610$ , tocilizumab/sarilumab=567/43). Selection bias was adjusted by propensity score-based inverse probability of treatment weighting (IPTW). The clinical disease activity index (CDAI) trajectory for all participants was analyzed using growth mixture modeling (GMM). Primary endpoint was CDAI remission rate at 26 weeks. [Results] No significant difference was observed in patient background and retention rate between the two groups after adjustment by IPTW. CDAI was significantly lower at Week 2 in JAKis group than in IL-6Ri group ( $13.6\pm 11.3$  vs.  $18.3\pm 12.6$ ,  $p<0.01$ ) and persisted at Week 26 ( $6.1\pm 7.5$  vs.  $9.9\pm 10.0$ ,  $p<0.01$ ). The CDAI remission rate at Week 26 was also higher with JAKis (40.5% vs 24.0%,  $p<0.01$ ). JAKis group had higher frequency of all adverse events ( $p<0.01$ ) and higher incidence of infection ( $p<0.01$ ) before and after IPTW adjustment. The trajectory of the CDAI was divided into five groups by GMM. Patients with high disease activity at baseline who achieved low disease activity (LDA) by Week 4 and maintained LDA until Week 26 (responder group) had a high proportion of patients received JAKis ( $p<0.01$ ). In the JAKis group, those with earlier Steinbrocker stages were more likely to belonging to responder group. In the IL-6Ri group, the patients who were bio-naïve tended to be belonging to responder group. [Conclusions] JAKis had higher remission rate; however, IL-6Ri might be superior in safety. Moreover, the population that responds to treatment may differ, suggesting that selecting treatment agents in consideration of efficacy-safety balance might be important.

## ICW20-4

### Comparison of the effects of Upadacitinib Monotherapy with Methotrexate on Protein Biomarkers in MTX-Naïve and MTX-Inadequate Responders in patients with active Rheumatoid Arthritis: Results from the SELECT-EARLY and SELECT MONOTHERAPY Phase 3 studies

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Conflict of interest: Yes

[Background] In MTX-naïve patients (pts), UPA 15 mg QD monotherapy (UPA Mono) showed significant improvements in RA signs vs MTX. In MTX-IR pts, switching to UPA Mono showed significant improvements in RA signs vs MTX. These study populations offer opportunities to analyze biomarkers. [Objective] To compare the biological activity of MTX and UPA Mono in MTX-Naïve and MTX-IR RA pts, via evaluation of protein biomarkers related to inflammation compared with disease activity. [Methods] Patients from the SELECT-EARLY (PBO,  $n=96$ ; UPA 15 mg QD,  $n=96$ ) and SELECT-MONO (PBO,  $n=79$ ; UPA 15 mg QD,  $n=99$ ) were randomly selected from the subsets with available plasma samples. The levels of 92 proteins were analyzed using the Olink platform; a Repeated Measure Mixed Linear Model identified proteins differentially modulated by MTX and UPA compared to Baseline. Pathway analysis was performed with Ingenuity Pathway Analysis. [Results] In MTX-Naïve pts, both UPA Mono and MTX modulated a broad range of biomarkers associated with key pathways implicated in RA pathogenesis. UPA Mono had a faster effect than MTX determined by biomarker levels. Moreover, UPA Mono had a more effect on biomarkers that are significantly associated with baseline disease activity measures. In MTX-IR pts, only UPA Mono exerted significant effects on the biomarkers, whereas MTX had no measured effect. Pathway analysis indicated that in MTX-naïve pts, UPA Mono and MTX were predicted to elicit similar effects on adaptive, innate immune cells and on non-immune related pathways; but UPA Mono did so faster than MTX. In MTX-IR pts, only UPA Mono was predicted to affect those pathways, although to a lesser extent than in MTX-Naïve pts. [Conclusions] UPA Mono exerted significant effects on biomarkers in MTX-Naïve and MTX-IR pts, whereas MTX did so only in MTX-Naïve pts. The more profound effects of UPA Mono in MTX-Naïve pts provide a possible mechanism for the superior efficacy of UPA Mono over MTX.

## ICW20-5

### Clinical outcome of sarilumab in patients with rheumatoid arthritis in Niigata Orthopedic Surgery Rheumatoid Arthritis Database (NOS-RAD)

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Conflict of interest: None

[Objective] To examine the clinical outcome of sarilumab in patient with rheumatoid arthritis (RA). [Methods] Twenty-three patients with RA were registered from Niigata Orthopedic Surgery RA Database (NOS-RAD) from 2018 to 2020. The mean age at the administration of sarilumab was 66 years old (27 to 87 years old), and woman was 18 cases (78%). The mean RA duration was 7.5 years (0.2 to 32 years). Positive rate of anti-CCP antibody was 82%. Methylprednisolone was treated with 1.8 mg/day on average in 7 cases (30%). Methotrexate was treated with 3.2 mg/week on average in 12 cases (52%). Bionave cases was 5 cases (22%). bDMARDs had been used in 17 cases and tDMARDs had been used in 3 cases. DAS28, DAS28-remission rate, CDAI, the retention rate at 1 year, and the reason of cessation of sarilumab were examined. [Results] DAS28 was 4.1 at the administration of sarilumab, and significantly improved to 2.4, 2.1, 2.0, and 1.7 at 1, 3, 6, and 12 months after the administration. DAS28-remission rate was 13% at the administration, and increased to 80% at 12 months. CDAI was 17.3 at the administration, and significantly improved to 9.9 at 1 month, and 7.7 at 12 months. The retention rate at 1 year was 78%. The reason of cessation was inefficacy in 5 cases. There were no reasons of cessation related to adverse events. [Conclusions] Our study demonstrates that sarilumab is useful agent for patients with refractory RA because of rapid good response and sustainable effect up to 12 months after the administration.

## ICW21-1

### Anti-Smith Antibody Stimulation to Endothelial Cells Directly Up-regulates MMP-2 Leading to Claudin-5 Degradation

Yoshiyuki Arinuma, Yu Matsueda, Kunihiro Yamaoka

Conflict of interest: None

[Objective] Breakdown of the blood-brain barrier (BBB) integrity is required for the development of psychiatric manifestations in SLE. The aim of this study is to investigate the direct effect of anti-Smith antibody (anti-Sm) on the breakdown of BBB integrity in endothelium cells, especially by MMP-2 that can degrade tight junction (TJ) proteins. [Methods] Human umbilical vein endothelial cells (HUVEC) were stimulated with monoclonal anti-Sm or anti-RNP antibody (anti-RNP). TJ composing protein, claudin-5 expression was measured by western blot. MMP-2 activity was measured by gelatin zymography. [Results] Compared to isotype control, claudin-5 was significantly reduced by anti-Sm ( $p=0.019$ ), but not by anti-RNP ( $p=0.590$ ). By the combination of anti-Sm and anti-RNP also reduced claudin-5. Active MMP-2 was induced by anti-Sm ( $p=0.090$ ), but anti-RNP ( $p=0.533$ ) and the combination of anti-Sm and anti-RNP ( $p=0.622$ ) did not up-regulate active MMP-2. Captopril, MMP-2 inhibitor treatment restored claudin-5 degradation by anti-Sm. Whereas, captopril did not influence the claudin-5 level by anti-RNP stimulation. [Conclusions] Anti-Sm Ab could directly affect HUVEC through up-regulation of MMP-2 expression and could cause degradation of claudin-5. Captopril may protect BBB from claudin-5 degradation by anti-Sm.

## ICW21-2

### Autoantibodies Against Malondialdehyde-modifications Promote Osteoclast Development by Reprogramming Cellular Metabolism

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Conflict of interest: None

[Objective] Malondialdehyde (MDA) is a highly reactive compound generated during lipid-peroxidation in conditions associated with oxidative stress and can generate protein modifications recognized by autoantibodies which are increased in the serum of patients with autoimmune diseases including rheumatoid arthritis (RA). In addition, Anti-MDA antibodies (Abs) have been shown to promote osteoclast (OC) differentiation *in vitro*. Here we elucidated the pathways specifically triggered by anti-MDA Abs in developing OCs. [Methods] Recombinant human monoclonal anti-MDA Abs cloned from RA patients were added to different OC assays. OCs were generated from monocyte-derived macrophages in the presence of RANK-L and M-CSF. OC development was monitored by light microscopy following tartrate-resistant acid phosphatase staining and in erosion assays using calcium phosphate-coated plates. Bone morphometrics were analyzed in anti-MDA-injected mice using X-ray microscopy. Cellular metabolism was analyzed by mass spectrometry, Seahorse XF Analyzer and a colorimetric L-Lactate assay. [Results] Anti-MDA Abs induced a robust OC differentiation *in vitro* and bone loss *in vivo*. The anti-MDA Abs acted on developing OCs by increasing glycolysis through an Fcγ receptor I-mediated pathway and the upregulation of the transcription factors HIF-1α and Myc. The anti-MDA treatment induced a shift in the tricarboxylic acid (TCA) cycle activity in developing OCs, increasing citrate production. A profound shift in cellular lipid compositions in developing OCs and essential role of phosphoglyceride/triacylglyceride biosynthesis for OC development were also shown. [Conclusions] Anti-MDA Abs promoted OC development by increasing glycolysis and modulating the TCA cycle through a signaling pathway that included Fcγ receptor I and transcription factors acting on glycolysis. A TCA cycle bias towards citrate production suggested that anti-MDA Abs might stimulate osteoclastogenesis via increasing lipid biosynthesis.

## ICW21-3

### Selectivity of Clinical JAK Inhibitors and the Impact on Natural Killer (NK) Cell Functional Responses

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Conflict of interest: Yes

**Objective** To compare the selectivity/potency of Janus kinase inhibitors (JAKinibs) on NK cell function by assessing proliferation mediated by IL-15 (JAK1/3) and IFNγ production driven by IL-12 (JAK2/TYK2)+IL-18. **Methods** Healthy donor NK cells were incubated with JAKinibs (baricitinib, tofacitinib, upadacitinib, filgotinib and FIL metabolite) and stimulated with IL-15 for proliferation (assessed after 6 days) or IL-12/18 for IFNγ production (assessed 4 hrs post-stimulation). IC<sub>50</sub> values were calculated for CD56<sup>bright</sup>, CD56<sup>dim</sup> and total NK cells. Steady-state pharmacologic profile was modelled from patients with RA. The times above IC<sub>50</sub> and average daily inhibition of IFNγ or proliferation were calculated for each JAKinib, NK cell population and donor. **Results** All JAKinibs showed dose-dependent inhibition of IL-15-induced NK cell proliferation. Tofacitinib had the highest inhibition and time above IC<sub>50</sub> (35-60% inhibition for 8-15 hrs; tofacitinib>upadacitinib>baricitinib ≈ filgotinib). Differences between JAKinibs correlated with differential pSTAT inhibition downstream of IL-15. All JAKinibs showed <25% mean inhibition of IL-12/18-induced IFNγ production over 24 hrs without time above IC<sub>50</sub> for IFNγ production or pSTAT4 inhibition. JAKinibs showed ~2-10-fold lower potency in CD56<sup>bright</sup> versus CD56<sup>dim</sup> NK cells for both pSTAT4 and IFNγ production. **Conclusions** NK cell proliferation was differentially inhibited by the JAKinibs while functional responses downstream of IL-12/18 were not substantially inhibited. Proliferative/functional responses aligned with proximal pSTAT inhibition. Modulation of NK cell proliferation, but not response to IL-12, reflect the unique profiles of the JAKinibs studied and may be a factor in safety observations, e.g. increased risk of viral infections/malignancy.

## ICW21-4

### A novel T cell population, IL-17RA+ITGB1+T cell, which shows immune suppression resistance and tissue homing, is involved in spondyloarthritis

Mitsuhiro Akiyama, Keiko Yoshimoto, Sho Ishigaki, Katsuya Suzuki, Tsutomu Takeuchi, Yuko Kaneko

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Conflict of interest: None

[Objective] Spondyloarthritis (SpA) is characterized by enthesitis, in which the adhesion molecules might play a role in tissue homing of the pathogenic T cells into enthesitis composed of fibronectin and collagens. Recently, IL-17RA-expressing T cell has been reported to be the promising cell population which shows the resistance to immune suppression. In this study, we examined the possible involvement of IL-17RA-expressing tissue-homing T cells in patients with SpA. [Methods] Transcriptome analysis of synovial T cells from patients with SpA was conducted with RNA-sequencing. Peripheral blood was obtained from patients with active treatment-naïve SpA and healthy individuals and analyzed for IL-17RA+ITGB1+population by multi-color flow cytometry. [Results] RNA-sequencing analysis revealed that the expression of *IL-17RA* was significantly higher than other subclass of IL-17 receptor family ( $P<0.0001$ ) in synovial T cells and that tissue-infiltrating synovial T cells expressed *ITGB1* most prominently among 24 integrin family members ( $P<0.0001$ ). Interestingly, we discovered that human T cells can be classified into 4 distinct populations according to the expression of IL-17RA and ITGB1 by FACS analysis using whole blood samples. Notably, circulating IL-17RA+ITGB1+T cell population was significantly increased in patients with SpA than in healthy controls ( $P<0.0001$ ). We further examined the proportion of IL-17RA+ITGB1+ cells in T cell subsets dividing into CD4 and non-CD4 (γδ T cells, iNKT cells, and CD8 T cells) and found that the increase in IL-17RA+ITGB1+population was constantly observed in both CD4 and non-CD4 subsets from patients with SpA comparing to healthy individuals ( $P<0.0001$ ). [Conclusions] IL-17RA+ITGB1+T cell population, which is “immune suppression resistant and tissue homing”, was increased in the disease lesion and peripheral blood from patients with SpA, suggesting that this newly identified T cell population is critically involved in the pathogenesis of SpA.

## ICW21-5

### Obesity and hyperlipidemia synergistically exacerbate psoriatic skin inflammation

Tomoyuki Mukai<sup>1,2</sup>, Takahiko Akagi<sup>2</sup>, Sumie Asano<sup>2</sup>, Ayano Yahagi<sup>1</sup>, Masanori Iseki<sup>1</sup>, Katsuhiko Ishihara<sup>1</sup>, Yoshitaka Morita<sup>2</sup>

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Conflict of interest: None

[Introduction] Psoriasis is an inflammatory and hyperkeratotic skin disorder influenced by genetic and environmental factors, resulting in excessive epidermal proliferation and aberrant immune response. Psoriasis is associated with a high rate of metabolic syndrome, but it is not fully understood how obesity and hyperlipidemia are involved in the pathogenesis of psoriasis. In this study, we investigated the mechanisms by which obesity and hyperlipidemia exacerbate psoriasis using murine models. [Methods] We administered a high-fat diet to mice for 10 weeks to induce obesity and used ApoE-deficient mice as a model of hyperlipidemia. Imiquimod, a TLR7 agonist, was applied to the ear for 5 days to induce psoriatic skin rash. Affected skin was analyzed histologically, and gene expression was determined by quantitative PCR. To examine innate immune responses of keratinocytes, normal human epidermal keratinocytes were treated with palmitic acid or leptin in combination with TNF $\alpha$  and IL-17, and gene expression was analyzed. [Results] Obesity alone and hyperlipidemia alone did not significantly worsen psoriatic lesions, but the pathological overlap between obesity and hyperlipidemia significantly deteriorated psoriatic skin inflammation with marked epidermal thickening. Gene expression of pro-inflammatory cytokines and chemokines was upregulated in the affected skin tissues, such as IL-23A/17A/17C/22, CXCL-1/3/5, CCL20. Immunohistochemistry of the skin showed enhanced phosphorylation of STAT3. In keratinocyte culture, palmitic acid and leptin enhanced gene expression of chemokines in combination with TNF $\alpha$  and IL-17. [Conclusions] These results revealed that the presence of obesity and hyperlipidemia synergistically exacerbates psoriatic skin inflammation. Palmitic acid and leptin are considered to be the aggravating factors for psoriasis. These results suggest that managing concomitant metabolic syndromes is essential to prevent disease exacerbation in psoriasis patients.

## ICW21-6

### Metagenome-wide association studies revealed the altered gut bacteriome and virome in autoimmune diseases

Yoshihiko Tomofuji<sup>1</sup>, Yuichi Maeda<sup>2,4</sup>, Eri Igashira<sup>2,4</sup>, Takuro Nii<sup>2,4</sup>, Mayu Yagita<sup>2,4</sup>, Hidetoshi Matsuoka<sup>3</sup>, Maiko Yoshimura<sup>3</sup>, Shiro Ohshima<sup>3</sup>, Atsushi Kumanogoh<sup>2</sup>, Yukinori Okada<sup>1</sup>

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Conflict of interest: None

[Objective] Alteration of the gut microbiome has been linked to the pathogenesis of autoimmune diseases. However, a comprehensive view of the gut microbiome in autoimmune diseases and its interaction with the host remains to be revealed. Metagenome shotgun sequencing technology is useful for evaluating the gut microbiome. For example, we previously applied metagenome shotgun sequencing technology to the patients with rheumatoid arthritis (RA) and multiple sclerosis for identifying the disease-associated bacterial taxa, genes, and pathways. However, evaluation of the microbiome-disease association based on shotgun sequencing is still limited to some diseases because of the high sequencing costs and methodological complexity. In addition, although the viruses infecting bacteria occupy a large fraction of the gut microbiome and actively interact with their bacterial hosts, previous metagenome shotgun sequencing studies had missed the viral components of the gut microbiome due to the technical difficulty. [Method] We performed a metagenome-wide association study (MWAS) of systemic lupus erythematosus (SLE;  $N_{\text{case}} = 47$  and  $N_{\text{control}} = 203$ ) and integrative analysis with plasma metabolite data. In addition, to analyze the changes in the gut virome of the autoimmune diseases, we

developed a new analytic pipeline for recovering the viral abundances from metagenome shotgun sequencing data and applied it to the data from 476 Japanese including the patients of RA, SLE, and MS and healthy subjects. [Results] Our MWAS of SLE revealed the SLE-related changes of the gut microbiome such as increases of *Streptococcus* and its interaction with the host via plasma acylcarnitine. In case-control comparison of the gut virome, disease-associated changes of the gut virome such as the decrease of crAss-like phages in the patients of RA and SLE were identified. [Conclusions] Our comprehensive analysis of the gut microbiome identified the autoimmune disease-associated changes of the gut microbiome.



## Poster Session

### P1-1

#### Relationship between frailty and grip strength in rheumatoid arthritis patients

Yasumori Sobue<sup>1</sup>, Hisato Ishikawa<sup>1</sup>, Mochihito Suzuki<sup>2</sup>, Yoshifumi Ohashi<sup>2</sup>, Toshihisa Kojima<sup>2</sup>

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Conflict of interest: None

[Objective] Grip strength is one of the diagnostic criteria for frailty and reflects physical function. On the other hand, patients with rheumatoid arthritis (RA) often have wrist or finger joint disorders, and it is highly possible that their grip strength is weakened. [Methods] Among 630 patients (T-FLAG Study) between June and August 2021, grip strength, DAS28-CRP and Kihon-Checklist (KCL) of 424 RA female patients were available. In KCL, 8 points or more was defined as frailty. The side with high grip strength was adopted. Tender or swollen joint in either wrist or finger joint was defined as “hand disorders”. We used multivariable logistic regression analysis adjusted for age, DAS28-CRP, and the presence of “hand disorders” for OR of grip strength in frailty. [Results] Of the 424 patients (mean age 66.8 years), 179 (42.2%) had frailty and 150 (35.4%) had “hand disorders”. The age of frailty group/non-frailty group were 72.4±12.7/62.7±14.5 years, DAS28-CRP were 2.6±1.1/2.0±0.9, and “hand disorders” were 42.5%/30.2%, which were significantly higher in frailty group. The OR of grip strength in frailty was 0.94 (95% confidence interval 0.91-0.98). [Conclusions] Weakness was correlated with frailty in female RA patients, regardless of age, disease activity and hand disorders.

### P1-2

#### Associated factors with the development of malignant lymphoma compared to solid cancers

Machiko Mizushima<sup>1</sup>, Takahiko Sugihara<sup>1</sup>, Keiichi Sakurai<sup>1</sup>, Hiroko Nagafuchi<sup>1</sup>, Masaaki Mori<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Kimito Kawahata<sup>1</sup>

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Conflict of interest: None

Objective: Older age and MTX use were reported as risk factors of lymphoma in RA. The aim of this study was to identify associated factors with lymphoma in the patients with malignancies. Methods: We identified 935 patients with malignancies from the National Database of Rheumatic Diseases by iR-net in Japan (NinJa) from 2012 to 2018, and 597 patients had clinical data 1 year prior to complication of malignancies. The predictive factors of lymphoma were examined for the 597 patients by multiple logistic analysis. Results: The mean age of the 597 patients was 69.9 years, 69% female, mean disease duration 14.2 years, mean CDAI 7.14, mean CRP 0.71, smoking history 44.5%, MTX 59.5%, TNF inhibitors 13.2%, IL-6 inhibitors 7.5%, abatacept 4.4%. Complicated malignancies included lymphoma in 15.1%, lung cancer in 14.9%, colorectal cancer in 14.7%, breast cancer in 12.4%, stomach cancer in 11.4%, urological in 9.0%, gynecological in 4.6%, hepatobiliary in 4.3%, and skin cancer in 4.7%. Predictors associated with lymphoma compared to solid tumors were MTX (odds ratio [OR] 2.33, 95% confidential interval [CI] 1.18-4.59), NSAIDs (OR 2.99, 95%CI 1.60-5.61), and elevated CRP. Conclusion: MTX use, NSAIDs use, and chronic inflammation were more associated with lymphoma than with solid tumors.

### P1-3

#### The association between medical costs of antirheumatic disease and the burden of treatment costs on daily life (financial toxicity) in RA patients: NinJa cohort study

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Conflict of interest: None

[Objective] In the present study, we investigated whether the medical cost of anti-rheumatic drugs is associated with financial toxicity in RA patients. [Methods] A cross-sectional study using the NinJa database conducted at 49 sites in 2020. Exposure was defined as antirheumatic drug cost per month. The outcome was financial toxicity and was measured by the 11-item COST (The Comprehensive Score for financial Toxicity) [total score 0-44]. We analyzed the association between antirheumatic drug cost and financial toxicity by multiple regression analysis, in which the adjusted variables were age, gender, DAS28-ESR, years of disease, type of work, medical expense assistance from the company, and high-cost medical care system. [Results] Among 15553 cases in the NinJa database, 1135 cases for which payment self-payment rate and COST were available were included. The median age was 70 years, and 83.1% were female. The median and IQR of antirheumatic drug co-payment and COST per month were 736.2 yen (196.3-8177.5 yen) and 26 (22-30), respectively. We found no association between antirheumatic drug co-payment per month and economic toxicity (-0.006 points (95% CI -0.5-0.39) per ¥10000). [Conclusion] The medical cost of antirheumatic drugs was not associated with the sense of economic burden.

### P1-4

#### The risk of dementia in rheumatoid arthritis (RA)

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Conflict of interest: None

[Objective] Inflammation and dementia have been reported to be related. Although RA is a disease that causes inflammation not only in the joints but also in the body, it has been thought that it is not susceptible to dementia. The purpose of this study was to investigate the actual status of dementia in RA and the relationship between disease activity and dementia. [Methods] This is the retrospective case-control study of 50 RA patients (mean age; 75.1±6.2 years) and 21 osteoarthritis (OA) patients (mean age; 77.8±4.5 years) who consented to the study among patients attending our hospital. Dementia was diagnosed using Mini-Mental State Examination (MMSE) and depression using Self-Rating Questionnaire For Depression (SRQ-D). We examined the relationship between these results, disease activity, and medications, and discussed the relationship with dementia risk. [Results] The MMSE and the SRQ-D were no significant difference between in the RA group and in the OA group. Both the MMSE and the SRQ-D involved age, VAS-Pt, CRP, DAS-CRP, and history of treatment with biologics in the RA group comparison (P<0.001). The MMSE was also associated with disease duration and MTX treatment (P<0.001). [Conclusions] Decreased disease activity is important for the prevention of dementia in patients with RA.

### P1-5

#### Transition from polymyalgia rheumatica to rheumatoid arthritis

Takahiro Netsu<sup>1</sup>, Tadamasa Hanyu<sup>1</sup>, Takako Saeki<sup>2</sup>

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Conflict of interest: None

[Objective] To investigate the outcome of polymyalgia rheumatica (PMR) and to clarify the characteristics of cases of transition to rheumatoid arthritis. [Methods] We studied 43 patients (27 males, 16 females, average age 74.7 (61-87) years) with PMR who were followed up for at least 2 years at our hospital. At the final observation, we investigated whether PMR was in remission (no symptoms of PMR and all medications were discontinued) and whether it had progressed to polymyalgia rheumatoid arthritis (RA) (developed polyarthritis). [Results] Eight patients

(19%) transitioned to RA, and 32 patients (74%) achieved remission of PMR. Of these, 11 patients received csDMARD for PSL resistance. At the onset of RA, arthritis was found in the fingers, wrists, feet, and ankles, and there were no cases of positive RF conversion. The CRP value at the baseline was higher in RA group than in PMR ( $14.9 \pm 5.29$  mg / dl vs  $9.05 \pm 5.73$  mg / dl,  $p=0.012$ ). [Conclusions] Approximately 20% of patients diagnosed with PMR have transitioned to RA. In cases of high CRP at the baseline, it might be necessary to pay attention to small joint inflammation.

## P1-6

### Clinical features of patients diagnosed with rheumatoid arthritis (RA) during treatment for polymyalgia rheumatica (PMR)

Kahori Ishida<sup>1</sup>, Makiko Ikoma<sup>1</sup>, Takehiro Suzuki<sup>1</sup>, Takeshi Kaneko<sup>1</sup>, Koji Nomura<sup>1,2</sup>, Takashi Hosokawa<sup>1</sup>, Hiroshi Fujiwara<sup>1</sup>

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Conflict of interest: None

[Objective] To identify the clinical characteristics of patients diagnosed with RA after diagnosis and during PMR treatment based on the 2012 EULAR/ACR clinical classification criteria for PMR. [Methods] Patients diagnosed with PMR based on the EULAR/ACR PMR criteria in our hospital between February 2012 and September 2019 were classified into two groups: those who were still treated as PMR after 2 years (PMR group) and those diagnosed with RA within 2 years (RA group). We retrospectively compared the features of the two groups. [Results] There were 32 patients in the PMR group and six patients in the RA group. Compared with the PMR group, the RA group tended to have a lower rate of morning stiffness (50.0% vs. 81.3%) and of systemic symptoms such as fever and weight loss (33.3% vs. 56.3%), and a higher RF positivity rate (50.0% vs. 3.1%); however, the differences were not statistically significant. Age at onset, female ratio, frequency of peripheral arthralgia, thigh pain, myalgia, CRP, and ESR did not differ between the two groups. [Conclusions] Patients diagnosed with PMR followed by RA in our hospital tended to have a lower rate of morning stiffness and systemic symptoms and higher RF positivity, although the differences were not statistically significant.

## P1-7

### Research of the risk of mortality in patients with rheumatoid arthritis - from the CHIKARA study -

Koji Mandai<sup>1</sup>, Yutaro Yamada<sup>2</sup>, Noriaki Hidaka<sup>3</sup>, Masahiro Tada<sup>3</sup>

<sup>1</sup>Orthopedics, Osaka Saiseikai Nakatsu Hospital, <sup>2</sup>Orthopedics, Osaka Metropolitan University, <sup>3</sup>Orthopedics, Osaka City General Hospital

Conflict of interest: None

[Objective] Rheumatoid arthritis (RA) is a systemic disease and has been reported to be associated with a higher risk of mortality compared to healthy individuals. The purpose of this study is to investigate the risk of mortality in RA patients, including sarcopenia and locomotive syndrome. [Methods] The data from a prospective observational study (CHIKARA study) were used. Mortality was studied using 5-year data from RA patients, and baseline data was used to examine factors associated with mortality. [Results] 100 RA patients were included. Mean age was 68 years old, median disease duration was 5.5 years. Mean DAS28-ESR was 3.55. The rate of MTX usage was 86%, biologics usage was 30%, and glucocorticoid (GC) usage was 26%. During the 5-year observation period, there were 6 deaths. eGFR was significantly lower in the death group (58.3 ml/min in the death group vs. 77.1 ml/min in the survival group,  $p=0.026$ ), and MTX dose was significantly lower in the death group (3.67 mg/week in the death group vs. 7.27 mg/week in the survival group,  $p=0.027$ ). In the COX hazard proportional model for death, MTX use, sarcopenia, and locomotive syndrome were not significant risk factors. [Conclusions] MTX use, sarcopenia, and locomotive syndrome were not significant risk factors for death.

## P1-8

### Clinical manifestations of rheumatoid arthritis (RA) with hip involvement -Analysis based on NinJa 2020 database

Tetsuji Sawada<sup>1</sup>, Susumu Nishiyama<sup>2</sup>, Toshihiro Matsui<sup>3</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Tokyo Medical University Hospital, <sup>2</sup>Kurashiki Medical Center, <sup>3</sup>NHO Sagami National Hospital, <sup>4</sup>NHO Tokyo National Hospital

Conflict of interest: None

[Objective] At JCR2020 meeting, we have shown that the distribution of affected joints in active RA can be divided into 5 patterns, including one characterized by hip-involvement. The purpose of this study was to clarify the clinical features of RA patients with hip joint involvement, based on *NinJa* 2020. [Methods] RA patients with hip involvement were compared to those without, in terms of various clinical parameters including joint index vector (Nishiyama, Rheumatol Int, 2012). [Results] The manifestations of hip-affected RA included longer disease duration, female predominance, high disease activity (DAS28, CRP, Vx [upper limbs], Vy [lower limbs], Vxy), severe functional impairment, and large-joint predominance (Vz). Age was not associated with hip involvement. [Conclusions] Assessment of hip joint involvement is important in RA clinical evaluation, albeit rare and not included in DAS28, since it is associated with high disease activity and functional impairment.

## P2-1

### Survey on Intention to Receive and Awareness towards SARS-CoV-2 Vaccine in Rheumatoid Arthritis/ Collagen Diseases Patients

Haruka Sugawara<sup>1,3</sup>, Hiroshi Doi<sup>1</sup>, Yoichi Nakayama<sup>2</sup>, Takeshi Iwasaki<sup>2</sup>, Yuri Nishida<sup>2</sup>, Yoshie Gon<sup>2</sup>, Takahiko Utsumi<sup>1</sup>

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Conflict of interest: None

[Objective] The purpose of this study was to investigate the awareness and background factors towards the SARS-CoV-2 vaccine among patients with rheumatoid arthritis/ collagen diseases, and to examine the influence on vaccination hesitancy. [Methods] A questionnaire survey was conducted on outpatients of our Immunology Department from 7/7/2021 to 8/20/2021. Questionnaire items included (1) vaccination status, (2) expectation of susceptibility to COVID-19 severity, (3) expectation of vaccine efficacy, and (4) anxiety about the vaccine. Those who had been or intended to be vaccinated were categorized as the acceptance group, and the others as the hesitation group. [Results] Of the 247 subjects, 30 (12%) were in the hesitation group. A univariate analysis of the questionnaire responses showed that expectation of vaccine efficacy was higher in the accepting group ( $p<0.001$ ), while all vaccine-related anxiety was higher in the acceptance group ( $p<0.001$ ). In multivariate analysis, only the expectation of vaccine efficacy had a significant effect on vaccination intention ( $p<0.001$ ). [Conclusions] Providing information emphasizing the efficacy of vaccines rather than their safety may be more effective in increasing vaccination rates among patients with rheumatoid arthritis/ collagen diseases.

## P2-2

### SARS-CoV-2 mRNA vaccines in rheumatoid arthritis patients

Satomi Kobayashi, Takeshi Kusuda, Kanae Kubo

Department of Medicine and Rheumatology, Tokyo Metropolitan Geriatric Hospital

Conflict of interest: None

[Objective] We aimed to reveal the side effects of SARS-CoV-2 mRNA vaccine including the effects on the disease activity in rheumatoid arthritis (RA) cases. [Methods] Patients with RA were enrolled in this study at our hospital. We picked up the patients' information from their medical records and analyzed the risk of side effects and the changes of the disease activities (SDAI and CDAI) after the vaccination. [Results] One hundred and forty-four RA cases were enrolled. The median age was 77 (range 41-93) years, and the female percentage was 80.5%. 80.5% of cases

were RF-positive, and 71.4% of cases were anti-CCP antibody-positive. 51.3% of cases used methotrexate and 34.7% of cases used glucocorticoid. As for biological agents, CTLA4-Ig, TNF-inhibitors, and IL-6 receptor antagonists were used in 9.72%, 5.55%, and 4.16% of cases, respectively. The main side effects included local pain (48.8%), fatigue (17.2%), and fever (12.7%). There were no significant differences in SDAI and CDAI between before and after the vaccination. Only one had the deterioration of RA needed for intensified treatment. [Conclusions] In this study, SARS-CoV-2 mRNA vaccine had an acceptable safety profile in patients with RA. There was no significant worsening in disease activities after taking the vaccine.

## P2-3

### Characteristics of RA patients who have Normal CRP but progress in Joint Destruction

Koji Nomura<sup>1,2</sup>, Kahori Ishida<sup>2</sup>, Makiko Ikoma<sup>2</sup>, Takehiro Suzuki<sup>2</sup>, Takeshi Kaneko<sup>2</sup>, Takashi Hosokawa<sup>2</sup>, Hiroshi Fujiwara<sup>2</sup>

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Conflict of interest: None

[Objective] There are some RA patients whose joints are progressively destroyed despite normal CRP. Here we examined the characteristics of such RA patients. [Methods] Of all the patients diagnosed with RA for the first time in our hospital, those who met the following four items were included, (1) normal CRP (0.3 or less), (2) one or more bone erosions in X-ray hand/foot images at the first visit, (3) within 3 years of onset and (4) no history of DMARDs or steroid treatment. We investigated patients background, blood test, bone erosion site and CRP elevation during observation. [Results] 18 patients (F13/M5) were included, whose average age of onset was 49.1±10.8 and CRP was 0.12±0.09. 33.3% had RA family history and 72.2% had smoking history. Although WBC and Platelet were normal in all patients, ESR was elevated in most patients. RF and anti-CCP were positive and high in most patients. ANA was also positive in many patients. Bone erosion was more common in the feet, especially 5th MTP. Most patients kept normal CRP during observation. [Conclusions] Most of these RA patients had bone erosions in foot, which made the treatment more difficult because foot is neglected in DAS28. This study clarified characteristics of such RA patients in terms of affected joints and antibody high titers.

## P2-4

### Medical treatment first choice after rheumatoid arthritis diagnosis using health insurance data

Takayoshi Nagahama<sup>1</sup>, Kaori Yokota<sup>2</sup>

<sup>1</sup>Keisen Clinic, <sup>2</sup>Yokota Clinic

Conflict of interest: Yes

[Objective] To inspect whether we followed rheumatoid arthritis medical treatment guidelines. [Methods] Rheumatoid arthritis data was extracted from the health insurance data, which JMDC held in receipt, to confirm the new antirheumatic drug. The pharmaceutical products categories were assumed to be methotrexate, csDMARD, bDMARD, and JAK inhibitor; their single and combined administration were computed. [Results] Data of 31,858 target people was extracted. The order of single administration was as follows: Methotrexate; 11462 (38.4%) > Salazosulfasalazine; 5137 (16.1%) > TNF inhibitor; 4561 (14.3%) > Tacrolimus; 4413 (13.9%). In addition, bDMARD and JAK inhibitor were administered to 5714 (17.9%) patients. The large difference in the ratio is not acceptable for pharmaceutical products before and after the guidelines publication. [Conclusions] The administration was convenient for each patient, but based on choice, JAK inhibitor medicine charge by 17.9%. It is important to make plans for quality medical treatments for improvement, but the tendency to reduce medical expenses makes one to take alternative way of medication.

## P2-5

### Palindromic rheumatism in patients with ACPA positive arthralgia

Tamaki Muramatsu, Isao Matsuura, Yohei Seto

Department of Rheumatology, Tokyo Women's Medical University Yachio Medical Center

Conflict of interest: None

[Objective] To determine palindromic episodes in ACPA positive patients with musculoskeletal symptoms before onset of rheumatoid arthritis. [Methods] Retrospective investigations were carried out for ACPA positive patients who had not fulfilled the ACR/EULAR classification criteria at the first visit of our rheumatology clinic. Date were collected regarding patient backgrounds, treatment interventions and fulfillment of the criteria during the follow-up period. [Results] Nineteen out of 32 patients presented palindromic symptoms: 13 female (68.4%), 61 year-old, ACPA 110 U/ml, and RF 39 U/ml during the follow-up (duration 20.5 months.) Clinical and/or imaging signs of inflammation were confirmed in 17 patients and all received treatment interventions. DMARDs were introduced in 12 patients, and 9 of those fulfilled the criteria when introduced. DMARDs were even effective in those who did not fulfill the criteria. [Conclusions] It was determined that treatment including DMARDs are indicated and effective in ACPA positive patients with palindromic rheumatism.

## P2-6

### Examination of Elderly Patients (pts) in Rheumatoid Arthritis (RA) Patients: The effects of Reclassification of Elderly Patients on disease activities, treatments, renal functions and other parameters

Akikatsu Nakashima<sup>1</sup>, Hiroshi Fujii<sup>1</sup>, Takuya Suda<sup>1</sup>, Ichiro Mizushima<sup>2</sup>, Mitsuhiro Kawano<sup>2</sup>

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Conflict of interest: None

[Objective] The number of patients (pts) with rheumatoid arthritis (RA) is highest in their late 60s. The new reclassification of elderly was advocated. whether this reclassification affects on disease activities, treatments, renal functions and other parameters in RA pts was not investigated and should be studied. [Methods] We enrolled 97 RA outpatients (19 males, average age 74.6 ± 6.5 years) aged 65 years or older treated at our hospital. The pts were reclassified into the pre-old, 65-74 years old (group I: G I), old, 75-89 years old (group II, G II) and 90 years old super-old (group III; G III). Clinical parameters among three groups were examined. [Results] Fifty-nine pts in G I (10 males), 30 patients in G II (8 males), 8 patients in G III (1 male) were observed. The significant difference of renal function expressed as eGFR was observed among the three groups, and in the G III was significantly lower than the other two groups (G I 68.2 ± 15.4, G II 65.3 ± 14.8, G III 50.5 ± 16.4). Prednisolone were administered in 25 pts group I, 11 pts group II, 3 pts group III, methotrexate (MTX) 26 pts group I, 14 pts Group II, 3 pts Group III. [Conclusions] It is necessary to pay attention to the elderly, especially the super-elderly patients regarding drug administration.

## P2-7

### Attempt to predict RA progression: Nagasaki Island Study (NaIS)

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Conflict of interest: Yes

[Objective] The Nagasaki Island Study (NaIS) is a cohort study of health checkups conducted by Nagasaki University in Goto City, Japan. We screened the high-risk group for RA from the NaIS and the outcomes of the high-risk group will be clarified through periodic observation. In addition, we evaluate the Clinically Suspect Arthralgia (CSA) score de-



finished by the EULAR and assess the usefulness of the CSA score in predicting the progression of RA. [Methods] The high-risk group was selected based on serum ACPA, joint symptoms and family history. RA was diagnosed based on the 2010 classification criteria, and the outcome was onset of RA in October 2021. The predictive rate of RA progression was calculated from the CSA score at initial diagnosis. [Results] Fifteen (14.2%) of 106 patients developed RA at 6 months (0-20). Twelve (24.5%) of 49 ACPA-positive patients developed RA at a median of 13 months (2.8-21.3). The CSA score was 0 (0-1), and 60.0% of patients with a score of  $\geq 3$  and 14.9% of patients with a score of  $< 3$  progressed to RA, with a sensitivity of 30%, specificity of 95.2%, PPV of 60%, and NPV of 85.1%. [Conclusions] The sensitivity of CSA score  $\geq 3$  was 30%, which was lower than that of previous reports (70%), although the specificity was high (95%).

## P2-8

### Validation in fulfilling classification criteria and evaluation of a prognosis in patients with SLE showing normal complement levels

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Conflict of interest: None

[Objective] To compare the frequencies of fulfilling the classification criteria of systemic lupus erythematosus (SLE) and a prognosis between SLE patients with normal and low complement levels. [Method] We included 197 patients with SLE. Patients with normal and low serum levels of complement at a diagnosis were classified as N-group and L-group, respectively. Comparisons, including classification rates of American College of Rheumatology (ACR)-1997, Systemic Lupus International Collaborating Clinics (SLICC)-2012, and the European League Against Rheumatism (EULAR)/ACR-2019 criteria, and annual SLICC damage index (SDI) after diagnosis of SLE, the period up to relapse defined by SELENA-SLEDAI Flare index, were performed between two groups. [Results] Classification rates of ACR-1997, SLICC-2012, and EULAR/ACR-2019 criteria were 92.3%, 100%, and 92.5% in N-group, while those were 92.5%, 100%, and 97.2% in L-group, despite not significantly different. There were no significant differences in comparing SDI and relapse between two groups. [Conclusion] This study suggests that fulfilling classification criteria, as well as a prognosis, may not be determined by serum values of complement at a diagnosis of SLE.

## P2-9

### Relationship of the missense mutation in TRPA1 gene with disease activity in rheumatoid arthritis

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Conflict of interest: None

[Objective] Transient receptor potential ankyrin 1 (TRPA1) is one of ion channels which is known as a sensor for pain. TRPA1 is activated by various stimulations such as stimulant compounds, mechanical stimulation and feeling cold. TRPA1 is also involved in not only nociceptive pain but also inflammatory pain. In addition, TRPA1 expression correlates with progression of rheumatoid arthritis (RA). Therefore, changing protein conformation of TRPA1 by amino acid substitution may result in affecting pathology of RA. Thus, we analyzed the relationship of *TRPA1* single nucleotide polymorphism (SNP) with disease activity in Japanese RA patients. [Methods] The subjects were 513 Japanese RA patients using biologics. They were categorized into two groups according to rs959976 (p. His1018Arg) on *TRPA1*: His (His-His or His-Arg) carrier and only Arg (Arg-Arg) carrier. The Disease Activity Score with 28 joints using C-reactive protein (DAS28-CRP) was used in order to assess the disease activity. We used the t-test to compare DAS28-CRP between the two groups. [Results] The mean of DAS28-CRP in only Arg carrier was significantly lower

than in His carrier. [Conclusions] Rs959976 on *TRPA1* gene may affect the disease activity in RA patients using biologics because of changing the protein conformation.

## P3-1

### Possible involvement of CX3CR1<sup>+</sup> CD14<sup>++</sup>CD16<sup>+</sup> monocytes in renal lesions of patients with systemic lupus erythematosus

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Conflict of interest: Yes

[Objective] Fractalkine receptor, CX3CR1, is presumably involved in pathogenesis of systemic lupus erythematosus (SLE). We found that the CX3CR1<sup>+</sup>/CD14<sup>++</sup>CD16<sup>+</sup> ratio of monocytes was remarkably decreased in active SLE patients. In this study, we investigated the possible involvement of CX3CR1<sup>+</sup> CD14<sup>++</sup>CD16<sup>+</sup> monocytes in the pathogenesis of SLE, focusing on renal lesions. [Methods] The CX3CR1<sup>+</sup>/CD14<sup>++</sup>CD16<sup>+</sup> ratio in patients with active SLE (SLEDAI:  $> 10$ , n=60), inactive SLE (SLEDAI:  $< 4$ , n=38) and healthy controls (HC, n=42) was analyzed by FACS. The expression of CD16 and CX3CR1 in renal tissue of patients were analyzed by immunohistochemistry. [Results] The CX3CR1<sup>+</sup>/CD14<sup>++</sup>CD16<sup>+</sup> ratio of monocytes was significantly lower in active SLE than that of inactive patients (p<0.001) and HC (p<0.001). Moreover, CX3CR1<sup>+</sup>/CD14<sup>++</sup>CD16<sup>+</sup> ratio of patients was negatively correlated with the SLEDAI score (p=0.019). Notably, the ratio in active SLE patients with renal lesions was lower as compared to lesion-free patients (p=0.05). In addition, CD16<sup>+</sup>CX3CR1<sup>+</sup> cells were infiltrated into renal tissue of patients, especially into glomerulus. [Conclusions] Our results imply that CX3CR1<sup>+</sup> CD14<sup>++</sup>CD16<sup>+</sup> monocytes are involved in renal lesions possibly due to the acceleration of migration of the cells into organs in SLE.

## P3-2

### Antigen presentation by rheumatoid arthritis sensitive HLA-DR promotes citrullination

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Conflict of interest: None

[Objective] Anti-citrullinated protein antibody (ACPA)-positive rheumatoid arthritis, the HLA gene is known to be the strongest susceptibility factor. Although it has been speculated that the presence of a "shared epitope", a common amino acid sequence among susceptible HLA alleles, enhances the presentation of citrullinated peptides, the details of this mechanism remain unclear. In this study, we investigated the involvement of HLA in citrullination by expressing HLA-DR in model cells in the presence of citrullinated enzyme (PADI4: Peptidylarginine deiminase). [Methods] We prepared 293T cells expressing susceptible allelic HLA-DR (0404) and non-susceptible allelic HLA-DR (0301) by gene transfer using plasmid, and 293T cells without HLA. The cells were then citrullinated by adding PADI4, and the degree of citrullination was compared. [Results] The 293T cells expressing the sensitive allele HLA-DR (0404) were well citrullinated and recognized by ACPA, whereas the cells expressing the non-sensitive allele HLA-DR (0301) and the cells not expressing HLA-DR showed only minor citrullination. [Conclusion] The results suggest that antigen presentation by sensitive HLA-DR promotes citrullination.

## P3-3

### Lack of association of rs12702634 in RPA3-UMAD1 with interstitial lung diseases complicated with rheumatoid arthritis in Japanese

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tology, National Hospital Organization Sagami National Hospital, <sup>4</sup>Department of Rheumatology, National Hospital Organization Sagami National Hospital, <sup>5</sup>Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

**Objectives:** Rheumatoid arthritis (RA) is occasionally complicated with interstitial lung disease (ILD). A recent genome-wide association study of ILD complicated with RA reported an association with the polymorphism rs12702634 in *RP43-UMAD1*. We conducted an association study of this variant with ILD in Japanese RA to replicate this association. **Methods:** Genotyping of rs12702634 was performed in 175 RA with ILD and 411 RA without chronic lung disease. **Results:** No association was detected for rs12702634 with ILD in RA ( $P=0.6369$ , odds ratio [OR] 1.13, 95% confidence interval [CI] 0.72-1.78). Meta-analysis of these data combined with the data from the recent report showed no significant association ( $P=0.0996$ , OR 1.52, 95% CI 0.92-2.49). **Conclusions:** The present study demonstrated no association of *RP43-UMAD1* rs12702634 with ILD complicated with RA, suggesting the heterogeneity of the disease.

### P3-4

#### **Linkage analysis of regulatory T cells, follicular helper or regulatory T cells in younger and elderly onset rheumatoid arthritis and its model**

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Conflict of interest: None

**[Objective]** To clarify age-related differences in Treg, Tfr, and Tfh cells in the peripheral blood of untreated RA patients and to examine whether similar changes are observed in young and old mice with GPI-induced arthritis (GIA) and evaluate the differences in arthritis phenotypes. **[Methods]** 1) For 27 untreated RA patients and 12 osteoarthritis (OA) patients, we analyzed the percentage of Treg, Tfr, and Tfh cells in peripheral blood by flow cytometry, defining 40 years old or younger as young and 65 years old or older as old. 2) GIA was induced in young and old mice, and phenotypic differences were verified using the arthritis score. We also analyze the proportions of Treg, Tfr, and Tfh cells in the spleen or inguinal lymph nodes on day28. **[Results]** 1) In RA, the proportion of Treg and Tfh cells was not significantly different between the two groups, but the proportion of Tfr cells was significantly higher in the elderly group. In OA, there was no significant difference in any T cell subset between the two groups. 2) In aged mice, significantly increased arthritis scores were observed compared to young mice, and significant increases in Tfh and Tfr cells were observed in the spleen. **[Conclusion]** It was suggested that Tfr and Tfh cells might be involved in elderly onset RA.

### P3-5

#### **CD14+ dendritic-shaped cells express CD90 and are involved in the pathogenesis of rheumatoid arthritis**

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<sup>1</sup>Hirosaki Memorial Hospital, <sup>2</sup>Hirosaki University Graduate School of Medicine, <sup>3</sup>Tohoku University

Conflict of interest: None

**[Objective]** CD14+ dendritic-shaped cells show a dendritic morphology under the electron microscope and engage in a pseudo-emperipolesis phenomenon with lymphocytes. CD90 has been used as a marker of a major subset of fibroblast-like synoviocytes in rheumatoid arthritis (RA). In this study, we investigated the significance of CD90 expression in CD14+ dendritic-shaped cells and their involvement in RA pathogenesis. **[Methods]** Double immunofluorescence staining for CD14 and CD90 was performed in the collected tissues included active RA synovial tissues. The localization and the percentages of CD14+CD90+ cells were investigated. Furthermore, CD14+CD90+ cellsorted from RA synovial cells were examined for the potential of dendritic cell differentiation. **[Results]** Double immunofluorescence staining showed that CD14+CD90+ cells were abun-

dant in RA synovial tissues. The percentages of CD14+CD90+ cells correlated with some of the Krenn synovitis scores. CD14+CD90+ cells were more likely to differentiate into dendritic cells *in vitro*. **[Conclusions]** CD14+ dendritic-shaped cells expressed CD90 in the perivascular areas of RA synovial tissue. CD14+CD90+ dendritic-shaped cells may contribute to RA pathogenesis as dendritic progenitor cells.

### P3-6

#### **Involvement of Cellular Communication Network 3 (CCN3) in development of local bone erosion in rheumatoid arthritis**

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Department of Orthopaedic Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University

Conflict of interest: None

**[Objective]** CCN3 belongs to the CCN family proteins and is involved in various kinds of inflammatory diseases as well as bone metastasis. However, the contribution of CCN3 to the progression of Rheumatoid arthritis (RA) has not been investigated. Therefore, the purpose of this study was to investigate the function of CCN3 in RA. **[Methods]** Synovial tissue from patients with RA was immunostained with CCN3 antibody. In vitro experiments using human macrophages and in vivo using osteolysis calvarial model were conducted to assess the effect of CCN3 on bone resorption. Furthermore, RNA-seq of human macrophages stimulated with CCN3 was performed to elucidate the molecular mechanism by which CCN3 promotes osteoclastogenesis. **[Results]** CCN3 was detected in RA synovial tissue. Recombinant CCN3 promoted osteoclast differentiation in vitro and induced bone resorption in vivo. RNA-seq analyses revealed that the upregulated genes in CCN3-stimulated macrophages were significantly enriched in the terms "PI3K-Akt signaling pathway" and "Regulation of actin cytoskeleton", suggesting the ability of CCN3 to promote cell fusion leading to osteoclasts formation. **[Conclusions]** Our results indicate that CCN3 is involved in the pathogenesis of RA through promoting osteoclastogenesis and bone resorption in RA.

### P3-7

#### **Histopathological Changes of Synovial Tissue in Rheumatoid Arthritis Patients Treated with TNF inhibitors or IL-6 inhibitors**

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Conflict of interest: None

**[Objective]** The purpose of this study is to investigate the changes in synovial tissue in RA patients treated with TNF inhibitors (TNFi) or Interleukin-6 inhibitors (IL-6i). **[Methods]** Synovial tissue were divided into 3 groups based on RA treatment: csDMARDs (control group), TNFi, or IL-6i. The samples were subjected to HE, TUNEL, and IHC staining for, respectively, histopathological assessment. The immunofluorescence was also performed to detect the feature of apoptotic cells. **[Results]** TUNEL-positive cells were detected surrounding the discoid fibrosis unique to the TNFi group. TUNEL and immunofluorescence staining showed the apoptotic cells around discoid fibrosis were macrophages. IHC revealed that in TNFi-treated tissue, CD86- and CD80-positive cells were detected only in the lining and sublining layer, while CD163- and CD206-positive cells were detected more broadly; in the IL-6i-treated tissue, all four were detected widely but their levels were lower than in the control group. Expression levels of CD20- and CD3-positive cells were remarkably lower in the IL-6i group. **[Conclusions]** TNFis and IL-6is target different action sites and synovial cell types, resulting in histopathological features of synovium distinct from one another.

### P3-8

#### **Blood coagulation factor XIII is produced in synovial tissue**

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Michinori Ishitoku, Naoya Ooka, Ai Yorishima, Sho Masuda, Kei Araki, Yusuke Yoshida, Tomohiro Sugimoto, Shintaro Hirata, Eiji Sugiyama  
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Conflict of interest: None

[Objective] We reported that the activity of blood coagulation factor XIII (F13) was low in patients with rheumatoid arthritis (RA) treated with tocilizumab. F13 has two subunits, F13A and F13B. In the proteomics database, F13B was detected high levels in joint fluid. Therefore, we analyzed the expression of F13 in synovial tissues. [Methods] RT-qPCR was used to analyze the gene levels of *F13A1* and *F13B* in synovial tissues (RA and osteoarthritis (OA)) and healthy human mononuclear cells. We also verified the localization of F13A and F13B in synovial tissues from RA and OA patients using immunohistochemistry. [Results] RT-qPCR showed that the expression levels of *F13A1* and *F13B* were higher in RA synovial tissues than in mononuclear cells. *F13B* expression levels were higher in OA synovial tissues. Immunohistochemistry showed that F13A was mainly present in the sublining layer, and a higher percentage of positive cells were detected in RA. F13B positive cells were widely distributed in the synovial tissue. [Conclusions] We found that synovial tissue produced F13. We speculate that IL-6 is involved in the regulation of F13 expression, and further investigation of tocilizumab and F13 deficiency is necessary.

### P3-9

#### Clock gene *Bmal1* regulates productions of inflammatory mediators in RA-FLS

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Conflict of interest: None

[Objective] We reported that the expressions of *MMP3*, *CCL2*, *IL6*, *IL7* and *IL15* mRNA of rheumatoid arthritis fibroblast-like synovial cell (RA-FLS) were regulated by *Bmal1*. In this study, we examined proteins of *MMP3*, *CCL2*, *IL6*, *IL7* and *IL15* produced in culture supernatants of RA-FLS to reveal the relationship between *Bmal1* and inflammatory mediators. [Methods] RA-FLSs were transfected with small interfering RNA (siRNA) of *Bmal1*, and stimulated with TNF- $\alpha$  (0,20 ng/ml), IL1- $\beta$  (0,20 ng/ml) and IFN- $\gamma$  (0,20 ng/ml), respectively. Subsequently, the productions of *MMP3*, *CCL2*, *IL6*, *IL7* and *IL15* in the culture supernatant were analyzed by ELISA. [Results] The productions of *MMP3*, *CCL2* and *IL6* were reduced by silencing *Bmal1* expression. [Conclusions] Results suggested that *Bmal1* was implicated in the pathogenesis of RA by regulating *MMP3*, *CCL2* and *IL6* in RA-FLS.

### P3-10

#### Influence of multi drug resistance factor MDR1 on the therapeutic effect of Janus kinase inhibitors

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Conflict of interest: None

[Object] Janus kinase inhibitor (JAKi) has been developed for the treatment of rheumatoid arthritis (RA). However, there are ineffective cases. We focused on multi drug resistance factor (MDR1). To the best of our knowledge, there is no reports on the association between JAKi and

MDR1. In this study, we assessed whether the expression of MDR1 affected the therapeutic effect of JAKi. [Methods] Primary cultured RA and osteoarthritis (OA) synovial fibroblast-like cells were seeded and treated with five JAKis (Tofacitinib, Baricitinib, Peficitinib, Upadacitinib, Filgotinib) at three levels of drug concentration, respectively. Cells were stimulated with IL-6 and soluble IL-6 receptor 100 ng/ml 2 hours after JAKi treatment and assessed by WST-assay after 24 hours. MDR1 expression was assessed by real time polymerase chain reaction. [Results] MDR1 expression was stronger in the RA synovial cells than in the OA synovial cells. All five types of JAKi decreased proliferation dose-dependently. The expression level of MDR1 had no effect on the efficacy of all five JAKis at clinical dose. [Conclusions] It was suggested that JAKi may be effective even in patients with strong MDR1 expression.

### P4-1

#### Analysis of the role of T-bet in B cells in murine autoimmune arthritis

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Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

[Objective] Although T-bet in CD4<sup>+</sup> T cells has a protective role against collagen-induced arthritis (CIA), the role of T-bet in B cells remains to be elucidated. [Methods] 1) T-bet knockout (T-bet KO) mice and CD4-Cre T-bet<sup>fl/fl</sup> (conditional KO; cKO) mice, which lack T-bet in T cells, were immunized with type II collagen to induce CIA. 2) The titers of CII-specific IgG of the sera from wild-type (WT), T-bet KO, T-bet<sup>fl/fl</sup>, and cKO mice were measured. 3) The frequency of T-bet<sup>+</sup> cells in B cell subsets was determined. 4) The frequency of plasmablasts and plasma cells in the draining lymph nodes (dLNs) and bone marrow was examined. [Results] 1) The severity and the incidence tended to be more severe in T-bet KO mice. 2) Whereas CII-specific IgG titer of the sera from T-bet KO mice was higher than WT mice, CII-specific IgG titer of the sera from cKO mice was comparable to T-bet<sup>fl/fl</sup> mice. 3) T-bet was expressed in 10~15% of transitional B cells, age-associated B cells, and regulatory B cells and 2~5% of plasmablasts and plasma cells. 4) The frequency of plasmablasts and plasma cells in the dLNs and bone marrow was comparable between WT and T-bet KO mice. [Conclusions] T-bet was expressed in various B cell subsets and T-bet in B cells might repress CIA by suppressing CII-specific IgG production.

### P4-2

#### The analysis for the inhibition of angiogenesis by peficitinib

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Conflict of interest: None

[Object] Many blood vessels are generated in the hyperplastic synovial tissue of patients with rheumatoid arthritis (RA). Janus kinase inhibitors have inhibitory effects on multiple signaling pathways, however, there were few reports concerning their effects on angiogenesis. In this study, we evaluated the influence of peficitinib on the angiogenesis of human umbilical vein endothelial cells (HUVEC). [Methods] HUVECs were treated with 20 ng/ml VEGF including various doses (0.1  $\mu$ M, 1  $\mu$ M, 5  $\mu$ M) of peficitinib. The activity of proliferation, tube formation, and migration were analyzed by cell counting assay, tube formation assay, and migration assay. In addition, the signal transducer and activator of transcription 3 (STAT3) phosphorylation of HUVEC stimulated by 50 ng/ml VEGF, and the suppression of STAT3 phosphorylation by peficitinib were evaluated by western blotting. [Results] The proliferation activity, tube formation, and migration activities were increased by VEGF and suppressed by peficitinib. STAT3 was phosphorylated by the VEGF stimulation, and peficitinib inhibited the phosphorylation. [Conclusions] VEGF could induce the angiogenesis of vascular endothelial cells via STAT3 phosphorylation, and peficitinib downregulates the angiogenesis by the suppression of STAT3



phosphorylation.

### P4-3

#### Autocitrullination switches peptidylarginine deiminase 4 from enzymatic to monocyte-chemotactic activities

Ken Yoshida<sup>1</sup>, Haruyasu Ito<sup>1</sup>, Kentaro Noda<sup>1</sup>, Mitsuru Saito<sup>2</sup>, Daitaro Kurosaka<sup>1</sup>

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Conflict of interest: None

[Objective] This study aimed to clarify the function of peptidylarginine deiminase 4 (PAD4) before and after autocitrullination and identify citrullinated PAD4 in the synovial fluid (SF) of rheumatoid arthritis (RA). [Methods] Enzymatic activities of unmodified and citrullinated PAD4 were compared based on the amount of citrullinated protein substrate. Monocyte chemotaxis was assessed *in vitro*, and the ability of citrullinated PAD4 to induce arthritis was evaluated *in vivo*. The level of citrullinated PAD4 in RA SF was measured using a new ELISA. [Results] Enzymatic activity was substantially lower for citrullinated, than unmodified PAD4. Chemotactic findings showed that citrullinated PAD4 recruited monocytes, whereas unmodified PAD4 did not. Citrullinated PAD4 induced more inflammation in mouse joints via monocyte migration than unmodified PAD4. The level of citrullinated PAD4 was higher in RA than osteoarthritis SF. Anti-cyclic citrullinated peptide titers and levels of citrullinated PAD4 did not correlate, and citrullinated PAD4 was detected even in seronegative patients. [Conclusions] The autocitrullination of PAD4 amplified inflammatory arthritis via monocyte recruitment, suggesting an anti-citrullinated protein antibody-independent role of PAD4 in the pathogenesis of RA.

### P4-4

#### The kinematics of arginine vasopressin expression and involvement in analgesia in neuropathic pain model rats

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Conflict of interest: None

[Objective] It was reported that arginine vasopressin (AVP) has an analgesic effect. [Methods] We investigated the kinematics of expression of endogenous AVP and its analgesic effect in neuropathic pain model rats induced by the unilateral lumbar spinal nerve ligation (SNL). We used two kinds of transgenic (Tg) rats, AVP-eGFP Tg rats that AVP expressed with eGFP, and AVP-hM3Dq-mCherry Tg rats that the AVP neurons can be specifically activated by Clozapine-N-oxide (CNO). [Results] The symptom of neuropathic pain was developed in all rats. The fluorescent intensity of Iba-1 and GFAP in the L5 dorsal horn and eGFP in the hypothalamus, median eminence and posterior pituitary significantly increased in the SNL group on 7 and 14 days after the SNL. The expression level of AVP mRNA evaluated by the *in situ* hybridization histochemistry significantly increased in the SNL group on 14 days after the SNL. The nociceptive threshold was significantly increased in AVP-hM3Dq-mCherry Tg rats after the CNO injection, and the analgesic effect was significantly attenuated by pretreatment of V1a receptor antagonist. [Conclusions] The endogenous AVP is upregulated by neuropathic pain, and the specific activation of endogenous AVP exerts analgesic effect via V1a receptor in neuropathic pain model rats.

### P4-5

#### Analysis of anti-fibrotic potential of JAK inhibitors in bleomycin-induced pulmonary fibrosis model

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Conflict of interest: None

Molecular targeted therapy has improved the prognosis of connective tissue disease (CTD) significantly in recent years. However, interstitial lung disease associated with CTD remains an intractable condition. Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinase that transduce cytokine-mediated signals via the JAK-signal transducer and activator of transcription pathway. In addition to major inflammatory cytokines, TGF- $\beta$ , a major profibrotic mediator, has been reported to transmit their signals particularly through JAK2. In the present study, we examined anti-fibrotic effect of two JAKi, tofacitinib and baricitinib, using human lung fibroblasts cell line and bleomycin (BLM)-induced pulmonary fibrosis model in mice. Baricitinib suppressed TGF- $\beta$  induced phosphorylation of JAK2 in lung fibroblasts more significantly than tofacitinib. Baricitinib also suppressed TGF- $\beta$  induced collagen1,  $\alpha$ -SMA expression in fibroblasts strongly compared with tofacitinib. Moreover, baricitinib, and not tofacitinib improved fibrosis in BLM-treated lung, especially when treated in late phase. These results suggest that baricitinib might contribute to amelioration of pulmonary fibrosis via selective inhibition of JAK2 phosphorylation in lung fibroblasts.

### P4-6

#### Involvement of cellular senescence mechanism in interstitial pneumonia

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Conflict of interest: None

[Objective] Interstitial lung disease (ILD) develops in the process of abnormal repair of lung tissue damage. Aging and cellular stress cause cellular senescence defined as irreversible cell cycle arrest. Senescent cells (SnCs) potentially acquire the senescence-associated secretory phenotype (SASP), causing inflammatory diseases. We investigated how cellular senescence is involved in the pathogenesis of ILD using murine bleomycin-induced pneumonia (BLM-ILD). [Methods] BLM-ILD was induced in 10 weeks-old C57BL/6 male mice. The expression of p16, p21, and  $\gamma$ H2AX in lungs were examined by immunohistology. Type 2 alveolar epithelial cell (AEC2)-enriched cell population was FACS-sorted using antibodies against CD31, CD45 and EpCAM and subjected to real-time PCR for SASP-associated genes. [Results] p16, p21 and  $\gamma$ H2AX were detected in a subset of AEC2 in BLM-ILD as early as 3 days after BLM administration, which preceded the development of interstitial fibrosis. The gene expression of Tnfa, Il6, Il1b, Mcp1, Pai1, Mmp12, and Tgfb was significantly increased in AEC2 in BLM-ILD compared with the control group. [Conclusion] Cellular senescence occurred in AEC2 prior to the development of fibrosis in BLM-ILD. The SnCs acquired SASP features and may be involved in the development of ILD.

### P4-7

#### Anti-Monomeric C-Reactive Protein Antibody Ameliorates Arthritis and Nephritis in Mice

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Conflict of interest: Yes

C-reactive protein (CRP) is a dynamic protein that can undergo conformational change between the circulating native, pentameric CRP (pCRP) and monomeric (or modified) CRP (mCRP) forms. For clinical purposes, pCRP is typically quantified rather than mCRP. Although previous research suggested that pCRP functions as a direct mediator of inflammation, it exhibits only weak anti-inflammatory activity. In contrast, numerous studies indicate that mCRP exhibits strong pro-inflammatory activity. In this study, we screened >1800 anti-mCRP mAb clones as part

of an effort to develop an anti-mCRP therapy. Clone 3C specifically recognized mCRP but not pCRP. The anti-mCRP mAb 3C blocked the binding of mCRP to peripheral blood mononuclear cells (PBMCs) and suppressed leukocyte infiltration in thioglycollate-induced peritonitis. Furthermore, the anti-mCRP mAb 3C attenuated the symptoms of rheumatoid arthritis in an arthritis mouse model and symptoms of lupus nephritis in an MRL/lpr lupus-prone mouse model. mCRP is thus a specific therapeutic target in the treatment of rheumatoid arthritis and systemic lupus erythematosus (SLE).

## P4-8

### Efficacy of abatacept (ABT) in autoimmune arthritis in SKG mice

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Kindai University Faculty of Medicine

Conflict of interest: None

[Objective] To examine the effects of ABT in SKG mice. [Methods] Zymosan A (ZnA) was administered intraperitoneally to 8-week-old male SKG mice, and ABT was administered on days 7, 9, 11, 14, 20, 27, 34, 41, 48, 55, and 62, and Sacrificed on day 84. In these samples, arthritis scores and inflammatory cytokines were measured to verify the impact of ABT treatment. [Results] The arthritis score was improved predominantly in the ABT-treated group compared with the control group, and IL-17A by PCR was also decreased predominantly in the ABT-treated group. And there was a positive correlation between arthritis score and IL-17A in spleen PCR. Serum IL-17A was also decreased predominantly in the ABT-treated group. And also in vitro, co-culture of ABT with splenocytes was clearly better than culture without ABT. In vitro, IL-17A was clearly lower when splenocytes were co-cultured with ABT than when they were cultured without ABT. [Conclusions] In SKG mice, we were able to show that treatment with ABT predominantly suppressed IL-17A, one of the inflammatory cytokines, and as a result, arthritis was also improved. The effects of ABT on IL-17A will be discussed.

## P4-9

### Abatacept suppresses T cell activation by internalizing CD80 and antibody production

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Conflict of interest: Yes

[Objective] Abatacept (CTLA-4 Ig) is used to treat rheumatoid arthritis by inhibiting co-stimulatory signaling to interact with CD80 on antigen-presenting cells. We analyzed the therapeutic effect of abatacept in rheumatoid arthritis mouse model in which express CD80 expressed in the joint. [Methods] A low dose of bovine type II collagen induced chronic joint inflammation in D1BC mice. Abatacept was administered thrice a week from weeks 3 to 10 after 1st immunization. Serological examination and flow cytometric analysis including abatacept bound CD80 internalization on isolated synovial cells were performed. [Results] Abatacept ameliorated inflammatory polyarthritis and reduced infiltrated lymphocytes in the joints of D1BC mouse. RF IgG was increased in human IgG-treated mice, but not in abatacept-treated mice. This was accompanied by a decrease B-cell population in the lymph nodes. Approximately 15% of synovial cells expressed CD80. Abatacept bound to CD80 and internalized into the cell. This binding and/or internalization does not alter gene expression significantly. [Conclusions] The therapeutic effects by abatacept may extend beyond the lymph nodes, because abatacept suppressed CD80-mediated T cell immune activation in the joints.

## P5-1

### The association between cytoplasmic staining patterns of fluorescent antinuclear antibody and type of anti-ARS antibodies

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Conflict of interest: None

[Objective] To evaluate cytoplasmic staining pattern of fluorescent antinuclear antibodies (Abs) (FANA) for predicting the type of anti-aminoacyl-tRNA synthetase (ARS) Abs, using EUROPattern [Methods] We identified FANA patterns of 81 patients with anti-ARS Abs positive polymyositis/dermatomyositis (PM/DM) in our hospital. We assessed the association between cytoplasmic staining patterns and type of anti-ARS Abs. [Results] Of the anti-ARS antibody-positive patients, 26% included FANA-negative patients. With the addition of visual confirmation, FANA-negative patients decreased to 8.6%. FANA cytoplasmic pattern-positive patients were 77%. Among anti-PL-7 antibody and anti-PL-12 antibody positive patients, the Cytoplasmic positive rate was as high as 93% and 90%, respectively. Dense fine speckled type included 21%, of which 71% were anti-PL-7 and PL-12 antibodies. [Conclusions] Patients with PM/DM are sometimes seen to be FANA-negative, but by visually confirmation, it was found that it is FANA-positive with a high probability. The Dense fine speckled type was positive for anti-PL-7 antibody or PL-12 antibody at a high rate. It was suggested that the clinical picture of PM/DM could be predicted from the FANA results by combining EURO Pattern and the visual confirmation.

## P5-2

### Five cases of Systemic Lupus Erythematosus in which anti-centromere antibody turned positive after corticosteroid treatment-Clinical significance of changes in autoantibody epitopes seen after treatment-

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Conflict of interest: None

[Objective] Anti-centromere antibody (ACA) is a specific autoantibody for limited scleroderma (SSc). We report five cases of SLE, in which the antinuclear antibody (ANA) pattern had changed to ACA after steroid treatment. [Cases] The median age of onset of SLE in 5 patients was 27 years (14-55 years), and all had severe organ damage (nephritis in 3 cases, 1 with thrombocytopenia and 1 with neuro-psychiatric lupus), and they received high-dose steroids therapy. Before steroid treatment all cases were positive for ANA but negative for discrete speckled pattern, 3 cases were positive for anti-DNA antibody. Positive ACA was found 50 months (14-96 months) after the treatment. At the time of ACA positivity, no clinical symptoms consistent with SSc were found. We have followed up for 14.5 years, and SLE was in remission in 2 patients at the final observation. [Conclusions] Changes in antibody epitopes are considered as "epitope progression" and are discussed as a mechanism for the production of pathogenic autoantibodies. The five cases shown here indicate that the corresponding antigen of ANA can change even after treatment and that it may affect the outcome of disease. The reason why the induced antibody was ACA is unknown, but it is interesting in considering the pathogenesis of SSc.

## P5-3

### Trends in rheumatoid factor IgM (IgM-RF). Analysis of long-term progress. - 1st Report -

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Conflict of interest: None

[Introduction] IgM-RF is currently treated as a major item along with anti-CCP antibodies in the ACR and Eular rheumatoid arthritis (RA) classification criteria. It is an important position in the early diagnosis of RA. As another benefit, it is known that this factor appears before the onset of RA and the value gradually rises. Although this factor shows various features as a biological marker, there is no report which investigated the trend in the course of treatment for a long time and analyzed the relation with RA in detail. [Purpose] To understand the significance of this factor during the RA clinical course. [Method] Measurement of RF during the course of treatment in RA patients. [Results] It is divided into groups with clear

significance and unknown groups. In the former, 1) it is accompanied by the improvement and deterioration of RA. 2) With changes in DMARDs. 3) Changes after biologics introduction. In the latter, 1) Titer of RF decreases during improvement, but rises after a certain period of time. 2) A certain movement is shown, but its significance is unknown. 3) It is completely unknown. [Conclusions] It is clear that this factor shows some movement in patients with RA in relation to disease activity and therapeutic agents.

## P5-4

### Examination of factors affecting fluctuations in anti-CCP antibody levels in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Anti-CCP antibody (ACPA) is an antibody having high specificity for rheumatoid arthritis (RA). The purpose of this study is to clarify the clinical factors that influence fluctuations in ACPA levels in RA. [Methods] 307 patients with RA in whom ACPA values were measured twice with an interval of more than three years were analyzed. Based on the results of two ACPA measurements, the cases were divided into an ascending group and a non-ascending group. The relationship between the two groups was investigated for usage of biologic agents, changes in rheumatoid factor, MMP3 levels, and as clinical background, the presence or absence of family history, smoking history, and periodontal disease. [Results] Of the 307 cases, the ascending group was 157 and the non-ascending group was 150. There was no association between the decrease in ACPA level and usage of biologic agents. Rheumatoid factor was elevated in the ascending group and decreased in the non-ascending group. MMP3 was reduced in both groups. There was no association between family history, smoking history, periodontal disease, and changes in ACPA levels. [Conclusions] Factors influencing fluctuations in ACPA levels in RA patients were investigated. The factors involved in the fluctuation of ACPA could not be pointed out.

## P5-5

### Examination of tuberculosis antigen-specific T cells in patients with rheumatic disease undergoing immunosuppressive treatment

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Conflict of interest: None

[Objective] To explore the characteristics of tuberculosis antigen-specific T cells in rheumatic disease patients with IGRA (Interferon- $\gamma$  release assay)-positive who have a history of tuberculosis. [Methods] From patients undergoing immunosuppressive treatment, 20 patients with a history of tuberculosis (HT, 6 IGRA-positive) and 15 non-tuberculosis-exposed groups (NT, 0 IGRA-positive) were selected. A tuberculosis-specific antigen was added to the patient's peripheral blood mononuclear cells and incubated. Next, the expression of T cell-related surface antigens and intracellular cytokines was analyzed by mass cytometry. [Results] The IFN- $\gamma$  high+ CD3+ T cells was 0.18% in the NT group and 0.50% in the HT group, showing a significant difference. Among the 10 T cell clusters (A-J) obtained by clustering using Flow SOM, three groups (C, E, H) express high IFN $\gamma$ . Among them, Cluster C of GM-CSF high+ CD4+ CD8+ was non-specific. On the other hand, in CD4+ CXCR3+, IL-2high+ TNF- $\alpha$  + Cluster E and CD4+ CD25+ CD161+ CXCR3 + Cluster H were significantly increased in the IGRA positive group. [Conclusions] IFN- $\gamma$ high+ CD4+ CXCR3+ IL-2high+ TNF- $\alpha$  and IFN- $\gamma$ high+ CD4+ CD25+ CD161+ CXCR3+ T cells were candidates as important T cell subsets for the immunosuppressed tuberculosis immune response.

## P5-6

### A study of first-time outpatients with Raynaud's syndrome using nail-fold videocapillaroscopy by appointment from the patient and general practitioner -Effectiveness in picking up collagen disease cases

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Conflict of interest: None

[Objective] Since 2016, we have established an outpatient clinic (Raynaud's clinic) specializing in Raynaud's symptoms (RS) for the early diagnosis of systemic sclerosis (SSc) examined with nailfold videocapillaroscopy (NVC). Patients with a chief complaint of RS can be referred from inside or outside the hospital, or can make an appointment in person without a referral only at this clinic. This study will focus on the final diagnosis of patients referred from general practitioners and those who visited this clinic without a referral, in order to clarify the usefulness of NVC in daily practice. [Methods] Of the 172 first-time patients who visited our clinic between April 1, 2016 and September 30, 2021, the route of consultation was categorized as no referral, referral from a general practitioner, or other, and the final diagnosis, NVC findings of patients who visited. [Results] Of the 13 patients seen without referral, 11 (85%) had primary RS with normal NVC, and 2 (15%) had secondary RS (both SSc). Of the 28 cases referred from general practitioners, 14 (50%) were primary RS and 11 (39%: 6 SSc, 4 MCTD, 1 SS) were secondary RS. [Conclusions] 15% of patients seen without referral and 39% of patients referred by general practitioners were eventually diagnosed with collagen disease.

## P5-7

### Comparison of characteristics at the onset of polymyalgia rheumatica and rheumatoid arthritis in our hospital

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Conflict of interest: None

[Objective] We compared Polymyalgia rheumatica (PMR) and Rheumatoid arthritis (RA) in the factors that influence the diagnosis of these two diseases at the time of onset. [Method] All cases of PMR were extracted from the names of health insurance diseases between 2013 and 2020, and the contents and progress of the medical records were confirmed. Patients diagnosed with PMR from the course. All cases of RA were extracted the same procedure. Among them, age and gender were matched with PMR as closely as possible, and physical findings, blood test findings, and ultrasonography findings were compared. [Results] The subjects of PMR were 36 patient, 28 women, and 8 men. The average age was 77 years, and the oldest was 90 years. In blood findings, inflammatory markers such as CRP, ESR, and WBC numbers were superiority difference higher in PMR. Physical findings showed that PMR was 83% for large joints alone and 8% for RA. On the other hand, joint ultrasonography findings showed clear active synovitis due to Power Doppler in 37% and 7.1%, respectively. [Conclusion] Some PMRs do not show definite active synovitis in painful joints with ultrasonography. It is necessary to comprehensively diagnose with various tests.

## P5-8

### Anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis caused by bacterial organizing pneumonia in a patient with Sjogren syndrome

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Conflict of interest: None

A 58-year-old woman with a history of Sjogren's syndrome was ad-



mitted to our hospital with cough, decreased right lung breath sounds and arthralgia in both thumbs. Chest computed tomography showed consolidation with air bronchogram in the right lung. Levels of anti-cyclic citrullinated peptide antibody and rheumatoid factor levels were significantly elevated. She was diagnosed with rheumatoid arthritis induced by bacterial organizing pneumonia. Treatment with salazosulfapyridine was added for rheumatoid arthritis and arthralgia gradually improved. This case highlights that respiratory infections could lead to anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis in patients with Sjogren's syndrome.

## P6-1

### Differences of ultrasonographic intra-articular synovitis findings between treatment drugs in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] We investigated the differences of ultrasonographic intra-articular synovitis findings between treatment drugs in patients with rheumatoid arthritis. [Methods] From January 2017 to August 2020, 750 RA patients who underwent ultrasound examination were included. The total grayscale and power Doppler score (GSUS/PDUS) findings were compared between treatment drugs of RA by using propensity score matching methods. [Results] There were 517 patients (68.9%) treated BIO/JAK, and 205 patients with or without BIO/JAK in each group were matched. GSUS were  $10.6 \pm 11.1$  vs  $9.2 \pm 10.4$  ( $p=0.218$ ) and PDUS  $7.4 \pm 9.2$  vs  $6.5 \pm 9.0$  ( $p=0.328$ ). There were 525 patients (70.0%) treated MTX, the average MTX dose was 9.3 mg, and 203 patients with or without MTX in each group were matched. GSUS were  $9.7 \pm 10.6$  vs  $11.4 \pm 12.0$  ( $p=0.119$ ) and PDUS  $6.6 \pm 8.8$  vs  $8.1 \pm 10.1$  ( $p=0.117$ ). There were 111 patients (14.8%) treated PSL, the average dose was 4.0 mg, and 105 patients with or without PSL in each group were matched. GSUS were  $15.7 \pm 13.9$  vs  $11.6 \pm 10.6$  ( $p=0.018$ ) and PDUS  $11.5 \pm 11.4$  vs  $8.1 \pm 9.6$  ( $p=0.021$ ). [Conclusions] PSL use did not suppress the ultrasonographic synovial findings. Joint destruction might progress in patients using PSL.

## P6-2

### Association of anti-CCP antibody with low-field magnetic resonance imaging findings in patients with RA or undifferentiated arthritis

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Conflict of interest: None

[Objective] To clarify the association of low-field MRI (compactScan; cMRI) findings and autoantibodies (anti-CCP antibody; aCCP and rheumatoid factor; RF). [Methods] RA or undifferentiated arthritis (UA) patients with hand arthralgia, who were evaluated by cMRI before the start of treatment, were enrolled. We divided into two groups according to 1) autoantibodies, 2) inflammatory findings in cMRI (bone marrow edema; BME and synovitis). And we compared age, sex, disease duration, diagnosis, cMRI findings, and laboratory findings, retrospectively. [Results] 114 cases (male: 35/female: 79), age:  $55.1 \pm 14.8$  years, disease duration:  $19.3 \pm 36.9$  months, RA: 83/UA: 31. 101 cases (88.6%) had erosion in cMRI. 1) Seropositive: 65/seronegative: 49. Age, sex, and disease duration was comparable. The proportion of patients who showed BME in cMRI was significantly higher in seropositive group (32.3% vs 14.3%,  $P=0.03$ ). 2) With inflammation: 99/ no inflammation: 15. aCCP positive rate (49.5% vs 20.0%,  $P=0.049$ ) and erosion score ( $7.1 \pm 6.9$  vs  $2.5 \pm 2.0$ ,  $P=0.004$ ) were significantly higher in inflammatory group, although RF positive rate was

comparable. [Conclusions] It was suggested that inflammatory findings in cMRI might be associated with aCCP.

## P6-3

### Examination of tendonitis and enthesitis of large joints in cases diagnosed with rheumatoid arthritis who visited the hospital with the chief complaint of hand symptoms

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Conflict of interest: None

[Objective] We examined the enthesitis of large joint with hand symptoms using ultrasonography (US). [Methods] At the first visit, the US was used to examine the symptomatic large joints. We compared three groups, the group A (GA) of 42 cases diagnosed with RA at the first visit, the group B (GB) of 17 cases diagnosed with RA after the first visit, and the group C (GC) of 34 ACPA positive cases not diagnosed with RA. [Results] Triceps enthesitis was found in 1/8 cases in GA, 2/5 cases in GB, 2/9 patients in GC ( $p=0.515$ ). Biceps tendonitis was found in 13/16 cases GA, 7/10 cases in GB, 9/13 cases in the GC ( $p=0.713$ ). Supraspinatus tendonitis was found in 6/16 cases in GA, 0/8 cases in GB, 3/13 cases in GC ( $p=0.129$ ). Quadriceps femoris enthesitis was found in 10/15 cases in GA, 4/9 cases in GB, 1/15 cases in GC ( $p=0.003$ ), and GA and GB were significantly more than GC. Patellar ligament enthesitis was found in 8/15 cases in GA, 1/9 cases in GB, and 3/15 cases in GC ( $p=0.049$ ), GA and GB were significantly higher than that of GC. Achilles tendonitis was found in 5/13 cases in GA, 2/7 cases in GB, and 3/11 cases in GC ( $p=0.820$ ). [Conclusions] Patella enthesitis was considered to be associated with the onset of RA. Enthesitis of the large joint may precede the onset of RA.

## P6-4

### Trial to distinguish early RA from menopausal arthralgia by sonography

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Conflict of interest: None

[Objective] With the evolution of treatment, the importance of differential diagnosis between early RA and menopausal arthralgia is increasing. [Methods] (1) 109 cases with joint pain were diagnosed with the criteria for menopause. 11 in 109 cases (10%) were diagnosed with RA, and 90 cases (83%) with menopausal arthralgia. Joint sonography was tried to 50 of 90 cases with menopausal arthralgia to search for synovitis. (2) Focusing on stiffness, 22 cases diagnosed with menopausal arthralgia were investigated by sonography. [Results] (1) No synovitis by sonography was found in 50 of 90 cases with menopausal arthralgia. Hormone replacement therapy was given to 56 of 90 cases, and the average pVAS which was 72.3 before treatment decreased to 44.5 on 1 month and 26.5 on 6 months after the start of treatment. (2) In 22 cases with menopausal arthralgia and stiffness, 20 cases showed clear vasodilation sign in sonography, and 2 cases did not. [Conclusions] There was no synovitis in arthralgia as a menopausal disorder, and it often showed only a clear vasodilatory imaging. Hormone replacement therapy is effective for menopausal arthralgia. Early initiation of treatment for RA with anti-rheumatic drugs affects the prognosis. It is very important to distinguish the two.

## P6-5

### Comparison of original and updated 2016 RAMRIS on Bilateral hand of MRI to Predict Relapse after MTX Reduction

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Conflict of interest: None

[Objective] To compare original and updated 2016 RAMRIS on Bilateral hand of MRI to Predict Relapse after MTX Reduction [Methods] Eligible patients had to have a diagnosis of RA with clinical remission defined by DAS28-CRP and obtained both hand of MRI. MRI images was scored by using original and updated RAMRIS. After MRI examination, MTX dose of these patients was reduced and compare both RAMRIS score about prediction of disease flare. [Results] A total of 5 patients was included in this study. Four patients were positive for RF and anti-CCP antibody test. The average age, disease duration, and DAS28-CRP at MRI examination was  $76.6 \pm 5.3$ ,  $9 \pm 7.4$  and  $1.37 \pm 0.15$ . The average dose of MTX before reduction was  $9.6 \pm 3.14$  mg/w. Disease flare was observed in 1 patient during a mean follow-up period of  $334 \pm 29.6$  days. In scoring original RAMRIS, the average synovitis score of patients who had disease relapse was  $1 \pm 1.0$  and that of patient who had not was same 1. In updated 2016 RAMRIS, their synovitis score was  $1.5 \pm 0.9$  and 5, respectively. Tenosynovitis was also detected in patients who had disease flare. [Conclusions] Updated 2016 RAMRIS might be more useful for prediction of disease flare after dose reduction of MTX who achieved clinical remission.

## P6-6

### Two preclinical RA suspected cases with interosseous peritendinitis and multiple tenosynovitis

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Conflict of interest: None

I report two cases of patients with peritendinitis of interosseous muscle (PI) and multiple tenosynovitis. PI is reported to occur in anti-cyclic citrullinated peptide (CCP)-positive at-risk individuals and can precede the onset of clinical synovitis. Two women, aged 74 and 42 years, complained difficulties making a fist and detected PIs (the former at left and the latter at bilateral third palmar interosseous tendons) by bilateral hand enhanced MRI, but did not meet the ACR/EULAR 2010 RA classification criteria, and both were negative for anti-CCP antibody. The former was also detected synovitis at bilateral flexor tendons and metacarpophalangeal (MCP) joints. Her swelling and numbness of fingers were gradually attenuated by administration of Iguratimod. The latter was diagnosed as bilateral MCP flexor tenosynovitis from 3 years ago and received local injection of corticosteroid four times and sheath incision for tenosynovitis without no effects. Administration of methotrexate and salazosulfapyridine were started and relief of symptoms was observed. PI has two implications. One is that connective tissue inflammation other than synovitis may be a part of the pathological features of RA, and the other is that future studies are needed as clue for early diagnosis of RA.

## P6-7

### Continuous measurement of finger range of motion over time with AI

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Conflict of interest: None

[Objective] To evaluate the movement of fingers continuously and quantitatively using artificial intelligence (AI). [Method] After recording of flexion and extension of fingers of healthy subject and two patients with rheumatoid arthritis, we assessed position estimation of fingertip, DIP, PIP, MCP and wrist using pose estimation AI model (Open Pose), and continuous measurement of flexion angle (30 times per second). [Results] In healthy subject and patient with early rheumatoid arthritis without joint destruction, estimation of the joints of fingers was good and the flexion angle over time could be measured. In patient with progressed joint destruction, it was often difficult to measure the angle due to poor estimation of the joints of fingers, but there is a possibility that the angle can be measured by estimating the continuity between the frames. The pattern of the Time-Angle transition graph was apparently different among healthy person and patients with early and progressed disease. [Conclusion] By processing the video of the fingers with the pose estimation AI, it was possible

to continuously measure the flexion angle over time. It can be expected as a new evaluation method for finger range of motion.

## P6-8

### Two cases of rheumatoid arthritis who observed the transition of MRI using a JAK inhibitor

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Conflict of interest: None

[Case] Case 1. A 65-year-old man. Baricitinib was started about 8 months after the onset of RA. At the start, DAS28CRP was 5.05, which was highly disease-active, but after 1.5 months of use, it became 3.61. Case 2. A 65-year-old woman. Tofacitinib was started about 5 years after the onset of RA. At the start, DAS28CRP was highly disease-active at 4.59, but after 3 months of use, it was in clinical remission of 2.04. [Methods] Hand MRI was performed on these two patients before, 6 months, 1 year, and 2 years after the use of the JAK inhibitor, and scored by the OMERACT-RAMRIS. [Results] In case 1, the MRI score before use was 20 points, but it decreased to 10 points after 6 months, and became 9 points after 2 years. In particular, bone marrow edema improved significantly. In case 2, the MRI score before use was 87 points, but decreased to 65 points after 6 months, and became 71 points after 2 years. In particular, synovitis improved significantly. [Discussion] JAK inhibitors are said to have the same effect on RA as biologics. But there are few reports of MRI evaluation of JAK inhibitors. In both cases, the MRI score improved after the use of the JAK inhibitor, indicating that MRI is useful for determining the therapeutic effect of the JAK inhibitor.

## P7-1

### Examination of diagnosis and joint ultrasonographic (US) findings in patients with knee joint pain

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Conflict of interest: None

[Objective] The knee joint is a predominant site for rheumatoid arthritis (RA), spondyloarthritis (SpA), and crystal-induced arthritis. We examined the US findings of these diseases. [Methods] Ankylosing spondylitis 7 cases, psoriatic arthritis 6 cases, ulcerative colitis 1 case in total 14 cases (SpA group), early rheumatoid arthritis 27 cases (eRA group), gout 43 cases (Gout group) were compared and examined. [Results] There was no significant difference in quadriceps tendon enthesitis, suprapatellar bursitis, patellar ligament enthesitis and joint synovitis among the three groups. Bone formation at quadriceps enthesitis was significantly higher in the other two groups than in the eRA group. Bone formation at the patellar ligament attachment was observed in 29/15/40%, which was significantly higher in the gout group than in the eRA group. Comparisons were also made between the eRA group and 15 patients (non-RA group) who were ACPA positive and did not diagnose RA. Quadriceps tendon enthesitis was significantly lower in the non-RA group than in the eRA group. [Conclusions] In gout, bone formation at the enthesitis suggested the involvement of IL-17 which is similar to SpA. The results of more enthesitis in the eRA group were similar to those of the shoulder joint we reported last year.

## P7-2

### Juxta-articular synovial involvement on ultrasound sonography in early ACPA-positive Rheumatoid Arthritis

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Utazu Hospital

Conflict of interest: None

[Objective] We picked up ACPA positive patients with clinically joints pain who had only US-detected tenosynovitis (TS), tendonitis without US-detected intra-articular synovitis. And analyzed the patterns. Also we examined about early spondyloarthritis (SpA). [Methods] 30 ACPA positive patients who didn't have US-detected intra-articular synovitis at wrists, fingers, shoulders, knees, MTP joints, were analyzed the patterns of US. Similarly 8 SpA patients were investigated. [Results] 20 ACPA positive patients in Group A were treated as early RA. 10 ACPA positive patients in Group B were only followed up. 8 SpA patients were belonged into Group C. The average of age in Group A: B: C=61.3:56.0:44.8. The % of patients who fulfilled EULAR criteria =70%:50%:0. CRP = 0.77 mg/dl:0.09:2.14. The average joint number of TS and tendinitis for each patient= 6.0: 2.0: 5.1. Positive % of patients who had TS and tendonitis in small joints =75%:40%:80%, other large joints= 35:50:80.) [Conclusions] We sometime meet the patients who have only Juxta-articular synovial involvement on US. In those patients, someone don't satisfy with EULAR criteria and it is difficult to diagnose the patients as RA. We suggest TS and tendinitis are signs of the early symptom of RA and sometime need to treat.

### P7-3

#### Efficacy of Diffusion-weighted Whole body Imaging with Background Suppression (DWIBS) in the Diagnosis and Evaluation of Large Scale Vasculitis

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Conflict of interest: None

[Objective] This study was to investigate the role of FDG-PET/CT in the diagnosis of vasculitis. In particular, FDG-PET/CT is useful not only because of its high sensitivity, but also because it can estimate the evolution of the disease. DWIBS is a non-contrast, whole-body imaging method of MRI, and is expected to be applied to large vessel vasculitis. We performed DWIBS and FDG-PET/CT in patients with large vessel vasculitis at our hospital, and reported on the efficacy of these tests. [Methods] We performed DWIBS and FDG/PET/CT within 3 months of each other in 11 patients with large vessel vasculitis (6 at diagnosis and 5 in remission) attending our hospital and affiliated hospitals. Clinical evaluation was performed by our department and imaging evaluation was performed by our radiologist. [Results] All five patients who remained in remission had negative vasculitis findings on both DWIBS and FGD/PET-CT. The overall diagnosis was consistent with large vessel vasculitis, although there was a discrepancy between the PET-positive and DWIBS-negative results in the carotid artery and ascending aorta in one case. [Conclusions] DWIBS may be useful in the diagnosis of large vessel vasculitis, with the same diagnostic accuracy as FDG-PET.

### P7-4

#### Usefulness of Gallium-67 scintigraphy for diagnosis and treatment of polymyalgia rheumatica

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Conflict of interest: None

[Object] Polymyalgia rheumatica (PMR) has a feature of bursitis in shoulder, trochanter of humerus (TOH), and vertebral spinous processes (VSP), easily detected with FDG-PET/CT. We evaluate usefulness of Gallium-67 scintigraphy (Ga scan) for diagnosis and treatment of PMR. [Methods] 142 patients with polyarthritis were examined with Ga scan from September 2014 to September 2019. Excluding other diseases, we retrospectively studied 48 patients who met PMR classification criteria (2012ACR/EULAR), treated with prednisolone (PSL) more than 1 year. [Results] The values are median (min-max). At baseline, age 75 (51-86)

years old, female 31 cases, CRP 5.91 (1.12-17.02) mg/dl, ESR 110 (40-120) mm/hr, MMP-3 189.8 (49.1-2970) ng/ml, RF positive 4 case, ACPA positive 1 case. 5 cases met RA classification criteria (2010ACR/EULAR). Ga scan showed increased uptake in shoulder (48 cases), TOH (48 cases), and VSP (31 cases). Before treatment, 5 cases used PSL 5 mg/day, 1 case used MTX 8 mg/week. Initial doses of PSL were 15 (5-20) mg/day. At 1 year after, CRP values significantly decreased to 0.09 (0-2.43) mg/dl ( $p<0.0001$ ), PSL dose was significantly decreased to 5 (0-10) mg/day ( $p<0.0001$ ). In all case, the diagnosis did not change after 1 year. 8 cases had relapse, 3 cases complicated RA. [Conclusions] These results suggest.

### P7-5

#### Giant cell aortitis diagnosed by repeated temporal artery ultrasonography following the previous normal ultrasonographic result

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Conflict of interest: None

[Introduction] The ultrasonography of the temporal artery has been shown to be a useful diagnostic tool of giant cell aortitis (GCA). We report the GCA diagnosed by the repeated temporal artery ultrasonography, 2 months after the previous normal ultrasonographic results. [Case] 72-year-old female was referred to our hospital because of the headache and normocytic anemia. The acute reactant substances such as ESR and CRP were elevated, and anemia of chronic disease was diagnosed. The investigations including the ultrasonography of the temporal artery did not show a diagnostic clue. As the symptoms of the patient had been stable, the careful follow-up to monitor any new sign and symptom for the diagnosis was planned. Two months after the first visit, the new onset of left temporal artery tenderness appeared and subsequent ultrasonography of the temporal artery showed the halo sign, and the temporal artery biopsy confirmed the diagnosis of GCA. [Clinical significance] When GCA is suspected, the repeated temporal artery ultrasonography may be considered even after the previous normal ultrasonographic result.

### P7-6

#### A case of Psoriatic Arthritis (PsA) with strong ACPA positivity, for which ultrasonography was helpful in diagnosis

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Conflict of interest: None

[Case] 67 year old male [Chief complaint] Poly arthralgia [Medical history] Psoriasis vulgaris [Clinical history] The patient came to our clinic with morning stiffness and swelling and pain in bilateral MCP and PIP joints. Erythema with scales on fingers and legs. [Physical examination findings] Swelling and tenderness in multiple joints such as hands, elbow, knee, and foot on both sides. [Examination findings] Blood test: RF 1150, ACPA1470. X-ray: Neither of osteogenesis nor bone erosion. US: In the MCP joint, high edema around the extensor tendon (ET) with strong PD signal (PTI). Enthesitis was observed elbow and knee. Synovitis was poor. MRI: Similar to the US, a strong contrast effect of Gd was observed around the ET of the MCP joint. Based on the above, we concluded that enthesitis were the main site of inflammation and diagnosed PsA, although the case was seropositive for serum reactions. [Progress] After stating MTX, the improvement was poor and TNF inhibitors were added. At the follow up after 3 months, PTI and enthesitis had disappeared and the course of treatment was good. [Clinical implications] PTI and CSE has been reported as a useful US finding to diagnose PsA. As this case, we should observe not only synovitis but enthesitis including PTI and CSE, especially in cases that need to be differentiated from RA.



## P8-1

### Patients with rheumatoid arthritis who developed sarcopenia frequently fall - 5-year data from CHIKARA study-

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Conflict of interest: None

[Objective] Patients with rheumatoid arthritis (RA) are likely to have sarcopenia due to decline of muscle mass and physical function. We longitudinally investigated sarcopenia condition and characteristics of RA patient using the prospective CHIKARA study. [Methods] We investigated the body compositions, laboratory data, disease activity, physical function, treatment, and history of fall and fracture among 100 patients with RA participated in the CHIKARA study at baseline and 5 years. They were divided into 4 groups depending on sarcopenia condition; no sarcopenia development (N group), sarcopenia development (S group), cure (C group), and maintain (M group). [Results] Seventy RA patients completed survey. N group, 67.1% of all, had high BMI, muscle mass, fat mass, estimated bone mass, and body metabolism rate at baseline. On the other hand, S group, 4.3% of all, fell significantly more frequent; 3.3 times during 4 years. M group, 10% of all, had high baseline MMP-3. 10.0% were C group. There were no differences between 4 groups regarding disease activity, physical function. [Conclusion] 4.3% of RA patients developed sarcopenia and fell frequently during 5 years. Patients with sarcopenia development should be cared, as they are at high risk of fall.

## P8-2

### Relationship between bone structure and age in anti-CCP antibody-positive (ACPA) cases ~ HR-pQCT Study ~

Shigenori Tamaki<sup>1</sup>, Takashi Kato<sup>2</sup>, Motokazu Kai<sup>3</sup>, Kunikazu Ogawa<sup>3</sup>, Ryosuke Hibi<sup>1</sup>, Yusuke Suzuki<sup>1</sup>, Hidenao Imada<sup>1</sup>, Hitomi Nagasaka<sup>1</sup>, Hiroaki Mizuno<sup>1</sup>, Hisaji Oshima<sup>4</sup>, Ikuko Tanaka<sup>1</sup>

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Conflict of interest: None

[Objective] Age is considered to be related to the duration of ACPA in the body, and the relationship between bone structure and age in ACPA-positive cases was examined using HR-pQCT. [Methods] Early group was 43 ACPA-positive women (39 ± 9 years) who were ACPA-positive within 3 months of the onset of symptoms. EstRA group was 39 ACPA-positive females Established RA (43 ± 9 years old) who maintained remission. Negative group was 43 arthritis-free ACPA and RF-negative females (44 ± 7 years old) were used as controls. Bone mineral density (BMD) and bone microstructure of cortical (Ct.) bone and trabecular (tb.) bone in the distal radius were measured by HR-pQCT. [Results] BMD was not correlated with age in the negative group and EstRA group in whole, Ct. and Tb. bones, and a positive correlation with Ct. bone and a negative correlation with Tb. bone was observed in the early group. The Ct. porosity was positively correlated in the negative group and EstRA group but not in the early group. The Tb. number was negatively correlated in the negative group and early group. but not in the EstRA group. [Conclusions] The negative correlation between age and Tb. structure observed in the early group was not observed in the EstRA group suggesting the effect of RA treatment.

## P8-3

### A case of rheumatoid arthritis with interesting structural changes on HR-pQCT

Ryosuke Hibi<sup>1</sup>, Shigenori Tamaki<sup>1</sup>, Takashi Kato<sup>2</sup>, Motokazu Kai<sup>3</sup>, Kunikazu Ogawa<sup>3</sup>, Yusuke Suzuki<sup>1</sup>, Hidenao Imada<sup>1</sup>, Hitomi Nagasaka<sup>1</sup>, Hiroaki Mizuno<sup>1</sup>, Hisaji Oshima<sup>4</sup>, Ikuko Tanaka<sup>1</sup>

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Conflict of interest: None

[Introduction] In a HR-pQCT study, we reported that healthy anti-CCP antibody (ACPA) -positive cases showed a decrease in trabecular (Tb.) bone and RA cases with wrist damage showed an increase in cortical (Ct.) porosity. [Case] 51-year-old woman with RF-positive and ACPA-positive showed left wrist joint damage and bilateral wrist joint synovitis. She started MTX therapy and her wrist synovitis improved, but her finger joint synovitis flared. The bone structure of the distal radius measured by HR-pQCT at the first visit and 4 years later was compared. At the first visit, The Tb. bone mineral density (Tb. BMD, mg / cm<sup>3</sup>) was 101.1, the Ct. BMD was 784.7, the Tb. number (Tb. N, / mm) was 1.056, and the Ct. porosity (Cr. Po, %) was 0.039. After 4 years, the Tb. BMD decreased to 33.7 and Tb. N decreased to 0.621. On the other hand, the Ct. BMD increased to 868.8, and the Ct. Po improved to 0.007. [Conclusions] In this case, the Ct. bone structure in the distal radius improved with the disappearance of wrist joint inflammation, but it was considered that Tb. bone resorption progressed due to the activity remaining. It was considered that if the activity of RA remains, the activation of osteoclasts by ACPA and inflammatory cytokines is sustained and the systemic bone resorption is also sustained.

## P8-4

### Clinical study of seronegative rheumatoid arthritis (SNRA)

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Conflict of interest: None

[Objective] To investigate the clinical characteristics of SNRA. [Methods] The medical records of 31 patients (males: 6, females: 25) with a diagnosis of SNRA attending our hospital as of September 2021 were retrospectively examined. [Results] Mean age: 68.7 years, median duration of disease: 24 months. Large joints only (n=3), including small joints (n=24), unknown (n=4). X-ray showed erosion (n=14 out of 29), unknown (n=2). MRI (contras: n=19, simple: n=4) showed synovitis (n=23) and erosion (n=22). The median of ACR2010 criteria score was 4 (≤5: 20, ≥6: 7, unknown: 4). With less than 5 points, X-ray showed erosion (n=10 out of 20), and all patients with MRI (n=17) had synovitis and erosion. With 6 points or higher, X-ray showed erosion (n=3 out of 5), and MRI showed synovitis (n=5 out of 5) and erosion (n=4 out of 5). Methotrexate alone (n=17), biologics (n=2), conventional synthetic DMARDs (n=3), prednisolone alone (n=2), and follow-up only (n=4). [Conclusions] 65% patients diagnosed with SNRA had a score of 5 or less, and erosions were found on imaging studies. The seronegative cases with less than 10 affected joints score less than 5 points in ACR2010, suggesting that it may not enough to pick up erosions that should be treated.

## P8-5

### Characteristics of onset age and symptoms/clinical laboratory data in Rheumatoid arthritis

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Conflict of interest: None

[Objects] In rheumatoid arthritis, it has been suggested that there are differences in symptoms depending on age at onset. The purpose of this study was to examine the actual data in Japanese patients. [Subjects and methods] We compared the data of patients diagnosed with rheumatoid arthritis for the first time in 2020 at our hospital by age group. [Results] The number of patients was 183 (47 males, 139 females, 98 patients under 65 years old, and 85 patients over 65 years old). when comparing younger patients (under 65 years old) and older patients (over 65 years old), inflammatory markers such as CRP (1.89 vs. 4.83 mg/mL) and ESR (34.6 vs. 54.0 mm/Hr.) were higher in older patients. On the other hand, RF (98.1 vs

74.4 IU/mL) and anti-CCP antibody titer (173.9 vs 148.2 U/mL) were lower in younger-onset patients. [Discussion] In general, the incidence of autoimmune diseases caused by immune abnormalities tends to be higher in younger patients, because the immune system of the elderly is weakened. The low titer of autoantibodies in the elderly may confirm this fact. On the other hand, the inflammatory response was higher in the elderly. This may be due to a decrease in endogenous glucocorticoids with age, which will be investigated in the future.

## P8-6

### A case of polymyalgia rheumatica and RS3PE syndrome followed by elderly-onset rheumatoid arthritis after ovariectomy due to cervical cancer

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Conflict of interest: None

A sixty-four-year old female was diagnosed with cervical cancer at a routine checkup and underwent ovariectomy. Two months post-surgery, morning stiffness, bilateral pitting edema of dorsal surfaces of the extremities, and arthralgia on both shoulders appeared. Rheumatoid factor, anti-citrullinated peptide antibody, antinuclear antibody, anti-SS-A antibody, anti-DNA antibody were positive. MRI and sonography of shoulders and hands detected subdeltoid and subacromial bursitis, bicipital tenosynovitis, and extensor tenosynovitis on right hand, but neither synovitis nor bone marrow edema. Polymyalgia rheumatica (PMR) and RS3PE syndrome were diagnosed, and prednisolone (PSL) 15 mg/day was started. Pitting edema and arthralgia disappeared, however, as the dose of PSL was reduced, polyarthritis on both knees, MCP, PIP joint, and right hand appeared. MRI of the right hand detected synovitis with erosion. Elderly-onset rheumatoid arthritis (EORA) was diagnosed, and methotrexate 6 mg/week was started resulting in great improvement. There was no recurrence of cervical cancer. In this case, we experienced PMR and RS3PE syndrome followed by EORA. Stress of operation, reduction of estrogen by ovariectomy and basal immune dysregulation might associated with clinical course.

## P9-1

### IL-18 contributes to autoantibody-induced arthritis via neutrophil recruitment and mast cell activation

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Conflict of interest: None

**Objectives:** This study investigated the contribution of IL-18/IL-18 receptor- $\alpha$  (IL-18R $\alpha$ ) signaling in autoantibody-induced arthritis. **Methods:** C57BL/6 IL-18R $\alpha$  gene deficient (-/-) mice were used in K/BxN serum transfer arthritis. Mouse bone marrow derived mast cells (mBMMCs) were stimulated with recombinant mouse IL-18. Murine fibroblast-like synoviocytes (FLS) and human RA FLS were stimulated with recombinant IL-1 $\beta$  and IL-18. mRNA levels of IL-18, CXCL1, IL-8 and IL-1 $\beta$  were analyzed in cultured cells. Synovial tissue expression of IL-18, IL-1 $\beta$  and TNF $\alpha$  mRNA was also investigated. **Results:** In IL-18R $\alpha$ <sup>-/-</sup> mouse, we observed a less disease severity that was accompanied by lower IL-1 $\beta$  gene expression in the joints as compared to WT control mice. The infiltration of neutrophils was reduced in IL-18R $\alpha$ <sup>-/-</sup> mice significantly with decreased CXCL1 mRNA expression in inflamed ankle tissues. Degranulated synovial tissue mast cells were reduced in IL-18R $\alpha$ <sup>-/-</sup> mice during arthritis and IL-18 stimulation can induce mBMMCs IL-1 $\beta$  mRNA expression. **Conclusion:** IL-18/IL-18R $\alpha$  signaling contributes to autoantibody-induced arthritis via inducing neutrophil recruitment and mast cell activation. Inhibition of IL-18/IL-18R $\alpha$  signaling could be an attractive therapeutic potential target in RA.

## P9-2

### Inflammatory cytokines trigger expression of the VEGF receptor Neuropilin in synovial fibroblasts

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Conflict of interest: None

[Objective] Neuropilin (NRP) is a receptor of the Vascular Endothelial Growth Factor (VEGF) family and is involved in angiogenesis and cell proliferation. The relationship between NRP and the pathogenesis of rheumatoid arthritis (RA) remains unclear. In this study, we investigated the expression of NRP in the synovial membrane. [Methods] There are two types of NRP genes, NRP1 and NRP2. We investigated the expression of NRP in the synovium of RA and osteoarthritis (OA) using immunohistochemistry and RT-qPCR. In addition, RA-derived synovial fibroblasts (RA-FLS) were stimulated with TNF $\alpha$  and IL-1 $\beta$ . The mRNA expression changes of NRP1 and NRP2 were measured by RT-qPCR. [Results] Immunohistochemistry showed the expression of NRP1 and NRP2 in both RA and OA synovium, consistent with CDH11-expressing cells (FLS). Stimulation of RA-FLS with TNF $\alpha$  and IL-1 $\beta$  resulted in a time-dependent increase in the expression of NRP1 and NRP2. [Conclusions] In synovial tissue, the expression of NRP was enhanced by stimulation with inflammatory cytokines, suggesting that NRP expression is affected by inflammatory cytokines, which may lead to the elucidation of the relationship between growth factors such as VEGF and inflammatory pathology in synovium.

## P9-3

### Baricitinib inhibits lung fibroblast proliferation and chemotaxis via pro-inflammatory cytokine production

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Conflict of interest: None

**Background:** Baricitinib is a selective small molecule inhibitor of JAK 1 and JAK2 enzymes. A direct role of baricitinib for lung fibroblasts has not been demonstrated. Here, we examine baricitinib inhibits lung fibroblast proliferation and chemotaxis. **Methods:** To determine whether baricitinib was involved in pro-inflammatory cytokine production, cytokines and chemokines in baricitinib treated interleukin (IL)-6 and IL-6 receptor (IL-6R) stimulated normal human lung fibroblast (NHLF) conditioned medium was measured using ELISA. To elucidate the function, proliferation assay and chemotaxis assay were performed for the proliferation inhibitory effect and chemotaxis inhibitory effect of NHLF. **Results:** Phosphorylation of STAT1,3,5 was observed by co-stimulation of IL-6 and IL-6 receptor, and the phosphorylation was suppressed by the addition of baricitinib. The concentrations of VCAM-1, fractalkine / CX3CL1, ENA-78 / CXCL5, MCP-1 / CCL2, and VEGF in the NHLF cell supernatant were all decreased by the addition of baricitinib. Furthermore, cell proliferation ability and migration ability were also significantly reduced. **Conclusion:** Baricitinib suppressed cell proliferation and migration through suppression of the production of the inflammatory cytokine chemokine from lung fibroblasts.

## P9-4

### ADAM-10 expression and cytokine production by osteoblasts in rheumatoid arthritis

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Conflict of interest: Yes

[Objective] ADAM-10 have been reported to play an important role in

tumor growth and inflammation. Osteoblasts play a central role in bone metabolism and have been reported to be involved in the pathogenesis of rheumatoid arthritis (RA). We investigated the cytokine production and expression of ADAM-10 in osteoblasts. [Methods] Human osteosarcoma derived cell line (MG-63) and osteoblasts isolated and cultured from the bone tissue of RA patients (RA-HOB) were stimulated with TNF- $\alpha$ , and the concentration of cytokines in the supernatant of the culture medium was measured by ELISA. The expression of ADAM-10 in MG-63 and RA-HOB was investigated using immunofluorescent antibody method. MG-63 and RA-HOB were stimulated with TNF- $\alpha$ , and the mRNA of ADAM10 was measured by qPCR. [Results] MCP-1, ICAM-1, RANTES, ENA78, and IL-8 were increased in the supernatant of the culture medium of MG-63 and RA-HOB stimulated with TNF- $\alpha$ , compared to the unstimulated. ADAM-10 was expressed on MG-63 and RA-HOB. In addition, MG-63 and RA-HOB with stimulated with TNF- $\alpha$  increased the expression of ADAM-10 compared to the unstimulated. [Conclusions] RA-HOB stimulated with TNF- $\alpha$  produces inflammatory cytokines. ADAM-10 is expressed on RA-HOB, which may be involved in the inflammation of rheumatoid arthritis.

## P10-1

### A study on improving prognosis prediction using joint index vector in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To improve predicting prognosis of the next-year groups by transformation matrix using joint index vector. [Methods] Data of 12,496 patients with rheumatoid arthritis who were serially registered in NinJa database 2019 and 2020 were extracted. Joint index vector  $V(x, y, z)$  was calculated as described previously<sup>1</sup>. Patients were classified into 4 groups as G1:  $V_{xy} \leq 0.1$ , G2:  $V_{xy} > 0.1$  and  $|z| \leq 0.2$ , G3:  $z < -0.2$ , and G4:  $z > 0.2$ , where  $V_{xy}$  equal square root of  $(x^2 + y^2)$ .  $eV_{2020}$  were estimated by applying transformation matrix<sup>1</sup> on  $V_{2019}$  and the difference between  $eV_{2020}$  and  $V_{2020}$  were computed. Accuracy of predicting the groups was calculated considering error of  $z$ . [Results] The mean (standard deviation) of the difference of  $z$  between  $eV_{2020}$  and  $V_{2020}$  was 0.015 (0.228). The concordance rate of group prediction by  $eV$ s was 57.7%. It increased adding error ( $dz$ ) to  $z$  and reached the peak level (68.5%) when  $dz = 0.2$ . [Conclusion] The predicting accuracy was improved by considering error of joint index vector.

## P10-2

### Predictors of frailty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To investigate predictors of frailty in patients with Rheumatoid arthritis (RA patients). [Method] Japanese-Cardiovascular Health Center criteria (J-CHS), which is a simplified diagnostic criterion for frailty was used. 298 RA patients who have pre-frailty in 2020 were chosen in this study from 505 RA patients who have taken part in our prospective study. Their one-year background changes were examined by dividing them into Frailty group, which includes patients who become frailty in 2021, and Non-frailty group, which includes patients who have not. Logistic regression analysis was used to obtain the odds ratio of becoming frailty. [Results] Frailty group (42 patients) was older (71.0 years old vs. 65.4), had a longer duration of disease (12.2 years vs 10.9), lower clinical remission rate (25% vs. 51%), lower functional remission rate (38% vs. 82%),

lower less than locomotive syndrome 25 score (locomo 25) grade 1 rate (33% vs. 71%) than Non-frailty group (256 patients). Adjusted odds ratios were clinical remission: 0.36, functional remission: 0.14, and less than locomo 25 grade 1: 0.23. [Conclusion] The independent predictors of becoming frailty were unachieved clinical and functional remission and locomotive syndrome of 2 or higher in RA patients with pre-frailty.

## P10-3

### Frailty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To investigate the frailty in RA patients and its relation to treatment selection. [Methods] RA patients aged 40-79 years are registered in the prospective observation study. The patients' background (age, disease duration, treatment status, and disease activity) was collected and physical function related to frailty (grip power, gait speed, Timed up and go test: TUG) were measured. [Results] 108 female RA patients were included in the analysis. The mean age, disease duration, the disease activity (CDAI), and BMI was 65 years, 11 years, 5.2, and 23.5, respectively. Measured gait speed, grip strength and TUG was 1.2 m / s, 17.7 kg, and 9.8s. Treatment was 64.3% with MTX, 27.9% with prednisolone, and 38% with Bio / JAK. Grip strength < 18 kg, which is an index of frailty, was 46.7%, and walking speed < 1.0 m / s was 19.8%. In logistic analysis, measured physical function values were associated with PSL use even after adjustment of patient background [grip strength < 18 kg OR: 7.89 95%CI (2.19-28.4), walking speed < 1.0 m / s, OR: 4.58 95%CI (1.18-17.8)]. [Conclusions] In RA patients, grip strength may overestimate frailty by criteria for the general population, but it correlates with other anthropometric measurements and is simple and requires indexing in RA patients.

## P10-4

### Relationship between residual symptoms and Locomo 25 score and Locomo level in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Subjective symptoms observed in rheumatoid arthritis (RA) patients after reaching the treatment goal are known as residual symptoms (RS), but the relationship between RS and locomotive syndrome is not clear. [Methods] The subjects were 68 RA patients who achieved low disease activity or less on the DAS28ESR. We compared the relationship between the Locomo 25 score or Locomo level and the duration, stage, functional disability, DAS28ESR, medications used, and the presence and duration of morning stiffness (MS), presence and degree of pain (pain VAS), and presence and degree of dullness (dullness VAS). [Results] The mean Locomo 25 score was 15.5 points, and 25.0% had Locomo level 1, 7.3% had level 2, and 27.9% had level 3. There were significant correlations between Locomo 25 score and disease duration, DAS28ESR, dullness VAS, pain VAS, PtVAS, DrVAS, and HAQ. The degree 3 group had significantly higher PtVAS and functional disability than the non-locomo group and the level 1 group, and significantly higher pain VAS, DrVAS, and use of bDMARDs than the non-locomo group. [Conclusions] The level of Locomo 25 was significantly correlated with pain and dullness, and rehabilitation intervention and daily exercise instruction can be expected to improve the therapeutic effect.



## P10-5

### Impact of lumbar spinal lesions on physical impairment (HAQ) in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] The relationship between rheumatoid lumbar lesions and physical function is still unknown. The purpose of this study was to examine the relationship between lumbar scoliosis and physical function in patients with rheumatoid arthritis. [Methods] A total of 59 patients with rheumatoid arthritis who underwent lumbar spine radiography were evaluated for physical dysfunction using the Health Assessment Questionnaire (HAQ), and those with a HAQ of less than 0.5 were classified as having functional remission, while those with a HAQ of 0.5 or greater were classified as having non-functional remission. The relationship between lumbar scoliosis and physical function in rheumatoid arthritis patients was statistically examined. [Results] There were 34 and 25 patients in the functional and non-functional remission groups, respectively. In univariate analysis, the functional remission group had a smaller lumbar Cobb angle and a lower DAS28CRP. Multivariate analysis using propensity score showed that lumbar Cobb angle tended to be an independent factor associated with functional remission (OR=1.077, p=0.068). [Conclusions] It was suggested that coronal plane alignment may affect physical function in patients with rheumatoid arthritis.

## P10-6

### The transition of the patients' characteristics of rheumatoid arthritis undergoing total joint arthroplasty for lower extremities and evaluation of disease activity with serum albumin levels

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Conflict of interest: None

(Purpose) We investigated the transition in the treatment for rheumatoid arthritis (RA) patients who underwent total joint arthroplasty (TJA) of the lower extremities and correlation between disease activity and albumin (Alb). (Methods) 109 joints underwent TJA of the lower extremities for RA in 2006 to 2019 were included. The period from 2006 to 2010 was defined as the early group (54 joints) and after 2010 as the late group (55 joints). The rate of patients received preoperative biologic agents (BIO) was investigated for each group. The correlation between DAS 28-CRP (4) (DAS28), Alb, and CRP was evaluated in the BIO group and the non-BIO group. (Results) 34 patients treated with BIO, 8 in the earlier and 26 in the later (p<0.01), the rate of remission was significantly higher in the later and BIO group; Alb was 3.9±0.5 overall, 4.0±0.4 in the BIO group, and 3.7±0.5 in the non-BIO group (p=0.02). Alb was negatively correlated with DAS28 (r=-0.35, p<0.01) and correlated with CRP (r=-0.68, p<0.01) in the overall and similarly in the non-BIO group. In the BIO group, Alb showed moderate correlation with CRP (r=-0.68, p<0.01). (Conclusions) While Alb did not correlate with DAS28 in the BIO group, suggesting that Alb may be a useful tool to assess disease activity for BIO-treated patient.

## P10-7

### Comparison of old and new criteria for sarcopenia among patients with rheumatoid arthritis - from the CHIKARA study-

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Conflict of interest: None

[Background] Patients with rheumatoid arthritis (RA) likely to have sarcopenia. Sarcopenia is assessed by Asian Working Group for Sarcopenia criteria, which is updated to be strict in 2019; cutoff value of gait speed (GS) and grip power (GP) got higher. We assessed sarcopenia by old and new criteria. [Methods] We investigated 70 RA patients enrolled in the prospective CHIKARA study. The GP and GS were examined. Appendicular skeletal muscle index was measured using body composition analyzer. Prevalence of sarcopenia, low muscle mass, low GP and slow GS were assessed by each criterion. [Results] The prevalence of sarcopenia was 22.9%/24.3% by old/new criteria, respectively. Their concordance was high (κ=0.96). The prevalence of low muscle mass and low GP was 31.4%, 72.9% by both criteria among all RA patients. That of slow GS was 27.1%/38.6% by each criterion. That of low GP and slow GS was 100%/94.1%, 37.5%/52.9% by each criterion among RA patients with sarcopenia. [Conclusions] The prevalence of sarcopenia and slow GS was increased by new criteria. Most of RA patients with low muscle mass was diagnosed as sarcopenia due to low GP. As patients with RA often have decline in GS and GP because of the disease, muscle mass measurement makes higher contribution to sarcopenia diagnosis.

## P10-8

### Examination of Factors Affecting the Progression of Joint Destruction by Highly Sensitive Imaging Evaluation in Abatacept Treatment for Rheumatoid Arthritis

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Conflict of interest: None

[Objective] To identify the factors responsible for joint destruction by performing high-sensitivity imaging in abatacept (ABT)-treated RA patients. [Methods] Nineteen RA patients who were introduced ABT in RA. 44 joints were assessed by US with GS and PD and contrast-enhanced bilateral joint MRI scoring with OMERACT-RAMRIS scoring. [Results] On joint MRI, the group with worsening total erosion score by the amount of change after 6 months of ABT treatment was classified as having progression, and the group without worsening was classified as having no progression. (1). In multivariate logistic analysis, EQ-5D-5L at baseline and ΔPD were extracted as independent factors with significant differences. (2). Stratified analysis showed that EQ-5D-5L at baseline of 0.4965 or higher and ΔPD of 0 or lower showed no progression of MRI-erosion at 6 months. [Conclusions] In ABT-treated patients, EQ-5D-5L caused by RA prior to treatment may affect MRI-erosion at 6 months, suggesting that administration of ABT prior to QoL impairment, such as EQ-5D-5L decline, and during treatment while monitoring PD changes, is important not only for preventing joint destruction but also for improving and maintaining long-term QoL.

## P10-9

### Factors Affecting Bone Destruction in Rheumatoid Arthritis

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Conflict of interest: None

[Objective] cases achieving clinical remission were divided by mTss progression and the background was examined. [Methods] The progression of mTss for 1 year was 3 points or more in group A, 12 cases, and less than 3 points in group B, 50 cases. The presence or absence was examined, and the MMP-3 values between the two groups were compared. The target joints of US were wrist joints, PIP joints, MP joints, and MTP joints, and the area of thickest part of the synovium was measured. The base of mTss. The line is 94.5 points in group A and 29.4 points in group B. [Results] Synovial thickening was 2.4-7.5 mm (average 4.5) in group A and 0-9 mm (3.1) in group B at the thickest part, and the area was 0.15-1.48 (0.63) in group A and 0-1.48 (0.35) in group B. The positive rate of MMP-3 was 92% in group A and 70% in group B, and the negative rate was 25% in

group A and 66% in group B. The amount of change was 3-38 (3.2) in group A and 0-2 (0.3) in group B ( $p=0.05$ ). Results of examining the background of bone destruction PD, synovial thickening, MMP-3 Significant differences were observed in the values ( $p=0.05$ ), and the cases satisfying these three conditions were 11 cases (91%) in group A and 5 cases (10%) in group B. [Conclusions] Follow-up by US and MMP-3 measurements would be useful.

## P10-10

### Diagnosis in rheumatoid arthritis (RA) and osteoarthritis (OA) using ultrasound in the knee joint

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Conflict of interest: None

[Objective] The purpose of this study was to evaluate knee arthritis in patients with RA and OA using US and to determine if there is a difference. [Methods] The subjects were RA 11 limb and OA 17 limb. The evaluation used were power Doppler area and grading using the grayscale method. The sites of observation were the anterior segment of the medial meniscus, the middle segment of the medial meniscus, medial collateral ligament, medial subpatellar fat, pes anserinus, suprapatellar bursa, lateral subpatellar fat, middle segment of the lateral meniscus, and the iliotibial ligament. The unpaired t-test was used to compare the Doppler area between the RA and OA groups, and the  $\chi^2$  to examine the presence or absence of Doppler response. [Results] The Doppler areas of the RA and OA groups was significantly larger in the RA group ( $p<0.05$ ). Doppler response was observed in the RA group (81.1%) compared with the OA group (0%) in the suprapatellar bursa ( $p<0.001$ ). No significant difference was observed in other sites. [Conclusions] Evaluation of the suprapatellar bursa using the US power Doppler method is useful in diagnosis RA and OA patients with knee pain.

## P11-1

### Type 1 soluble tumor necrosis factor receptor (sTNFR1) as a new biomarker associated with disease activity in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Type 1 soluble tumor necrosis factor receptor (sTNFR1) is one of the biomarkers that compose multi-biomarker disease activity (MBDA), but its clinical significance is unknown. In the FLAIR study we reported in 2021, Since the blood concentration of sTNFR1 was useful for predicting relapse, the purpose was to clarify the significance of the blood concentration of sTNFR1 as a disease activity index at baseline and at the time of disease relapse. [Methods] We investigated the correlation between the baseline of all 36 patients enrolled in the FLAIR study, the baseline of 20 patients with relapse, and the variation of biomarkers including sTNFR1 at the time of relapse and the disease activity index. [Results] In 20 patients with relapse, blood levels of IL-8, IL-10, and VEGF in addition to sTNFR1 were significantly increased at the time of relapse compared to baseline. sTNFR not only correlated with the erythrocyte sedimentation rate at relapse ( $r^2=0.3$ ,  $p=0.011$ ), but also at baseline remission ( $r^2=0.14$ ,  $p=0.027$ ). [Conclusions] Not only was sTNFR1 useful for predicting relapse after discontinuation of biopharmacy, but it also correlated with the erythrocyte sedimentation rate regardless of the degree of disease activity, suggesting that it is a clinically useful biomarker.

## P11-2

### A novel multi-biomarker combination predicting relapse from long-term remission after discontinuation of biological drugs in rheumatoid arthritis

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ternal Medicine, Jichi Medical University, <sup>2</sup>Department of Biochemistry, Jichi Medical University

Conflict of interest: None

[Objective] Biological disease modifying anti-rheumatic drugs (bDMARDs) show dramatic treatment efficacy in rheumatoid arthritis (RA). Long-term use of bDMARDs, however, has disadvantages such as high costs and infection risk. Therefore, a methodology is needed for RA patients to predict relapse from long-term remission after discontinuation of biological drugs. [Methods] Forty patients with RA in remission for more than 12 months were enrolled. bDMARDs were withdrawn and they were followed monthly for the next 24 months. Serum samples obtained longitudinally from patients in remission were assessed for the relapse-prediction biomarkers and index from 73 cytokines by the exploratory multivariate ROC analysis. [Results] Fourteen patients (35%) of 40 in the cohort remained in remission at 24 months, whereas 26 (65%) relapsed at various time-points. The relapse-prediction index calculated from the 5 cytokines, IL-34, CCL1, IL-1 $\beta$ , IL-2 and IL-19, strongly discriminated between patients who relapsed and those who stayed in remission. [Conclusions] We report a novel multi-biomarker combination which predicts relapse after bDMARDs-withdrawal in patients in remission. These findings could contribute to clinical decision-making as to the timing of when to discontinue bDMARDs in RA treatment.

## P11-3

### Glycosylation abnormalities in the serum IgG of RA patients

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Conflict of interest: Yes

[Object] Previous studies have demonstrated the presence of glycosylation abnormalities in the serum IgG of RA patients (RA). We analyzed the sugar chain structure of IgG in RA using the novel technique, and examined its value as a marker for early diagnosis. [Methods] IgG was extracted from the serum of RA patients, and the proportion of galactose-deficient IgG (G0) and sialic acid-deficient IgG (S0) was analyzed by a sugar chain analysis method combining high performance liquid chromatography (HPLC) and mass analysis (MS). Furthermore, the addition rate of sialic acid was examined using MS. [Results] The proportions of G0 and S0 were significantly higher in RA than in healthy subjects. Furthermore, MS revealed that the rate of S0 was high in RA. These abnormalities were observed from the early stage of onset, and it was also confirmed that they decreased in remission. [Conclusions] Glycosylation abnormalities may be useful as markers for RA diagnosis, activity, and remission. Furthermore, it was suggested that these abnormalities might play a important role in the etiology and pathophysiology.

## P11-4

### Impact of shared epitope and ACPA positivity on DAS28-ESR remission or low disease activity in patients with rheumatoid arthritis receiving abatacept

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Conflict of interest: None

[Objective] The aim of this study was to investigate the impact of

ACPA and shared epitope (SE) on achieving remission or low disease activity (LDA) at week 24 in patients with rheumatoid arthritis (RA) receiving abatacept (ABT). [Methods] We have reported the impact of the SE on responses to treatment with tofacitinib (TOF) or ABT in patients with RA (Arthritis Res Ther 2021;23:R228). In the present study, 70 patients receiving abatacept were included, and the influence of SE and ACPA on the clinical effectiveness at week 24 was investigated. [Results] The abatacept treatment group consisted of 38 patients with remission or LDA and 32 patients with moderate or high disease activity. ACPA positivity was found to have an influence on achieving remission or LDA in DAS28-ESR in patients receiving abatacept using a univariate analysis ( $p=0.0386$ ). However, ACPA positivity did not reach a statistical difference using a multivariable logistic analysis ( $OR=5.17$ ,  $95\%CI$  0.895-29.877,  $p=0.0664$ ). On the other hand, the presence of SE had a statistically significant effect on achieving remission or LDA ( $OR$  8.986,  $95\%CI$  1.999-40.390,  $p=0.0042$ ). [Conclusions] The presence of SE significantly associated with the achievement of remission or LDA, but ACPA did not in multivariable logistic analysis.

## P11-5

### Serum high MMP-3 level after normalization of CRP may predict the future joint destruction in RA patients treated with MTX

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Conflict of interest: None

[Objective] To investigate whether serum MMP-3 level predicts the progression of joint destruction in RA patients whose CRP levels became negative by MTX treatment. [Methods] Ninety-two RA patients whose CRP became negative by MTX treatment were analyzed retrospectively. We primarily compared serum MMP-3 values and radiographic progression (modified van der Heijde modified total sharp score: mTSS). SPSS was used for statistical analyses. [Results] In a total of 92 RA patients, 51 were MMP-3-negative and 41 were MMP-3-positive. Progression of joint destruction in the MMP-3-negative group / MMP-3-positive group were 13.7% (7/51 cases) / 29.3% (12/41 cases), the amount of change from mTSS baseline was  $0.43 \pm 1.28$  /  $0.62 \pm 1.36$  ( $p=0.49$ ), non-progression rate ratio (change from mTSS baseline  $< 0.5$ ) was 87.3% / 72.0% ( $p=0.058$ ), serum MMP-3 was  $77.86 \pm 46.80$  /  $82.96 \pm 39.17$ , and baseline PSL use was 23% (12/52 cases) / 55% (23/42 cases), respectively. [Conclusions] In RA patients treated with MTX, residual MMP-3 activity may predict the future progression of joint destruction even after the normalization of CRP is achieved.

## P11-6

### Correlation between retention rate of Abatacept and blood differential count -Results from ANSWER Cohort-

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Conflict of interest: None

[Objective] To investigate correlation between blood differential count and clinical outcomes of Abatacept (ABT) using ANSWER, a multicenter cohort database. [Methods] The relationship between blood differential count before ABT initiation and clinical outcomes was analyzed using t-test, logistic regression, and Kaplan-Meier method. [Results] Out of 734 ABT initiated RA patients in ANSWER Cohort from 2010, patients who were followed more than 6 months and whose blood differential test data was available before ABT were analyzed ( $n=313$ ). Median age: 70, Female percentage: 85.3%, Bio-naïve rate: 63.6%, initial DAS28-ESR: 4.11, retention rate at the last visit was 43.1%. Monocyte and Basophil counts were tend to be higher in ABT retention group ( $p=0.062$ , 0.135). MB-score, defined as a sum of z-scored monocyte and basophil counts, was significantly higher in ABT retention group ( $p=0.042$ ), but improvement of disease activity was not different. Logistic regression analysis showed that age and MB-score were significantly correlated with ABT retention. In Kaplan-Meier method, retention rate of ABT in high MB-score ( $\geq 0.65$ ) group was significantly higher compared to low MB-score group ( $p=0.01$ ). [Conclusion] Higher monocyte and basophil counts might correlate with ABT retention rate.

## P11-7

### The incidence of chronic kidney disease (CKD) in RA and its risk factors results from 10 years of observational study

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Conflict of interest: None

[Objective] The objective of this study was to determine the incidence of chronic kidney disease (CKD) in RA and its risk factors. [Methods] A retrospective cohort study. Subjects were consecutive 499 RA patients who had visited our department in April 2010 and were included in this cohort study. CKD was diagnosed according to the criteria by KDIGO. [Results] Of the 499 RA patients (134 males, 365 females), 269 (58 males, 211 females) who did not have CKD at the start of the study and were observed for 10 years were analyzed. Over the 10 years-observation periods, 49 patients developed CKD (13 males and 36 females). The 10-year incidence of CKD in RA was 18.2%. Older age, gender, hypertension, diabetes, and pulmonary diseases were identified as risk factors for the development of CKD. Biologics suppressed the onset of CKD ( $(+)$ : 17/132 (12.9%) vs  $(-)$ : 32/137 (23.4%),  $p=0.02$ ). Glucocorticoid use or MTX had no effects on the development of CKD. [Conclusions] The 10-year incidence of CKD in RA was 18.2%. Biologics suppressed the development of CKD.

## P11-8

### Factors associated with the progression of renal dysfunction in patients with rheumatoid arthritis undergoing treatment with biologics

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Conflict of interest: None

The purpose of this study was to investigate the factors involved in the progression of renal dysfunction in patients with rheumatoid arthritis. In this study, we investigated the factors associated with the progression of renal dysfunction in rheumatoid arthritis patients with high disease activity who require treatment with biologics in a hyper-aged society such as Japan. In this study, 127 patients who were diagnosed with rheumatoid arthritis by rheumatologists and treated with biologics were included, and



progression of renal dysfunction was defined as an increase in Cr<sub>e</sub> more than 0.15 over 3 years from the start of evaluation. Joint ultrasonography was performed by two or more rheumatologists at our department at the start of treatment and six months to one year later, and the relationship between disease activity and the findings of joint ultrasonography was examined. The results showed that the CRP, ESR, and DAS28 (ESR) were significantly higher in the group of patients who showed progression of renal dysfunction over 3 years than in the group of patients who did not show progression during treatment with biologics. Conclusion: High inflammatory response and disease activity at the start of biologic therapy may affect not only joint destruction but also renal function.

## P11-9

### The effect of smoking on therapeutic efficacy of biological DMARDs and JAK inhibitors on rheumatoid arthritis - ANSWER longitudinal cohort study -

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Conflict of interest: None

[Objective] Smoking is associated with the development of RA, and is reported to affect the therapeutic efficacy in RA. We investigated the effects of smoking on treatment with biological DMARDs and JAK inhibitors (bDMARDs/JAKi). [Methods] 545 RA patients who continued the 1st bDMARDs/JAKi for 6 months were included. We classified them into non-smokers/ex-smokers/smokers. The extent of smoking was quantified in pack-years (py). In the smokers the correlation between the py and the treatment response was analyzed, and further analyzed divided into a non-TNF inhibitor (non-TNFi) group and a TNF inhibitor (TNFi) group. [Result] Three groups had 299/159/87 patients respectively, and there were no differences in background other than gender/age/stage. A negative correlation between py and  $\Delta$ DAS28ESR/ $\Delta$ CDAI was suggested in the smokers ( $r=-0.2289/r=-0.2405$ ). Among them, no correlation between the py and  $\Delta$ DAS28ESR/ $\Delta$ CDAI ( $r=-0.1181/r=-0.1089$ ) was found in the non-TNFi group, but a negative correlation ( $r=-0.3068/r=-0.3132$ ) was suggested in the TNFi group. [Conclusion] When the first bDMARDs/JAKi treatment is given to RA patients, there is no correlation between the amount of smoking and the effect by non-TNFi, but the effect by TNFi may be diminished in relation to the amount of smoking.

## P12-1

### How do central sensitization features affect subjective symptoms among patients with rheumatoid arthritis?

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Conflict of interest: None

[Objective] Central sensitivity syndrome (CSS) comprises various symptoms due to central sensitization. However, the pain features and the effect of CSS on subjective symptoms among patients with rheumatoid arthritis (RA) remain unknown. We examined pain features and the degree of CSS on subjective symptoms among multiple clinical parameters.

[Methods] The central sensitization inventory (CSI) and short-form McGill pain questionnaire were used to evaluate CSS and pain qualities among 240 outpatients with RA. Disease activity, fibromyalgia, neuropathic pain, anxiety, depression, pain catastrophizing, and health-related quality of life were evaluated. We analyzed the pain features of CSS and the effect of CSS on patient global assessment (PGA), evaluator global assessment (EGA), and PGA minus EGA among the relevant clinical parameters using multivariate analysis. [Results] CSI score was associated with 'heavy', 'sharp', and 'stabbing' pain. CSS was associated with EGA ( $p=0.000$ ,  $\beta=-0.199$ ) and PGA minus EGA ( $p=0.021$ ,  $\beta=0.147$ ), but not with PGA. [Conclusions] The pain features with CS were different from those with disease activity among RA patients. CSS may be one of the important factors causing the discordance between PGA and EGA.

## P12-2

### A cross-sectional study of central sensitization pain using the Central Sensitization inventory in rheumatoid arthritis patients

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Conflict of interest: None

[Objective] The purpose of this study was to investigate the relationship between central sensitization pain, disease activity, and functional disability in rheumatoid arthritis patients using the Central Sensitization inventory (CSI), a screening tool for central sensitization. [Methods] A total of 188 patients of mean age  $66.9 \pm 13.4$  years were included. We assessed associations between clinical parameters (SJC, TJC, CRP, ESR, EGA, PGA, pain VAS, DAS28CRP, HAQ-DI) and Central Sensitization inventory. And we compared between the two groups, CS group (CSI  $\geq 40$  N=20) and non-CS group (CSI <40 N=168). [Results] The following were significantly higher in CS group than in non-CS group: Pain VAS [CS group  $39.6 \pm 28.9$  mm non-CS group  $17.9 \pm 22.4$  mm  $p < 0.01$ ]; PGA [CS group  $34.9 \pm 25.2$  mm non-CS group  $17.7 \pm 22.5$  mm  $p < 0.01$ ]; TJC [CS group  $0.9 \pm 1.4$  non-CS group  $0.4 \pm 1.2$   $p < 0.01$ ]; DAS28CRP [CS group  $2.26 \pm 0.67$  non-CS group  $1.83 \pm 0.80$   $p < 0.01$ ]; HAQ-DI [CS group  $2.25 \pm 1.92$  non-CS group  $0.67 \pm 1.35$   $p < 0.01$ ]. There were moderately significant correlations between CSI and Pain VAS, PGA, HAQ-DI. The strongest positive association was found between CSI and HAQ-DI ( $r=0.477$ ;  $p < 0.001$ ). [Conclusions] We concluded that central sensitization pain may affect subjective assessment and functional disability in rheumatoid arthritis patients.

## P12-3

### Evaluation of quality of life of patients with rheumatoid arthritis in our department

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Conflict of interest: Yes

[Background] Many new drugs have been developed for rheumatoid arthritis (RA) to provide tight control of disease activity. However, these drugs are expensive, and cost-effectiveness needs to be considered. Cost-effectiveness of drugs is assessed by quality-adjusted survival years. To measure this, quality of life (QOL) score, which is assessed by the EuroQol 5 dimensions 5-levels (EQ-5D) is necessary. However, in Japan, the QOL score is rarely measured in daily practice, so we investigated the usefulness of the QOL score in patients of our department. [Methods] Data were extracted from RA patients who responded to the EQ-5D in both 2018 and 2019. The association between patient characteristics and QOL score was assessed. [Results] The mean QOL scores in 2018 and 2019 were 0.83 and 0.80, respectively. One hundred eighty-one patients (group A) had increased QOL scores in 2019 compared to 2018, 216 patients (group B) had decreased, and 105 patients (group C) had remained the same. The percentage of patients in each group who fulfill DAS-28 remission as of 2018 differed. On the other hand, the percentage of patients using biologics, methotrexate and prednisolone were similar. [Conclusion] DAS-28 was found to be a factor associated with QOL score in RA patients of our department.

## P12-4

### Differences between RAPID3 and other indices of disease activity in rheumatoid arthritis

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Department of Rheumatology, Tokyo Metropolitan Ohtsuka Hospital

Conflict of interest: None

[Objective] RAPID3 is a patient-reported disease activity index for rheumatoid arthritis (RA) that can be used to assess patient status using only questionnaires. However, the usefulness of RAPID3 in comparison with other disease activity indices is not clear. To evaluate the usefulness of RAPID3, we examined the differences between RAPID3 and other disease activity indices (DAS28, CDAI, SDAI) and the factors affecting the differences. [Methods] 500 consecutive RA patients were enrolled. The correlation between RAPID3 and DAS28-CRP, CDAI, SDAI was statistically examined. Factors related to disease activity were also examined in the moderate to high disease activity group. [Results] There was a high correlation between RAPID3 and DAS28-CRP, CDAI, and SDAI ( $\rho = 0.68, 0.79$ , and  $0.78$  respectively). Remission to low disease activity rate was significantly lower in RAPID3 (59.0%,  $p < 0.01$ ). Moderate to high disease activity was associated with disease duration, glucocorticoid and analgesic, but it was associated with age (OR 1.04,  $p = 0.05$ ) only in RAPID3. None of the other medication to RA were associated with disease activity. [Conclusion] RAPID3 was strongly correlated with other indices of disease activity, but the remission rate was lower, and age was associated with differences.

## P12-5

### Discordance between global assessment of the disease and fatigue assessment by patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objective] To analyze the discordance between global assessment (GA) of the disease and fatigue assessment (FA) by patients with rheumatoid arthritis (RA) and the clinical factors that associated with discordance. [Methods] We investigated GA, FA, physician global assessment (PhGA) and mHAQ of patients. FA was measured using VAS. We also evaluated disease activity, and analyzed the association between clinical factors and concordance/discordance between GA and FA. [Results] We collected data from 537 patients (115 males and 422 females, average 63.8 years). There was a moderate correlation between GA and FA ( $r = 0.700$ ) and GA and PhGA ( $r = 0.637$ ), but a weak correlation between FA and PhGA ( $r = 0.452$ ). When the concordance was defined as a difference of 10 mm or less, 371 patients (69%) showed concordant between GA and FA, 84 patients (16%) showed worse GA, and 82 patients (15%) showed worse FA. Among these three groups, age and sex was not different, but tender joint count, swollen joint count, GA, PhGA, DAS28CRP, SDAI, and mHAQ was worse in patients who reported worse GA than FA. [Conclusions] GA and FA were concordant in many patients. There were no characteristics in worse FA group, but disease activity, and physical function were different in the worse GA group.

## P12-6

### Factors associated with work disability in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To investigate the clinical features associated with work disability in patients with rheumatoid arthritis (RA) using the Work Productivity and Activity Impairment Questionnaire (WPAI). [Methods] The WPAI was annually obtained from the patients in a Nagahama City Hospital RA cohort, 'the Nagahama Riumachi Cohort' from March 2017 to February 2020. The association between work disability and clinical parameters was investigated in the employed patients. [Results] Totally 471 patients answered the WPAI, and 201 patients were analyzed. Multiple regression analysis revealed that HAQ-DI (partial regression coefficient [ $\beta$ ] = 0.157,  $p < 0.0001$ ), tender joint count (TJC) of the upper extremity ( $\beta = 0.0139$ ,  $p = 0.0010$ ), and patient global assessment (Pt-VAS) ( $\beta = 0.00146$ ,  $p = 0.0030$ ) were predictors of presenteeism. In multiple regression analysis of the 137 patients with the second annual WPAI answers, the second-to-first difference ( $\Delta$ ) in presenteeism was associated with  $\Delta$ HAQ-DI ( $\beta = 0.526$ ,  $p < 0.0001$ ) and  $\Delta$ Pt-VAS ( $\beta = 0.00197$ ,  $p = 0.0834$ ). [Conclusions] HAQ-DI, upper extremity TJC, and Pt-VAS were suggested as predictors of work disability. The Pt-VAS is more predictive of work disability than the physician's global assessment, and work disability in patients with high Pt-VAS should be paid attention.

## P13-1

### A study of patients with rheumatoid arthritis according to the time of onset

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Conflict of interest: None

[Introduction] Treatment strategies for rheumatoid arthritis (RA) have changed with advances in treatment. In this article, we report on a study of ADL and QOL according to the onset of disease. [Patients] A total of 525 patients with RA (107 males and 418 females, mean age 67.0 years) were included in the study. The patients were divided into 6 groups: those with onset before 1994 and those with onset every 5 years from 1995. The cases were 68, 48, 65, 101, 121, and 122, respectively. The mean ages were 72, 69, 67, 69, 65, and 63 years, respectively. The percentages of Class 1/2/3/4 at the time of the study were 17/29/50/4, 12/48/40/0, 35/43/22/0, 46/42/11/1, 70/22/8/0, and 73/21/6/0% in each group, respectively; the percentages of Stage 1/2/3/4 were 1/1/21/78, 2/8/19/71, 6/25/29/40, 15/36/30/19, 36/32/24/8, and 56/30/11/3%, respectively. The DAS28ESR and HAQDI were 3.51 and 1.18, 3.43 and 1.01, 2.94 and 0.54, 3.05 and 0.49, 2.9 and 0.41, and 2.86 and 0.36, respectively. 6/68, 17/56, 15/54, 34/68, 65/74, and 60/69%, respectively. [Summary] The earlier the onset of RA, the worse the disease activity and radiographic changes over time, and the better the treatment outcome after 2000, when MTX became widely available.

## P13-2

### The actual situation and the effectiveness of medication for rheumatoid arthritis on the cohort study of rheumatic patients by Koto Medical Association in Tokyo

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Conflict of interest: None

[Objective] To recognise the actual situation and the effectiveness of the medication for rheumatic patients living in Koto-ku, Tokyo. [Methods] Koto Medical Association sent the questionnaire to the hospitals and the

clinics where RA patients in Koto-ku go. The questionnaire was consisted of age, sex, body height, body weight, the year of onset, pain VAS, global VAS, MDHAQ, the counts of swollen joints and tender joints (28 joints), the value of ACPA, RF, CRP, and serum creatine, and drugs. [Results] The Association received the data of 628 RA patients from 11 institutions. The rate of men to women was one to four. The mean of age was 65.9 years, the mean of onset age was 54.9 years, the mean duration was 12 years. The positive rate of RF and ACPA was 70.5% and 72.5%, respectively. The rate of double seropositive and double seronegative was 59.0% and 18.4%, respectively. The rate of remission on DAS28-CRP, CDAI, and RAPID3 was 65.3%, 25.1%, and 30.2%, respectively. The rate of steroid usage was 27.1% and the mean dose was 3.2 mg per day. The rate of MTX usage was 63.9% and the mean dose was 7.21 mg per week. The rate of bDMARDs usage was 19.9%. [Conclusions] The actual situation and the effectiveness of medication for rheumatic patients in Koto-ku was evaluated for the first time.

### P13-3

#### A one-year study of medication adherence (MMAS) in rheumatoid arthritis patients using pharmacist intervention

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Conflict of interest: None

[Objective] We conducted a questionnaire survey of rheumatoid arthritis (RA) patients using the Morisky Medication Adherence Scale-4 (MMAS4), a medication adherence (AD) scale. In this study, we investigated how each item, including the MMAS, changed in order to understand the factors that improve AD. [Methods] The subjects were 59 patients who completed the self-administered Morisky's Adherence Scale (MMAS-4) questionnaire twice between March 2020 and September 2021. The changes in the MMAS-4 items, AD scale (MAS), Efficacy Expectancy (Eex), Outcome Expectancy (Oex), Social Support (SS) were observed. Each clinical information were investigated from patients and their physician, and medical records. [Results] Fifteen patients in the MAS improved group and 44 patients in the MAS unchanged to worsening group were compared in terms of age ( $66.1 \pm 12.5/68.4 \pm 11.7$  years), sex ratio (1/14, 14/30), and frequencies of pharmacist interventions ( $3.7 \pm 1.4/4.0 \pm 1.4$ ). There was no significant difference in Eex, Oex, SS, DAS28-CRP, SDAI, CDAI, CRP, ESR, and MMP-3. Group A tended to have a lower medical satisfaction. [Conclusion] Increasing the frequencies of interventions did not lead to improvement in AD. Improvement of AD may not simply mean medical satisfaction.

### P13-4

#### Progression of bone erosion was dominantly suppressed by IL-6 inhibitor than TNF inhibitor in RA patients

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Conflict of interest: None

[Objective] We previously demonstrated the predictive factors for effective selection of tocilizumab for the patients with rapid progressive joint erosion. This study aimed to investigate the prevention effect of IL-6, TNF, and JAK inhibitor for progression of joint erosion in patients with RA. [Methods] This is a retrospective cohort study. The 173 patients analyzed in this study were divided into three groups: etanercept treatment (TNFi, 69 patients), tocilizumab or Sarilumab treatment (IL-6i, 70 patients), tofacitinib, baricitinib, or peficitinib (JAKi, 34 patients). The mean yearly progression of modified total Sharp scores (mTSS) at the initiation of treatment and after 12 months of therapy were measured and compared among the three groups. [Results] The mean yearly progression of mTSS was not significantly changed among three groups. However, the mean yearly progression of erosion score in mTSS was significantly changed

among groups ( $p=0.017$ ). Post-Hoc analysis demonstrated that the mean yearly progression of erosion score was significantly lower in IL-6i than in TNFi ( $p=0.013$ ). [Conclusions] Current study demonstrated that IL-6 inhibitor dominantly suppressed joint erosion. We propose that IL-6 inhibitor may use for the patients with rapid progressive joint erosion.

### P13-5

#### Treat-to-target strategy for patients with rheumatoid arthritis in daily clinical practice

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Center for Rheumatic Disease, Marunouchi Hospital

Conflict of interest: None

[Objective] We examined whether the rheumatoid arthritis (RA) treatment goal of achieving remission within 6 months was achieved in clinical practice and what factors hindered its achievement. [Methods] RA patients visiting our outpatient clinic from September 2020 to March 2021 were examined. Among the cases treated with the treat-to-target (T2T) strategy, the target achievement rate, treatment contents, and factors in the cases that did not achieve the target were analyzed. [Results] Twenty-five patients were treated with the T2T strategy during the study period. After 6 months, 9 cases reached remission, 12 showed low disease activity, and 4 showed moderate disease activity. Sixteen patients were judged to have achieved the goal. Nine cases did not achieve the goal. The groups achieving and not achieving the target were compared. The disease activity before treatment was SDAI average 18.7 and 22.2 in the groups achieving and not achieving the target, respectively (no significant difference). The factors associated with not achieving the goal were residual pain, complications, and financial circumstances. [Conclusions] The target achievement rate with the T2T strategy was 64%. It will be necessary to pay attention to pain relief to further increase this rate in future.

### P13-6

#### The Correlation between prognosis and when bDMARDs or tsDMARDs was started in ACPA positive RA patients

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Conflict of interest: None

[Objective] To exam if the starting time of bDMARDs or tsDMARDs (BTS), gave an effect to the treatment course or not. [Methods] We examined ACPA positive RA patients on treatment for more than 3 years from onset, in 2019 to 2020 at our hospital. We looked in cases, onset only after 2005, which was when bDMARDs without MTX was available in Japan. All cases were treated according to EULAR recommendations. T2T were not practiced in 6 cases because of complications or economic reason and was excluded from the study. [Results] 105 cases were valid. Average age was  $70.0 \pm 12.6$  years old, 78.1% was female and average duration of RA was 10.2 years. 49 cases (46.7%) used MTX and 48 cases (45.7%) used BTS. DAS28-CRP showed remission in 85 cases (81.0%), LDA in 8 cases (7.6%), MDA in 12 cases (11.4%) and no cases in HDA. Average time before the use of BTS was 3.3 years after onset. RA patient who used BTS before 3 years after onset (Group A) was 26. Number of patients who used more than 3 kinds of BTS was 10 in Group A, 4 out of 79 in non-Group A. 3 or more kind of BTS were used in Group A than non-Group A. [Conclusions] When bDMARDs or tsDMARDs needs to be used, to ACPA positive RA patients before 3 years after onset, there is a possibility of becoming multi-drug invalid.

### P13-7

#### PMR and Pseudogout as Causes of Secondary Failure During Biological Therapy in Elderly Rheumatoid Arthritis Patients

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Conflict of interest: None

[Object] In general, when arthritis worsens during treatment with biologics, it is considered a so-called secondary failure, and a switch to another



er biologic or JAK inhibitor is recommended. Here, we introduce two cases in which the cause of secondary failure was thought to be polymyalgia rheumatica (PMR) and pseudogout. [Methods] (Case 1) A 75-year-old man who suddenly complained of general pain while being treated with Tocilizumab (TCZ). (Case 2) A 79-year-old man who complained of cervical pain while being treated with Etanercept (ETN). [Results] In the first case, it took a long time to diagnose PMR because the elevated CRP was masked by the use of TCZ and the patient was seropositive. The second case was diagnosed as Crowned dens syndrome based on cervical CT (C1/2) findings. Both cases were remitted with concomitant PSL. [Conclusion] With the aging of RA patients under treatment, the number of complications of PMR and pseudogout is expected to increase, but these have been rarely reported. This is because PMR is defined as seronegative in principle, which may be a blind spot in differentiation, and pseudogout may be dismissed as an exacerbation of RA. It is necessary to recall these complications as the cause of secondary failure.

## P14-1

### Cricoarytenoiditis in rheumatoid arthritis presenting as refractory aspiration pneumonia

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Conflict of interest: None

[Background] Rheumatoid arthritis causes arthritis mainly in small joints, and cervical spine lesions may be seen in long-term affected individuals. It also causes damage to not only joints but also organs such as lungs and kidneys. Bronchial dilatation and middle lobe tongue syndrome are common as airway lesions, but Cricoarytenoiditis has been reported as a rare complication. [Case] A 79-year-old woman with a history of 18 years. Both RF and anti-CCP antibodies were positive. The patient was referred to our hospital because of exacerbation of dyspnea. Chest CT revealed interstitial pneumonia, mediastinal emphysema, pneumonia, and chronic aspiration pneumonia. When the swallowing function was evaluated to investigate the cause of chronic aspiration pneumonia, it was caused cricoarytenoiditis with rheumatoid arthritis. [Discussion] At present, the importance of early diagnosis and early treatment is recognized, the number of cases leading to serious joint lesions is decreasing. It seems that it is difficult to diagnose cricoarytenoiditis because there are few subjective symptoms until the disorder worsens. Thus, It is useful to consider There is no laryngeal lesion due to rheumatoid arthritis in the background, or whether treatment for rheumatism is appropriate.

## P14-2

### Effect of Abatacept on Interstitial Lung Disease associated with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] To study the effect of abatacept (ABT) on interstitial lung disease (ILD) associated with rheumatoid arthritis (RA) in our department. [Methods] Of the 116 patients diagnosed with RA-ILD in our department between 2015 and 2019, 38 consecutive patients with ABT who could be followed for more than 1 year were included. Clinical data, imaging, treatment, and prognosis were investigated. [Results] ABT was used in 38 RA-ILD patients, median age 73 years, duration of RA 43 months, smoking 17 (45%), RF positive 32 (88%), 218 IU/mL, anti-CCP antibody positive 32 (88%), 328 U/mL, DAS28-CRP 2.1, SDAI 5.5, CDAI 5. Concomitant medications included MTX in 7 patients (18%), 6 mg, PSL in 12 patients (32%), and 5 mg, TAC in 22 patients (58%). KL-6 486 U/mL, FVC 95.1%, HRCT UIP like pattern 16 (42%), non UIP 22 (58%), total GGO score 5.2, total Fibrosis score 3.3. The change in HRCT scores at 1 year showed a significant improvement in GGO score ( $p < 0.0001$ ), UIP/non UIP like pattern ( $p = 0.009/0.002$ ) and no significant difference in Fibrosis score. [Conclusions] Treatment of RA-ILD with ABT resulted in an improvement in GGO in the short term of 1 year.

## P14-3

### ACPA, RF, and anti-CarP Ab in rheumatoid arthritis patients with interstitial lung disease

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Conflict of interest: None

[Objective] Interstitial lung disease (ILD) is characterized by interstitial inflammation and fibrosis of the lung. ILD is often complicated with rheumatoid arthritis (RA) as one of extra-articular manifestations. A few studies were reported on rheumatoid factor (RF), anti-citrullinated peptide antibody (ACPA), and anti-carbamylated protein (CarP) Abs in RA complicated with ILD (RA-ILD). In the present study, we investigated the association of RF, ACPA, and anti-CarP Abs with RA complicated with ILD. [Methods] Sera from RA patients with ILD or without chronic lung diseases were collected. Serum RF, ACPA, and anti-CarP Ab were measured by enzyme-linked immunosorbent assay. [Results] RF IgA was associated with ILD ( $P = 1.13 \times 10^{-8}$ ), particularly usual interstitial pneumonia (UIP) ( $P = 1.00 \times 10^{-7}$ ). ACPA secretory component (SC) was associated with RA complicated with ILD ( $P = 0.0003$ ), particularly nonspecific interstitial pneumonia (NSIP) ( $P = 0.0017$ ). Anti-CarP Ab was associated with RA complicated with ILD ( $P = 1.04 \times 10^{-11}$ ). [Conclusions] RF IgA and ACPA SC in RA were associated with UIP and NSIP, respectively, suggesting different specificities in patients with RA. These results may help elucidate the different pathogenesis of UIP and NSIP in RA.

## P14-4

### Biologics and MTX had little effect on the worsening of pre-existing pulmonary abnormalities

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Conflict of interest: None

Purpose: To clarify the worsening rate of pulmonary abnormalities in RA in the real world and to identify their risk factors METHODS: A cohort study. Subjects were consecutive RA patients who had visited our department in April 2010 and were included in this cohort study and observed for 10 years. In this study, patients with pulmonary abnormalities were analyzed. Pulmonary abnormalities were classified into four categories, interstitial pneumonia, airway lesions, nodular lesions, and others on CT images. We reviewed medical records and examined the rate and the worsening and their risk factors. Results: Subjects were 163 patients (61 males / 102 females) with an average age of 65.9 years. Biologics, MTX and glucocorticoid were used in 32%, 50%, and 71%, respectively. The subjects included 71 with ILD, 54 with airway disease, and 30 with nodular lesions. Worsening was found in 85 (52%) with pulmonary abnormalities and 46 (66%) with ILD. Seven of ILD died from acute exacerbation. The risk factors for worsening of ILD were NSAID use, smoking, and UIP pattern. The use of MTX, biologics, and GS had little effect on the worsening of ILD. Conclusion: The use of MTX, biologics, and GS had little effect on the worsening of pre-existing pulmonary abnormalities.

## P14-5

### An case of rheumatoid arthritis for which differentiation of bronchiolitis was considered important

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Conflict of interest: None

A 68-year-old woman had rheumatoid arthritis (RA) 8 years ago, she had been treated with methotrexate. So her RA had been in remission or low disease activity. Sjögren's syndrome was not complicated. She had no particular history. At the age of 66, a dry wheeze was heard on the dorsal side. KL-6 was 535 IU / L. The chest CT showed granular shadows central to the lobule, branched shadows, and thickening of the bronchial wall, suggesting follicular bronchiolitis. She had no subjective symptoms and was observed, but from around the age of 67, she began to be chronic coughing and swelling and the disease activity of rheumatoid arthritis worsened. Administration of a small amount of prednisolone alleviated joint symptoms, but did not improve respiratory symptoms. Although there was no complication of chronic sinusitis, clarithromycin was administered because it was similar to the imaging findings of diffuse panbronchiolitis, but it was ineffective. Macrolide therapy may be effective for RA related bronchiolitic lesions, and they may improve the disease activity of RA, but were ineffective in this case. In patients with RA accompanied by bronchiolitis, differentiation of bronchiolitis was considered to be important for predicting the therapeutic effect on the disease activity of RA.

### P14-6

#### **Jute-Induced Hypersensitivity Pneumonitis during treatment for rheumatoid arthritis: A Case Report**

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Conflict of interest: None

A 67-year-old woman with rheumatoid arthritis presented with fever and cough. Five years ago, she was diagnosed with rheumatoid arthritis and her disease activity was stable by taking 6 mg methotrexate and 1 g salazosulfapyridine. Therefore, the internal medicine was discontinued in July. Since fever and cough continued from the end of August, she visited our hospital and underwent a close examination. But the cause was unclear, so she admitted to our hospital. Although his general condition and respiratory condition were good, plain chest CT showed frequent nodular opacities in both lungs. It was improved by the hospitalization. There was a medical history of starting knitting using jute at the time of discontinuing MTX, and acute hypersensitivity pneumonitis by jute was suspected. She was discharged because her condition improved. The patient was positive for a lymphocyte proliferative reaction to jute at a later date, and was diagnosed as having a strong suspicion of acute hypersensitivity pneumonitis based on the clinical features, onset environment, and immunological findings. Conclusion: There are few reports of acute hypersensitivity pneumonia caused by jute, and the immune response during the absence of anti-rheumatic drugs may have been involved.

### P14-7

#### **Methotrexate is effective in the treatment of pharyngeal stenosis due to hypocomplementemic urticarial-like vasculitis with comorbid rheumatoid arthritis: A case report**

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Conflict of interest: None

A 43-year-old woman with hypocomplementemic urticarial vasculitis (HUV) and rheumatoid Arthritis (RA) complained of feeling of pharyngeal stenosis. In X-4, she was treated with methotrexate (MTX) 16 mg/week and tocilizumab and adalimumab, but she had progressive joint pain and she was referred to our department (ACPA: 25.3 U/mL and rheumatoid factor (RF): 158 IU/mL). She was then switched from abatacept to tofacitinib in July X-1, which improved joint pain. In December X-1, she complained urticarial erythema, feeling of pharyngeal stenosis and polyarthrititis. Skin biopsy showed consistent findings of urticarial-like vasculitis. She was initiated on therapy with prednisolone 30 mg and tacrolimus, the rash and arthralgia was improved. When her therapy with prednisolone 20 mg, she complained worsening of feeling of stenosis. In June X, RF in-

creased from 528 to 1178 IU/mL before and after the onset of urticarial vasculitis, and MTX 4 mg/week was started as a treatment for RA, the primary disease. 3 weeks after dosing, feeling of pharyngeal stenosis has improved. Since then, she has progressed without recurrence of feeling of pharyngeal stenosis. There are few reports of HUV associated with RA, or of improvement in feeling of pharyngeal stenosis by MTX.

### P14-8

#### **A case of rheumatoid pleuritis associated with bucillamine-related yellow nail syndrome**

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Conflict of interest: None

[Objective] To report a case of rheumatoid pleuritis, associated with bucillamine (BUC)-related yellow nail syndrome (YNS). [Case] A 68-year-old female with rheumatoid arthritis (RA) experienced a dyspnea on exertion 4 months before the first visit to our hospital, when she was treated with 2 mg/day of prednisolone (PSL), BUC, and iguratimod. A CT scan was performed at her first visit, which revealed bilateral pleural effusions and sinusitis. Her pleural effusion showed predominant lymphocytes, no depletion of glucose level, normal adenosine deaminase, and an increased rheumatoid factor. We diagnosed her as having rheumatoid pleuritis and treated with 32 mg/day of PSL, however, the pleural effusion did not ameliorate. Since she presented yellow nails, we judged that the pleural effusion was refractory due to the administration of BUC and discontinued it, resulted in the resolution of the pleural effusion. [Clinical Significance] YNS is a disorder which presents yellow nails, lymphatic edemas, sinusitis, and pleuritis. BUC is a representative agent which can cause YNS, and is still widely used for RA patients who cannot receive methotrexate. We should be cautious about YNS, including refractory pleuritis, when using BUC.

### P14-9

#### **Rheumatoid Arthritis that Initially Presented as Carpal Tunnel Syndrome: A Report of Three Cases**

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Conflict of interest: None

Introduction Carpal tunnel syndrome (CTS) is a common extra-articular manifestations of rheumatoid arthritis (RA). RA is usually diagnosed based on joint symptoms, and few reports have described RA that initially manifested as CTS. We report three cases of RA in patients who presented with suspected CTS. Case Report We describe three women (aged 66-77 years) who presented between 2019 and 2020 for suspected as CTS (two patients with unilateral and one with bilateral median neuropathy). All patients showed edema of the affected. Ultrasonography (US) revealed synovial hypertrophy and a power Doppler signal. One patient did not meet the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria; however, comprehensive evaluation confirmed diagnosis of RA. All patients received steroids and anti-rheumatic drugs, which led to improvement in pain and edema. However, patients' neurological symptoms persisted, necessitating carpal tunnel release and synovectomy. Histopathological evaluation of the resected synovium showed nonspecific chronic inflammation, consistent with RA. Conclusion Clinicians should consider the possibility of latent RA in patients with suspected CTS, and US is a useful modality for early diagnosis in such cases.

## P14-10

**Acquired pure red cell aplasia in a patient with rheumatoid arthritis**  
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Conflict of interest: None

A 68-year-old woman had a 25-year history of rheumatoid arthritis (RA) and was treated with prednisolone 5 mg/day, leflunomide (LEF) 10 mg/day, and mizoribine (MZR) 100 mg/day. She was diagnosed with anemia two months ago. She presented with fatigue two weeks ago and laboratory tests showed hemoglobin (Hb) 6.6 g/dL with reticulocytes 0.7%. Drug-induced anemia was suspected, and she was discontinued LEF and MZR and was administered cholestyramine. However, her anemia progressed further. Laboratory tests showed normal serum iron, folate, vitamin B12, zinc and copper, and elevated erythropoietin. Bone marrow examination showed erythroblastopenia and no abnormality was found in lymphocyte subset, T cell receptor rearrangement, and chromosome test. Viral infection was ruled out by viral antibody tests and PCR tests. She was diagnosed as pure red cell aplasia (PRCA) associated with RA and treated with cyclosporine (CyA). Her reticulocytes raised and Hb sustained up to 9 g/dL two months after the treatment. There have been only a few reports of PRCA associated with RA. Most of the cases developed PRCA in patients with RA of long duration without any trigger. This case, however, indicated that surgical invasion may be a trigger.

## P14-11

**Successful treatment with Tofacitinib in refractory rheumatoid arthritis complicated by macrophage activation syndrome**

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Conflict of interest: None

Macrophage activation syndrome (MAS) is a life-threatening complication of autoimmune diseases. Rheumatoid arthritis (RA) is rarely complicated by MAS. The optimal treatment in RA complicated by MAS is unclear. We describe here successful treatment with Tofacitinib (TOF) in refractory RA complicated by MAS. A 79-year-old man was admitted to our hospital with a high fever and polyarthritis. His past medical history was RA. Laboratory tests showed anemia, thrombocytopenia, abnormal liver function tests, and hyperferritinemia. Bone marrow aspiration and biopsy revealed hemophagocytosis. He was diagnosed as MAS associated with RA. He was given methylprednisolone (mPSL) 1,000 mg daily intravenously for 3 days and then prednisolone (PSL) 70 mg daily. He temporarily had a positive therapeutic response but fever, polyarthritis, and elevated inflammatory response recurred. He was given mPSL 500 mg daily intravenously for 3 days and also added to Tocilizumab (TCZ) intravenously, but the disease activity was poorly controlled. PSL was increased to 140 mg daily, and then the steroid dose was tapered to PSL 100 mg daily, but MAS recurred. We changed TCZ intravenously to TOF 10 mg daily, so He had a positive therapeutic response and the steroid dose was tapered to PSL 5 mg daily.

## P14-12

**Patient with refractory malignant rheumatoid arthritis with respiratory infection complicated sigmoid colon penetration: a case report**

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Conflict of interest: None

Case: A 69-year-old female with malignant rheumatoid arthritis (MRA) treated by corticosteroid and methotrexate for 24 years, developed bronchogenic cavity on right lower lobe, found incidentally by computed tomography (CT) scan. Bronchoalveolar lavage culture revealed non-tuberculosis mycobacterial infection. Furthermore, Aspergillus antigen was found positive in blood examination. As a result, her lower leg ulcer and

arthritis deteriorate with methotrexate discontinuation. Increasing prednisolone to 20 mg was not effective, we resumed methotrexate and started itraconazole concomitantly. Accordingly, her symptoms improved and enabled to decrease steroids gradually. But 9 months later, she admitted to our hospital for abdominal pain. CT scan showed the appearance of free air in the abdomen, thereby she was transferred to another hospital for emergency surgery. As a result of operation, sigmoid colon penetration was suspected. She was discharged after 20 days from operation, followed by uneventful recovery. Clinical significance: This case of MRA showed reactivity to corticosteroids and methotrexate. On the other hand, it indicated the difficulties of reducing the dose of medicine and led to complications in consequence.

## P15-1

**Actual conditions of treatment by life stage in women with rheumatoid arthritis who are visiting our hospital**

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Conflict of interest: None

[Objective/Methods] We conducted a fact-finding survey on the treatment content and disease activity of each age group in 603 RA women who were visiting our hospital as of September 2021 and whose data were registered. Patient groups are divided into four groups: (1) fertile age: under 45 years old, (2) menopause: 45 years old to under 55 years old, (3) middle age 55 years old to under 65 years old, and (4) elderly age 65 years old. We conducted a fact-finding survey of each treatment content and disease activity (DAS28CRP) on the last visit day during the period from April to September 2021. [Results] There were 96 cases in the (1) group, 79 cases in the (2) group, 69 cases in the (3) group, and 359 cases in the (4) group. RA disease activity was 1.7 or less in all groups, meeting the remission criteria. The frequency of use of methotrexate was highest in group (2) (70.8%) and lowest in group (1) (38%). The frequency of biopharmacy use was highest in group (1) 60.4% (of which TNF inhibitors were used in 60.3%) and lowest in group (3) 30.4%. Regarding the use of Janus kinase inhibitors, the highest rate was 7.5% in group (2). [Conclusion] With various treatment options available these days, it is important to perform Treat to target treatment at any time.

## P15-2

**Cost and effectiveness analysis of DMARDs therapy (annual report from NinJa 2020)-The cost-effectiveness of DMARDs improved-**

Yasuo Suenaga<sup>1</sup>, Masataka Torigoe<sup>1</sup>, Daisaku Kimura<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Shigeto Tohma<sup>3</sup>

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Conflict of interest: None

[Object] To evaluate the balance between the clinical effects of recent anti-rheumatic treatment and its cost [Methods] The Data from RA patients registered in the large cohort database (NinJa) in 2002-2020 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 488,000 yen / patient in 2020, 7,000 yen lower than the cost in 2019. The rate of the cost of biologics was 65.5% and decreased in 6 years. However, the rates of the cost of JAK inhibitors increased to about 16.3%. Their annual costs /patient were higher than other DMARDs in Japan. ([The rate of the number of low activity patients to that of high activity patients] / cost) were decreased in 2017, but increased in 2018 - 2020. [Conclusions] The NHI price revision led to the stop of increase of the DMARDs' cost in 2014. And it continued from 2015 to 2020. The usage of biologics decreased, but that of JAK inhibitors increased. Those prices are still high in Japan. So, the revision of those prices may be needed for



improvement of cost-effectiveness of DMARDs.

## P15-3

### Examination of the patients with rheumatoid arthritis about disease activity and medication

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Conflict of interest: None

[Objective] To understand the present status of the patients of rheumatoid arthritis (RA) at our department, this study was made. [Methods] Age, disease activity by DAS28ESR, the kind of the treatment medicine, and history of orthopedic operation were evaluated about 262 outpatients with RA treated for certain consecutive three months of 2020. [Results] The age was 67.4±11.6 (mean±SD) years, and 65 years or older accounted for 65% of the whole, and 70s was the most. About disease activity, remission was 63%, low disease activity (LDA) was 13%, moderate disease activity (MDA) was 23%, and high disease activity (HDA) was 1%. DMARD was used in all cases. 63% of patients used MTX, 46% of patients used bDMARDs or tsDMARDs, and 18% of patients used oral steroid. The rate and use of MTX decreased with age, the rate after 70 years old became about 50%. 47% of patients who were MDA or HDA activity used bDMARDs or tsDMARDs, on the other hand, 25% of them could not be treated with bDMARDs or tsDMARDs because of complication. The rate of patients who had had orthopedic surgery was 40%, and 76% of them were remission or LDA. Half of patients after 70 years had had surgery. [Conclusions] The present status of patients with RA treated at our hospital could be understood.

## P15-4

### Clinical profile of RA patients with smoking habits

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Conflict of interest: None

[Objective] We investigated the pathophysiology and treatment status of smoking RA patients. [Methods] Age, duration of illness, disease activity score, laboratory test values, and therapeutic agents were compared between 8 smoking patients and 54 non-smoking patients. [Results] Female ratio were 25.0/75.9% (P=0.0035), age were 61.3±16.8/72.4±9.6 years (P=0.01), disease duration were 7.4±6.5/13.9±10.4 years (P=0.09), SDAI were 3.5±3.5/4.6±4.8 (P=0.54), HAQ-DI were 0.1±0.2/0.9±1.1 (P=0.074), ESR were 17.5±15.3/24.9±20.7 mm/h (P=0.34), CRP were 0.5±0.6/0.8±1.9 mg/dl (P=0.59), ACPA were 248.2±404.2/431.0±715.1 U/ml (P=0.49), RF were 89.6±134.9/111.8±242.9 IU/ml (P=0.81), eGFR were 76.3±18.2/61.8±21.0 ml/min (P=0.075), MTX usage were 37.5/50.5 % (P=0.51), MTX dose were 14.0±2.8/7.9±3.9 mg/W (P=0.016), maximum MTX dose were 12.8±3.9/6.6±5.6 mg/W (P=0.020), PSL usage were 12.5/7.4% (P=0.62), PSL dose were 8.0±0.0/3.6±1.4 (P=0.016), maximum PSL dose were 11.7±2.4/7.7±2.9 (P=0.020), b/tsDMARD usage were 25.0/16.4% (P=0.56), b/tsDMARD experience rate were 37.5/25.9% (P=0.49) in smoking / non-smoking patients. [Conclusions] Smokers needed more intense treatment to control disease activity. This suggests that smoking reduces the effectiveness of the drug, but differences in patient background should be considered.

## P15-5

### Administration of iguratimod to patients with rheumatoid arthritis can be expected to be sufficiently effective even in small doses

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Conflict of interest: None

[Objective] In patients with rheumatoid arthritis (RA) treated with iguratimod (IGU), to examine the clinical use of IGU 25 mg/day and 50 mg/day. [Methods] The effectiveness of the IGU 25 mg/day and 50 mg/day groups was examined in RA patients who used IGU for 12 weeks or longer and were observable for 24 weeks after IGU administration. [Results] The subjects were 81 patients (21 patients in the IGU 25 mg/day group, 59 patients in the IGU 50 mg/day group). The mean age was 59.6±20.1 years and the mean disease duration was 8.1±7.5 years. Baseline DAS28-ESR for IGU 25 mg/day and IGU 50 mg/day are 2.63±1.10 and 2.65±1.37, baseline CDAI is 7.7±3.6 and 10.1±6.9, baseline eGFR was 73.2 ml/min/1.73 m<sup>2</sup> and 72.1 ml/min/1.73 m<sup>2</sup>, respectively. DAS28-ESR 24 weeks after IGU administration was 2.21±1.38 and 2.19±1.36, CDAI was 4.3±3.9 and 6.2±5.4, and eGFR was 69.5 ml/min/1.73 m<sup>2</sup> and 66.3 ml/min/1.73 m<sup>2</sup>, respectively. Both the IGU 25 mg/day group and the IGU 50 mg/day group were effective (P<0.01), and there was no significant difference in the efficacy and patient background between the two groups. eGFR was significantly lower in the IGU 50 mg/day group (P<0.01). [Conclusions] In clinical practice, IGU administration to RA patients may have a sufficient therapeutic effect at 25 mg/day.

## P15-6

### Influence of multimorbidity on the treatment of elderly patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Multimorbidity occurred early in the disease course of rheumatoid arthritis (RA) and progressed more rapidly. To elucidate the influence of multimorbidity on the treatment of elderly RA patients. [Methods] Retrospective study in a single general hospital in Japan. RA patients who first visited our outpatient clinic between April 2011 and March 2016 and had been there for at least a year were included in the study. Information was collected from medical record. [Results] The study included 79 patients with RA. By the end of October 2021, 21 patients died, 31 were transferred to the hospitals where long-term care was available or other outpatient clinics, and 27 was still in our clinic. The number of comorbidities increased during follow-up, and the rate of patients with two or more chronic diseases other than RA increased from 52% at the first visit to 71% at the final visit. Although most of the patients were taking DMARDs during follow-up. The reasons for discontinuing were diverse, including worsening or increasing comorbidities, the patient's preference and poor adherence. [Conclusions] There is little evidence for RA therapy in the elderly RA patients with MM. Additional clinical studies are needed.

## P15-7

### A case of new onset of rheumatoid arthritis (RA) and a case of flare in RA after COVID-19 Vaccination

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Conflict of interest: None

[Case 1] An 81-year-old man. A few days after the first COVID-19 vaccination, he had morning stiffness, and gradually developed polyarthralgia. He had elevated CRP and increased MMP3, but RF and anti-CCP antibodies were negative. A score was 6 according to the EULAR/ACR (2010) criteria. The patient was treated with low dose of steroids because of the possibility of reactive arthritis caused by the non-specific adjuvant effect of the vaccine, but the effect was poor and the disease shifted chronic arthritis. [Case 2] A 74-year-old man with RA treated with csDMARDs and BioDMARDs (GLM) and maintained LDA for more than 1 years. After second COVID-19 vaccination, DAS28-CRP increased from 2.38 to 5.23, serum MMP3 level developed, and ultrasonography revealed severe synovitis. There were no other triggers, suggesting a vaccine-induced flare of RA. The response to steroids was poor, requiring a drastic change in treatment. [Discussion] COVID-19 vaccine is strongly recommended because it's unlikely to induce flare of RA. On the other hands, some rare case such as Case 2, have been reported and should be noted. There have been no reports of new-onset RA induced by COVID-19 vaccination, and

it is debatable whether Case 1 is truly RA. We report these cases with a discussion of the literature.

## P15-8

### A study on the development of pneumocystis pneumonia in patients treated with rheumatoid arthritis

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Conflict of interest: None

**Objective:** Pneumocystis jirovecii pneumonia (PCP) is the most important adverse event during administration of therapeutic agents for rheumatoid arthritis (RA) including biopharmacy. We will examine the onset of PCP in patients receiving RA therapeutic agents who are undergoing medical examination at the Department of Internal Medicine for Rheumatoid Arthritis, JR Hiroshima Hospital (hereinafter referred to as our hospital). **Method:** We will retrospectively confirm the onset of PCP and the patient's dosing history in patients undergoing RA treatment from April 2019 to March 2021. **Results:** PCP in all 94 cases, and PCP was contracted in 2 cases. Only the history of taking methotrexate was one case of pcP. Another case was metotrexate and prednisolone. There was a history of latent tuberculosis as a patient background. Patients who were taking corticosteroids and developing PCP had taken ST combinations or salazusulfapyridine (SASP) in all but one case that developed. **Conclusions:** No onset in patients using biological preparations. Regular chest X-rays and CT are also mentioned in the appropriate use guide by drug, but in actual medical care, vital (SpO2) and inquiry are often found. The necessity of the pharmacist outpatient clinic is able to be made.

## P15-9

### Immune thrombocytopenic purpura in patient with rheumatoid arthritis

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Conflict of interest: Yes

**Case report:** A 78-year-old woman was admitted to our hospital for evaluation of severe thrombocytopenia. She was diagnosed with rheumatoid arthritis (RA) at 55 years of age and received methotrexate (MTX, 6 mg/week). In December 2020, she developed purpura over the extremities, and her PLC decreased to 6,000/ $\mu$ L, so she was admitted to our hospital. Based on bone marrow examination, the patient was diagnosed with immune thrombocytopenic purpura (ITP) and was administered prednisolone (25 mg/day) and intravenous immunoglobulin (IVIG) therapy for 3 days. Her PLC increased on Day 3, but the PLC again decreased to 6,000/ $\mu$ L on Day 5. Therefore, eltrombopag therapy (12.5 mg/day) was initiated. The PLC continued to reduce, and we added a 5-day course of IVIG and increased the dose of eltrombopag. She also received *Helicobacter pylori* eradication therapy. The PLC increased to 27,000/ $\mu$ L on Day 34, and she was discharged. **Clinical importance:** This report describes a case of ITP in a patient with a history of MTX therapy for RA, in whom the PLC was restored only after a prolonged period (>1 month). MTX-induced myelosuppression may be associated with this. Only a few reports in have discussed MTX-induced ITP in patients with RA; we report a rare case of this condition.

## P15-10

### A case of rheumatoid arthritis that became drug free using sarilumab

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Division of Internal Medicine/Rheumatology, Sasaki Foundation Kyoundo Hospital

Conflict of interest: None

[Objective] The biologics has dramatically changed the treatment of

rheumatoid arthritis (RA), with the ultimate goal of bio-free, and drug-free beyond clinical remission. However, even within biologics, there are differences in the achievement of biofreeness, and the expectation of IL-6 receptor inhibitors is lower than that of TNF inhibitors. We describe a case in which drug free was achieved using sarilumab. [Methods] A 38-year-old female patient. She presented polyarthritis, and synovial thickening and abundant blood flow signals on echography. Serological examination revealed elevated inflammatory response and positive anti-CCP antibody, indicating RA. [Results] Although the disease duration was 5 months, the patient already had limited range of motion of the right hand joint. We started with methotrexate and prednisone because of high disease activity. Tocilizumab was introduced due to persistent high activity. The patient achieved remission but relapsed with prolongation of the dosing interval, so sarilumab was switched. After that, remission was maintained even with prolonged dosing intervals, and drug-free was achieved. [Conclusion] Bio-free is an important issue in terms of economic and long-term safety, and it was shown that sarilumab can be bio-free and even drug-free.

## P16-1

### Clinical evaluation of abatacept and golimumab in patients with rheumatoid arthritis in our department

Yuji Akiyama<sup>1,2</sup>, Takuma Wada<sup>2</sup>, Mayuko Takamatsu<sup>2</sup>, Maiko Yanagisawa<sup>2</sup>, Takashi Maruyama<sup>1,2</sup>, Yoshihiro Yoshida<sup>1,2</sup>, Kazuhiro Yokota<sup>2</sup>, Noritsune Kozu<sup>2,3</sup>, Hiroshi Kajiyama<sup>2</sup>, Yasuto Araki<sup>2</sup>, Yu Funakubo Asanuma<sup>2</sup>, Toshihide Mimura<sup>2</sup>

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Conflict of interest: None

[Objective] To investigate the efficacy and the adherence of abatacept (ABT) and golimumab (GLM) in RA patients. [Methods] Efficacy of ABT and GLM was evaluated by DAS28-ESR4, CDAI and SDAI for 416 weeks. [Results] 1) Mean DAS28 at the baseline (ABT/GLM): 5.87/5.80, CDAI 25.47/23.42, SDAI 28.64/27.48. The disease activity was significantly decreased in both groups. As time went by, the ratio of LDA + remission increased significantly until 24 weeks and maintained until 416 weeks in both groups. No significant difference in both groups. 2) The adherence at 52 weeks showed more than 80% in both groups and that at 104 weeks 69.2%, at 156 weeks 61.5%, at 208 weeks 46.2%, at 260 weeks 42.3%, at 312 weeks 34.6%, at 416 weeks 26.9% in ABT, 56.0%, 40%, 36%, 32%, 28%, 24% in GLM. No significant difference in both groups. 3) HAQ-DI was significantly improved after 12 weeks in ABT. 4) Both levels of CRP and MMP-3 were significantly reduced in GLM after 12 weeks, while the only CRP level in ABT after 52 weeks. 5) Drop-out reasons (ABT/GLM); inadequate response 5/7, cancer 1/1, organizing pneumonia 0/1, pneumonia 1/1, EBV reactivation 1/1, remission 1/0 and so on. [Conclusions] The efficacy and the adherence of ABT and GLM were similar.

## P16-2

### Significance of body mass index as a prediction factor for treatment effect of anti-TNF agents in rheumatoid arthritis - Results from Kansai Consortium for Well-Being of Rheumatic Disease Patients

Kosaku Murakami<sup>1</sup>, Hideo Onizawa<sup>2</sup>, Takayuki Fujii<sup>2,3</sup>, Akira Onishi<sup>2</sup>, Koichi Murata<sup>2,3</sup>, Masao Tanaka<sup>2</sup>, Ryota Hara<sup>4</sup>, Toru Hirano<sup>5</sup>, Kosuke Eina<sup>6</sup>, Kengo Akashi<sup>7</sup>, Takaichi Okano<sup>7</sup>, Koji Nagai<sup>8</sup>, Tohru Takeuchi<sup>8</sup>, Yonsu Son<sup>9</sup>, Hideki Amuro<sup>9</sup>, Masaki Katayama<sup>10</sup>, Wataru Yamamoto<sup>11</sup>, Motomu Hashimoto<sup>12</sup>, Akio Morinobu<sup>13</sup>

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Conflict of interest: None

[Object] To assess whether body mass index (BMI) affects clinical outcomes in rheumatoid arthritis (RA) patients starting anti-TNF agent. [Methods] From Kansai consortium for well-being of rheumatic disease patients (ANSWER) cohort, we analyzed RA patients administered by anti-TNF agents. Dividing these patients between BMI more than 23 (overweight group) or not (not overweight group), we compared the achievement rate of low disease activity (LDA) in Disease Activity Score 28-CRP (DAS28-CRP) defined as lower than 2.7. [Results] In each drug, patients number and LDA in DAS28-CRP rate ("not overweight", "overweight", p-value by Fisher's exact test) as follows; Infliximab (IFX, 160): 73%, 67%, not significant (NS); Etanercept (ETN, 283): 68%, 59%, NS; Adalimumab (ADA, 237): 75%, 71%, NS; Golimumab (GLM, 426): 72%, 63%, NS; Certolizumab pegol (CZP, 154): 64%, 82%, p=0.0259. [Conclusions] A contribution of BMI for therapeutic outcome seems to vary with each anti-TNF agent in real world observation.

## P16-3

### Predictive clinical factors for the efficacy of golimumab in patients with rheumatoid arthritis ~From the database of 101 cases in our clinic~

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Conflict of interest: Yes

[Objective] We analyzed the predictive clinical factors for the efficacy of golimumab in patients with rheumatoid arthritis (RA). [Methods] We analyzed 101 out of 109 patients with 83 female and 18 males, mean age of 60.4 years, mean disease duration of 11.1 years, 60 bio-naïve, mean HAQ-DI of 0.59, mean MTX of 6.59 mg/W, mean PSL of 2.87 mg/D. Baseline clinical factor including age, disease duration, MTX, PSL, golimumab 100 mg, HAQ-DI, CRP, RF were analyzed to correlated with DAS28 (CRP) at 24 W by multiple logistic regression analysis. [Results] Mean DAS28 (CRP) was changed from 3.43 at baseline to 2.16 at 24 W. The rate of clinical remission was 67.3% at 24 W. Continuation rate of golimumab for 3 years was 73.4% by Kaplan-Meier method. 5 cases were bio-free of golimumab. High dose of MTX or low HAQ-DI were correlated with DAS28 (CRP) at 24 W. HAQ-DI at baseline was correlated with CRP and DAS28 (CRP) at 24 W. [Conclusions] Predictive clinical factors of the efficacy for golimumab was HAQ-DI at baseline, therefore HAQ-DI should be valuable and measured for the treatment of RA patients by using golimumab.

## P16-4

### Achieving remission after 1 year in patients with rheumatoid arthritis who switched from etanercept reference product to biosimilar

Hideo Sakane<sup>1,2</sup>, Yukio Yonemoto<sup>3</sup>, Makoto Inoue<sup>3</sup>, Hiroshi Inoue<sup>3</sup>, Yasuyuki Tamura<sup>3</sup>, Hirofumi Mitomi<sup>3</sup>, Kosei Tsuchida<sup>3</sup>, Koichi Okamura<sup>2</sup>, Takahito Suto<sup>2</sup>, Tetsuya Kaneko<sup>2,4</sup>, Hirotaka Chikuda<sup>2</sup>

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Conflict of interest: None

[Objectives] To investigate disease activity in patients with rheumatoid arthritis (RA) who switched from etanercept reference product (ETN) to biosimilar (BS). [Method] The subjects were 41 RA patients (5 males and 36 females) who switched from ETN to BS for 1 year. The average age, disease duration, prior treatment period for ETN was 62.8 years, 17.4 years, 108 months respectively. The disease activity (DAS28) 1 year after switching was divided into 2 groups (R group: DAS28 < 2.6, N group:

DAS28 ≥ 2.6), and the baseline characteristics were statistically examined. [Results] There was no significant difference in DAS28 between the subjects at baseline and 1 year after the switching (p = 0.834). Univariate analysis revealed that the RF values (p = 0.038) and DAS28 (p < 0.001) were significantly lower in the R group than N group. Furthermore, logistic regression analysis was performed, DAS28 was defined as an independent factor (p = 0.004). ROC curve analysis also showed that the optimal cutoff value for DAS28 at baseline to achieve remission at 1 year was 2.5, with a sensitivity of 76.2%, specificity of 85.0%, and AUC 0.84. [Conclusion] RA patients have achieved remission using ETN, they could maintain remission even if they switch to BS.

## P16-5

### Ozoralizumab, a novel anti-TNF-alpha NANOBODY® compound, migrates more rapidly to inflamed joints than Adalimumab

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Conflict of interest: Yes

[Objectives] Ozoralizumab (OZR) is a novel trivalent humanized antibody consisting of two anti-TNF-alpha NANOBODIES® (variable region domain of heavy-chain antibodies) and one anti-serum albumin NANOBODY®. OZR has been reported to improve symptoms of RA patients from an early stage of treatment. To elucidate the mechanism of the rapid onset of effects of OZR, we compared the biodistribution kinetics of OZR and adalimumab (ADA) after subcutaneous injection in an animal arthritis model. [Methods] 35 days after induction of collagen-induced arthritis (CIA), the Alexa Fluor 680-labeled OZR and ADA were administered once subcutaneously (2 mg/kg). The amounts of antibodies in the paws and serum were fluorescently evaluated over time. [Results] The absorption rate constant (ka [hr<sup>-1</sup>]) of OZR was significantly higher than that of ADA (0.154±0.016 vs. 0.0561±0.0155; P<0.001). The area under the curve (AUC [10<sup>9</sup>·hr·(photons/s)/(μW/cm<sup>2</sup>)] of paws fluorescence by 24/72 hours was significantly higher in OZR than in ADA (2.74±0.67 vs. 1.19±0.27; P<0.001/7.74±1.75 vs. 5.20±1.57; P< 0.001 [mean ± standard deviation]). [Conclusions] OZR migrated more rapidly into the systemic circulation than ADA and was shown to accumulate at higher levels than ADA in inflamed joints at 24 and 72 hours.

## P16-6

### Examination of the efficacy of half-dose Etanercept biosimilar Therapy in clinic

Michihito Sato

Sato Saitama RA Clinic

Conflict of interest: None

[Objective] Biosimilar preparations are highly expected in terms of reducing the burden on patients and medical economics. But there are few reports examining the efficacy of low-dose administration of the biosimilar Etanercept. [Methods] Sixty-four rheumatism patients who started treatment with Etanercept BS 50 mg (administered every other week) were extracted. The disease activity before the start of treatment with Etanercept BS 50 mg (administered every other week), 1 month after the start of treatment, and 3 months after the start of treatment, and the presence or absence of continuation of treatment were evaluated. [Results] Of the 64 patients, 52 (81.2%) achieved clinical remission one month after the start of treatment. 10 patients achieved clinical remission 3 months after the start of treatment. A total of 62 (96.8%) were in clinical remission. [Conclusions] This study is a retrospective study, and it cannot be denied that the choice of etanercept BS 50 mg (administered every other week) is biased. But it was suggested that Etanercept BS 50 mg (administered every other week) may be useful not only in terms of economics but also in terms of efficacy.



## P16-7

### Maintenance effect of efficacy and safety with switching to etanercept biosimilar in rheumatoid arthritis patients treated with etanercept

Hiroki Wakabayashi<sup>1</sup>, Masahiro Hasegawa<sup>1</sup>, Ayako Nakajima<sup>2</sup>, Akihiro Sudo<sup>1</sup>

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Conflict of interest: None

[Objective] This study was aimed at evaluating the continued maintenance of treatment efficacy and safety by switching to etanercept biosimilar (ETN-BS) in RA patients treated with etanercept (ETN). [Methods] We investigated retrospectively the therapeutic effect and safety of switching to ETN-BS in 17 RA patients with treated with ETN. [Results] One patient had complication with injection site reaction and were withdrawn treatment after 3 months. Other 16 patients continued to treat ETN-BS until 52 weeks. During the treatment period, all patients were maintained RA disease activity. [Conclusions] The switched treatment of ETN-BS was tolerable and clinically effective for patients treated with ETN.

## P16-8

### Golimumab treatment at our hospital for 10 years

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Center of Rheumatology, Allergy & Clinical Immunology, National Hospital Organization Chiba Higashi Hospital

Conflict of interest: None

[Objective] Ten years have passed since golimumab was clinically available for patients with rheumatoid arthritis. The characteristics of this drug were examined in administration continuation rate. [Methods] The drug was administered to 42 patients (40-86 years old, average 64.1 years old, 36 female patients) at our hospital, and the administration continuation rate was examined. The relationship with dose, dosing interval, concomitant drug, age, etc. was examined. [Results] Approximately 10% of cases were discontinued about 1 year after the start of administration, and were considered to be primary ineffective cases. After that, it was continued to be used in 70% of cases for more than 7 years. In the cases introduced as the first bio and as the second bio, the administration continuation rate of the first bio tended to be high. There was no difference in the administration continuation rate between the presence and absence of MTX and there was no relationship with steroids. With long-term administration, the administration interval was extended. [Conclusions] Golimumab is a drug whose efficacy is maintained for a long period due to its low immunogenicity, and is considered to be particularly useful for elderly patients who cannot self-inject.

## P16-9

### Efficacy of switch from etanercept biosimilar in rheumatoid arthritis patients

Tatsuo Watanabe<sup>1</sup>, Yoichiro Haji<sup>2</sup>, Mizuki Kato<sup>2</sup>, Mitsuru Watanabe<sup>2</sup>, Takanori Ito<sup>2</sup>, Yui Amari<sup>2</sup>, Mirai Hozumi<sup>2</sup>

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Conflict of interest: None

[Object] To investigate the efficacy of switch from etanercept biosimilar in rheumatoid arthritis patients. [Methods] 4 Rheumatoid arthritis patients who were treated with etanercept biosimilar were recruited. Efficacy in disease activity scores and adverse events were investigated. [Results] All were women. Mean age was 61.25±21.6 years old, and mean disease duration 15.8±5.2 years. All case were switched to adalimumab biosimilar. Mean DAS28-CRP were, baseline: 1.41±0.31, after 4 weeks: 1.39±0.37, after 12 weeks: 1.12±0.18, which continued remission. There were no adverse events. [Conclusions] Switching etanercept biosimilar to adalimumab biosimilar continued remission.

## P16-10

### A Case of Rheumatoid Arthritis with Elevated KL-6 During Infliximab Administration

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Conflict of interest: None

[Objective] Infliximab (IFX) is one of the drugs used for rheumatoid arthritis, and the risk of drug-induced lung disease (DILD) is relatively low. We report a case of elevated KL-6 during IFX administration. [Case Presentation] The case is a man in his 70s. The duration of RA is 20 years. Combined with MTX 8 mg/w. 10 months after IFX administration, changed to infliximab biosimilar (IFXBS). There is a history of foot callus infection and there is a drug holiday. Six years after administration, the KL-6 became high at 935 U/mL, and IFXBS was discontinued and abatacept (ABT) was changed. Eight months have passed, KL-6 decreased to 624 U/mL. Although chronic lung findings were observed on chest CT, no obvious acute changes were observed. [Discussion] Although the risk of DILD due to IFX is relatively low, DILD can occur with all drugs, and MTX, which is often used for RA with IFX, Since the risk of DILD is relatively high and MTX is an anchor drug and is dose-independent, if DILD suspected, the causative drug It may be difficult to identify or an alternative drug. In this case, only IFX was discontinued, and although the KL-6 value tended to decrease, it was still high at 624 U/mL, and if the high value prolonged in the future, it will be necessary to consider the factors due to MTX.

## P16-11

### Usage experiences of Adalimumab BS in our Hospital

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Niigata Prefectural Central Hospital

Conflict of interest: None

Since February of this year, we have administered adalimumab BS to 13 patients. Ten of them had rheumatoid arthritis, two had spondyloarthritis, and one had intestinal Behcet. 6 of them were treated with newly, and others were switched from Adalimumab. Adalimumab BS worked for newly introduced patients and 5 switched patients as well as Adalimumab, but 2 switched patient's disease activities got worse. we reviewed the two cases.

## P17-1

### Sarilumab was able to achieve remission in a case of rheumatoid arthritis with refractory arthritis and interstitial pneumonia for which JAK inhibitors and TNF inhibitors were ineffective

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Conflict of interest: None

[Background] Rheumatoid arthritis (RA) is often associated with interstitial pneumonia (IP). The treatment for IP is mainly steroids, and there is no definite opinion on the effects of biologics for IP. [Patients] A patient with RA for 8 years maintained remission with methotrexate (MTX). Because exacerbation of arthritis was observed, we increased the dose of MTX and added baricitinib, but it was ineffective. We switched to sarilumab (GLM), but arthritis were not be improved and exacerbation of IP was observed. With withdrawal of MTX and GLM, methylprednisolone (mPSL) 500 mg pulse for 3 days and post-treatment prednisolone (PSL) 40 mg was performed, and arthritis and IP were improved. Tacrolimus was added and the dose was carefully reduced to PSL10 mg, but arthritis and IP was worsened. As remission therapy, mPSL 250 mg pulse for 3 days, and PSL 20 mg was performed and arthritis and IP were improved. But arthritis and IP was worsened, we added sarilumab and nintedanib, arthritis was rapidly improved and maintained remission without aggravation

of IP. [Discussion] The IL-6 receptor inhibitor has been shown to be effective in SARS-CoV-2 pneumonia by cytokine storms. TNF inhibitors may exacerbate IP, suggesting that IL-6 receptor inhibitors may be effective in management of RA-IP.

## P17-2

### Safety and effectiveness of sarilumab in Japanese patients with rheumatoid arthritis refractory to previous treatments: An interim analysis of a post-marketing surveillance

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Conflict of interest: Yes

[Objective] To investigate the safety and effectiveness of sarilumab in Japanese patients with rheumatoid arthritis (RA) who also had insufficient response to previous treatments, in the clinical practice setting. [Methods] This was an interim analysis of a post-marketing surveillance in patients with RA initiating sarilumab therapy between June 2018 and January 2021. The primary objective was safety with an observation period of 52 weeks. [Results] Case report forms were collected from 678 patients (mean age, 65.8 years); of these, 511 (75.4%) were female. Adverse drug reactions (ADRs) were reported in 170 (25.1%), of which 48 (7.1%) had serious ADRs. Most common ADRs by MedDRA Preferred Term were white blood cell count decreased (n=30, 4.4%), stomatitis (n=11, 1.6%) and neutrophil count decrease (n=11, 1.6%), and by System Organ Class was infections and infestations (n=32, 4.7%). ADRs associated with serious infections were observed in 17 (2.5%) patients. No ADR associated with malignancy was observed. Among patients who had active disease at baseline, 53.3% (n=248/465) achieved clinical remission at the end of sarilumab treatment. [Conclusions] The safety results were consistent with those from previous phase 3 studies, with no new safety signals identified.

## P17-3

### Long-term Tocilizumab Treatment in Patients with Rheumatoid Arthritis in Daily Clinical Practice

Yusuke Ono, Yuji Hirano

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Conflict of interest: None

[Objective] To describe the long-term trends in tocilizumab (TCZ) use in clinical practice. [Methods] This was a 5-year retrospective study (Toyohashi RA database) of 59 patients with rheumatoid arthritis (RA) who started TCZ therapy during the study period. Data were collected at 0, 1, 3, and 5 years for baseline characteristics, disease activity, treatment persistence, discontinuation, and concomitant use of methotrexate (MTX) and prednisolone (PSL). [Results] Patients included 17 males and 42 females. The mean age and RA duration were 58.6 years and 8.7 years, respectively. The mean simple disease activity index score was 27.9 at baseline and 5.2 at the end of the study. TCZ treatment persistence was 86.9%, 78.7%, and 68.9% at 1, 3, and 5 years, respectively. TCZ was discontinued due to adverse events (n = 11, 18.0%; infection was most common) and inadequate efficacy (9, 14.8%). Concomitant use declined from 63% to 15% for MTX and from 63% to 24% for PSL. [Conclusions] Long-term treatment with TCZ was acceptable. Treatment persistence was high, but careful monitoring for infection is required.

## P17-4

### Variation in Sarilumab Persistence Rate with Different Prior Medications

Eisuke Ogawa<sup>1,2</sup>, Ryosuke Hara<sup>1</sup>, Masahiro Yasumura<sup>1</sup>, Yuta Koiwai<sup>1</sup>, Yukiya Iimura<sup>1</sup>, Tatsuo Nagai<sup>1</sup>, Sumiaki Tanaka<sup>2</sup>, Sadahiro Suzuki<sup>1</sup>

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Kitasato University Medical Center

Conflict of interest: None

[Objective] The purpose of this study was to evaluate whether the drug used prior to the administration of SAR had any effect on the persistence rate. [Methods] We retrospectively analyzed 23 cases of Rheumatoid Arthritis treated with SAR at Shinonoi General Hospital or Kitasato University Medical Center. [Results] There are 8 males and 15 females, the mean age is 62.96 years, and the mean duration of disease is 9.2 years. 6 received SAR at 1st BIO, 17 received SAR at 2nd or subsequent BIO. 7 received IL-6 inhibitor before SAR, and 7 received TNF inhibitor before SAR. DAS28-CRP was 3.6±1.1 before SAR, and 2.3±1.0 at the most recent visit or at the end of SAR, indicating a significant decrease in disease activity (p=0.0001). There was no significant difference in the rate of continuation of SAR between the 1st BIO or the 2nd BIO, nor was there a significant difference in the rate of continuation depending on the previous drug. [Conclusions] SAR sufficiently suppressed disease activity both as the first and the second or subsequent biologic agents. The persistence rate was not affected by the previous agent in the second or subsequent administration.

## P17-5

### Efficacy and Safety of Sarilumab in b/tsDMARDs Naïve and b/tsDMARDs-IR Patients with Rheumatoid Arthritis

Masaomi Yamasaki

Shin-Yokohama Arthritis and Rheumatology Clinic

Conflict of interest: None

[Objective] We analyze efficacy and safety of Sarilumab real-world data. [Methods] Cases were recruited to SHin-yokohama Arthritis Register (SHARE) between 2015 and 2021 (n=3,869). 51 patients were diagnosed according to ACR/EULAR 2010 classification criteria and treated with Sarilumab over 26 weeks. [Results] 16 b/tsDMARDs naïve, 16 b/tsDMARDs-IR and 19 D2T RA patients were enrolled. Sarilumab withdrawal for inefficacy showed no difference between b/tsDMARDs naïve and b/tsDMARDs-IR patients (Kaplan-Meier, log-rank p=0.4659). There were no significant changes from baseline CDAI between MTX+/MTX- in all treatment phase (log-rank p=0.8809). There were no significant changes from baseline CDAI between pre-treatment group, TNFi, IL-6i and JAKi-naïve, in phase III patients (log-rank p=0.7930). In D2T RA patients, predictors to detect patients who achieved LDA and/or remission in 6 weeks were RDCI≤2.0 at baseline (p=0.0259). [Conclusions] Our data confirm the efficacy and safety profiles of sarilumab in RA. It also showed sarilumab was effective in all treatment phases including D2R RA.

## P17-6

### Study on the RA cases of switching from anti-IL-6 agents to JAK inhibitors

Yoshinobu Matsuura

Saiseikai Senri Hospital

Conflict of interest: None

[Objective] In the treatment of rheumatoid arthritis (RA), the suitability of biologic agents and JAK inhibitors (JAKi) remains unclear. In particular, anti-IL-6 receptor antibodies (αIL-6R-Ab) have some overlapping effects with JAKi terms of mechanism, so we studied the difference of treatment response to these agents. [Methods] We examined consecutive RA patients switched to JAKi due to inadequate response to αIL-6R-Ab, and those who continued αIL-6R-Ab. The diagnosis of RA was made based on classification criteria of ACR/EULAR 2012 or comprehensively by a rheumatologist. [Results] There were 9 patients switched from αIL-6R-Ab and 19 patients continued. Age was 63 years in the switch group and 71 years in the continuation group. There was no significant difference in anti-CCP antibody titer and RF level. However, the percentage of seronegative cases was 11% and 26%, respectively, which was predominantly higher in the continuation group (P = 0.016). The proportion of ANA positive cases was 88% and 60%, respectively (P = 0.03). [Conclusions] The switch from anti-IL-6 inhibitor to JAK inhibitor was more common in seropositive and ANA positive cases. Cytokine signaling other than IL-6

may be involved in these patients with immune abnormalities.

## P17-7

### Efficacy of tocilizumab in elderly onset of rheumatoid arthritis

Takako Hashimoto, Shusaku Fukaya, Jo Nishino, Daisuke Hirano, Megumi Kurumizawa, Konomi Akamatsu, Jun Fukui, Tatsuki Naganawa, Masashi Suzuki, Marika Sawada, Naoki Dosoden, Hidekata Yasuoka  
Rheumatology, Fujita Health University School of Medicine

Conflict of interest: None

[Object] We investigated the efficacy of subcutaneous injection of tocilizumab in patients older than 65 years of age with rheumatoid arthritis. [Methods] We investigated patients who were able to follow up for more than 52 weeks after introducing tocilizumab (TCZ) in 138 newly diagnosed rheumatoid arthritis (RA) patients who were seen between 2014 and 2019 in our department. Among them, RA patients < 65 years (YORA: young group) and RA patients ≥ 65 years (EORA: elderly group) were stratified and compared. [Results] In the YORA group vs. EORA group at baseline, the mean age was 55.8 years vs. 71.2 years. The disease duration was 70.2 months vs. 110.5 months. All patients in the EORA group had high disease activity (HDA), and both the average DAS28ESR and CDAI tended to be higher than those in the YORA group. All patients in the EORA group were naive, of which 3 had interstitial pneumonia, and received shortly doses of TCZ early in the onset. DAS28ESR was low disease activity (LDA) at 12 weeks in the YORA group, but 5 of 13 cases remained moderately active after 24 weeks. In the EORA group. [Discussion] In the EORA group, disease activity improved rapidly. Received shortly doses of TCZ was used effectively and safely even in cases with interstitial pneumonia.

## P17-8

### A retrospective review of anti-IL-6 therapy for patient with rheumatoid arthritis

Ichiro Yoshii

Musculoskeletal Medicine, Yoshii Hospital

Conflict of interest: None

[Objective] A retrospective review of cases of failure to administer IL-6 inhibitors in our hospital was undertaken in order to provide further lessons. [Methods] The number of patients treated with IL-6 inhibitors in our hospital was 48, and the patients were classified according to the outcome. [Results] Results were 3 withdrawals after clinical remission, 15 continuations, 15 non-responders, 12 adverse events (AEs), and 2 stop by the patient. The characteristics were as follows: (1) there were many difficult to treat RA cases in the non-responders and AEs (2) there were many cases with high ACPA level (3) there were many MTX non-administration (4) in AEs, administration was started in old age and high dose administration of glucocorticoid steroid (5) in non-responders, DAS28 improvement under 1.0 and MMP-3 improvement under 0.2 at 3 months (6) SJC at 3 months was significantly higher in the non-responders than in the continuations. [Conclusions] In the administration of the IL-6 inhibitor, attention to patient background and disease activity at the baseline and change of MMP-3 at 3 months were indicated to be connected with the decrease in the failure example.

## P17-9

### Efficacy and safety of sarilumab in patients with rheumatoid arthritis in the daily clinical practice

Shoichi Yoshinaga, Takahiko Kurasawa, Yusuke Okada, Akiko Shibata, Ryota Sakai, Tsuneo Kondo, Koichi Amano  
Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

Conflict of interest: None

[Objective] To clarify the clinical safety and efficacy of sarilumab (SAR) in patients with rheumatoid arthritis (RA) in daily clinical practice. [Methods] We retrospectively investigated the medical records of 32 RA patients who were treated with SAR at our hospital. [Results] At the start

of SAR, the average age was 66.3 years, SDAI was 22.4, HAQ-DI was 1.2. Glucocorticoid was used in 43.8% (average 7.3 mg/day) and MTX was used in 40.6% (average 7.8 mg/week). Fourteen patients received SAR as the first biologics (BIO), 14 had SAR switched from another BIO (TNF inhibitor: 8, IL-6 inhibitor: 4, abatacept: 2), and 4 received SAR switched from JAK inhibitor. SDAI remission was 23.3% at 1 month (M) (N=30), 34.8% at 3 M (N=23), and 34.8% at 6 M (N=19). Low disease activity or less achieved 80.0% of patients at 1 M, 91.3% at 3 M, and 100% at 6 M. There were 23 adverse events in 15 patients (observation period: 363 person-months); infection 6 (25%), gastrointestinal disorders 4 (12.5%), and blood disorders 4 patients (12.5%). [Conclusions] SAR was effective and well tolerable without increasing serious infections even in this cohort which included many elderly RA patients.

## P17-10

### Experience of 10 RA patients that changes treatment to sarilumab from JAK inhibitor, and continues more than one year

Keio Ayabe, Akira Inoue, Wataru Iriyama, Yurina Iwasaki  
Keiyu Orthopedic Hospital

Conflict of interest: None

[Objective] Consensus has not been provided for the next treatment for JAK inhibitor controlling a function of plural cytokine at the same time yet. JAK inhibitor and the IL-6 inhibitor are common at the point called the restraint of IL-6, but are different by the way of action. As I experienced 10 RA patients that changes treatment from JAK inhibitor to an IL-6 inhibitor, and continues more than one year, I report it. [Methods] Six four male women, average age: 79.5 years old, mean disease duration: 13.9 years, mean antiCCP antibody titer: 746.8 U/mL, mean DAS28ESR: 4.3, no combination example of MTX, PSL combination rate: 80%, mean KL-6: by 422 U/mL, RA-ILD evaluated by the chest CT reading shadow result: 70%, the JAK inhibitor before the dosage: 8TOF, 1BAR, 1PEFI. I evaluated the effectiveness and safety of one year about ten objects. [Results] Mean DAS28ESR of one year was improved with 2.3 after the dosage start. The PSL combination rate fell to 40%. The stroma-related pneumonia merger example did not have the one-year progress by the reading shadow result in the chest CT. [Conclusions] The changes from JAK inhibitor to SAR were effective, and the progression of RA-ILD was not seen in the case not to use MTX together, too.

## P17-11

### 5 patients of rheumatoid arthritis weighing >60kg who switched from intravenous Tocilizumab infusion to subcutaneous Sarilumab injection

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Conflict of interest: None

(Objective) We report 5 patients of rheumatoid arthritis (RA) weighing >60 kg who switched from intravenous Tocilizumab (TCZ) infusion to subcutaneous Sarilumab (SAR) subcutaneous injection (Case) The subject were case of intravenous TCZ weighing >60 kg, 2 males, 3 females, average age 54.3 years, average height 162.3 cm, average weight 70.3 kg, average BMI 26.4, average disease period 7 years. 4 patients were treated with first biological therapy. 1 patient treated with third biological therapy. TCZ average usage period was 7.4 months, TCZ average usage was 536 mg/4 week. RA disease activity before the SAR change was all remission. 200 mg of SAR subcutaneous injection was used in all cases. The average MTX usage is 12 mg/week and the average PSL usage is 3.75/mg/day. The average observation period after switching to SAR is 8.2 month. (Results) All patients maintained remission after switching to SAR. dMARDs were reduced in 4 patients. (Discussion) It has been reported that Japanese patients weighing >60 kg who switched from intravenous TCZ to subcutaneous TCZ tended to have worse disease activity. We switched from intravenous TCZ injection to subcutaneous injection of SAR. Remission is maintained in all cases after switching to SAR. Subcutaneous SAR injection may have the same effect as intravenous TCZ.



## P18-1

### Long-term efficacy and safety of abatacept for rheumatoid arthritis

Toshiki Kido<sup>1</sup>, Isao Matsushita<sup>2</sup>

<sup>1</sup>Toyama University Hospital, <sup>2</sup>Kanazawa Medical University

Conflict of interest: None

[Objective] The objective of this study is to analyze the long-term efficacy and safety of abatacept (ABT) for rheumatoid arthritis (RA) in clinical practice. [Methods] A retrospective analysis was performed on 35 patients who started ABT treatment for RA from September 2013 to February 2021. [Results] There were 9 males and 26 females, the average age was 74 years (45-91 years), and the average duration of illness was 15 years (0 months to 49 years and 6 months). The positive rate of RF or ACPA was 85.7%, the mean SDAI before the start of treatment was 20.1, high disease activity was 7, moderate disease activity was 14, low disease activity was 8, and remission was 6 cases. The mean values of SDAI from 3, 6 months, and 1 to 5 years after the start of ABT administration were 9.6, 8.6, 8.5, 8.3, 8.3, 8.5, and 8.7, respectively. At 5 years after administration, the achievement rate of SDAI remission was 37%, and the achievement rate of low disease activity was 71%. The ABT continuation rate at the 5th year was 68.9%, and the breakdown of discontinued cases was insufficient effect in 4, patient convenience in 2, adverse events in 4, and others in 1 case. [Conclusions] ABT is considered to be a treatment that has a good continuation rate and can maintain its effect on RA.

## P18-2

### Tocilizumab was effective for the case of right wrist monoarthritis with severe edema

Takuya Izumiyama<sup>1,2</sup>, Yoshiyuki Kuwahara<sup>1</sup>, Taichi Irie<sup>1</sup>, Ryuichi Kanabuchi<sup>2</sup>, Yu Mori<sup>2</sup>

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Conflict of interest: None

[Background] There are few reports of chronic monoarthritis with severe edema which does not meet the diagnostic criteria for rheumatoid arthritis of ACR / EULAR and for RS3PE syndrome. We report a case of unclassifiable monoarthritis with severe edema that responded well to tocilizumab (TCZ). [Case] A 65-year-old man. Pain and edema of the right wrist joint appeared from the beginning of May 20XX and gradually worsened. At the first visit, severe swelling and tenderness of the right wrist joint and marked edema from wrist joint to finger were observed, but there were no swollen and tender joints. Laboratory test showed CRP 16.5 mg/dl, but all the antibody tests were negative. No joint deformity and bone erosion were found in the radiographs but massive synovitis were found in the MR image. The treatment was started with prednisolone (PSL) 20 mg / day and symptom were improved initially, however when the dose of PSL was reduced, the symptom were worsened regardless of addition of MTX treatment. Therefore, subcutaneous injection of TCZ every 2 weeks was administrated, and after 12 weeks administration, the symptom was almost remitted and are still maintained. [Conclusion] TCZ was effective in the case of PSL and MTX refractory monoarthritis with severe edema.

## P18-3

### Dose interval prolongation and clinical characteristics of sarilumab administration

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Rheumatology, Takarazuka City Hospital

Conflict of interest: None

[Objective] It is specified that the dose of sarilumab (SAR) can be reduced depending on the patient's condition. In this study, we investigated the clinical characteristics of patients who were able to reduce the dose of SAR after a certain period of remission or maintenance of low disease activity. [Methods] 13 patients who were introduced to SAR at our hospital were included in the analysis. The backward comparative analysis was conducted for the group that continued at 200 mg and the group that was able to reduce the dose. [Results] 5 patients were able to reduce the duration of the dose with a mean of 9.4 months. There was no statistically

significant difference in patient background before induction in the two groups. The SDAI and DAS28ESR after 4, 8, 12, and 24 weeks of SAR administration were also not statistically significant. However, there was a statistically significant difference in the neutrophil count after 8 and 12 weeks of SAR administration. ROC analysis showed that the AUC value was 0.875 at 8 weeks, and the AUC value was 0.850 at 12 weeks. [Conclusions] In cases who have maintained low disease to remission after SAR administration, we suggest that the reduction and extension of the duration of SAR is possible, if neutrophils are low at the 8 and 12 week evaluations.

## P18-4

### Clinical features of patients with good response to IL-6 inhibitor for long-term; comparison to long-term TNF inhibitors

Ayae Tanaka<sup>1</sup>, Azusa Kikuchi<sup>1</sup>, Sara Komatsu<sup>1</sup>, Yusuke Sakae<sup>1</sup>, Yoriko Tasaka<sup>1</sup>, Yuhi Yoshida<sup>1</sup>, Yuta Takamura<sup>1</sup>, Tomoyuki Miyao<sup>1</sup>, Junya Nagasawa<sup>1</sup>, Ryutaro Yamazaki<sup>1</sup>, Satoko Arai<sup>1</sup>, Takayoshi Owada<sup>2</sup>, Reika Maezawa<sup>1</sup>, Masafumi Arima<sup>1</sup>, Kazuhiro Kurasawa<sup>1</sup>

<sup>1</sup>Dokkyo Medical University, <sup>2</sup>Dokkyo Medical University Saitama Medical Center

Conflict of interest: None

[Object] To determine the patient characteristics for long-term IL-6 inhibitor (IL-6i) users compared to long-term IL-6 TNF inhibitor (TNFi) users. [Methods] Subjects were consecutive 157 RA patients who used TNFi or IL-6i for more than 6 months. To determine characteristics of IL-6i long-term users, the following analyses were conducted; 1. comparison of the clinical features (background, disease activity, and treatment) between patients with TNFi as the longest-used biologics and those with IL-6i, 2) comparison of the clinical features between patients who treated with TNFi as the 1st biologics and continued it, and those with IL-6i, 3) comparison of the clinical features between patients who started TNFi and continued it and those who changed TNFi to IL-6i that was continued. [Results] 128 patients (81.5%) were long-term TNFi user and 29 patients (18.5%) were IL-6i user. Long-term IL-6 users had long disease duration, arthritis of the ankle and/or MTP joints, high CRP, ESR, and patient VAS, and high dose corticosteroids, compared to long-term TNFi users. [Conclusion] IL-6i is effective in patients with high levels of CRP, ESR, and patient VAS, long disease duration, ankle and MTP arthritis, and high doses of glucocorticoid.

## P18-5

### Study on retention rate of sarilumab in patients with rheumatoid arthritis in a real-world setting

Tomoyuki Mutoh<sup>1</sup>, Mikihiro Takahashi<sup>1</sup>, Taichi Nagai<sup>1</sup>, Soshi Okazaki<sup>2</sup>, Hiroko Sato<sup>2</sup>, Tsuyoshi Shirai<sup>2</sup>, Hiroshi Fujii<sup>2</sup>

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Conflict of interest: None

[Objective] To evaluate performance of sarilumab (SAR) in rheumatoid arthritis (RA). [Methods] We enrolled 29 RA patients receiving SAR till 2021 and analyzed data. [Results] During 15.0 (9.0-22.5) months, the age (female: 82.8%) was 63.0- (49.5-68.0) year, with RF (79.3%) and ACPA (82.8%). Disease duration was 7.8- (2.3-15.2) year. MTX and PSL were used in 41.4% with 6.0 (4.0-8.0) mg/w and in 51.7% with 6.0 (5.0-9.0) mg/d. Biologic or JAKi before SAR was used in 23 (79.3%) patients. Retention rates at 0.5-, 1-, and 2-year were 74.1%, 70.0%, 64.2%, respectively. The ≥65 aged, MTX use, and naïve groups showed higher retention rates in 0.5-, 1-, and 2-year than <65 aged, monotherapy, non-naïve groups (74.1% vs. 75.6%, 74.1% vs. 56.7%, 74.1% vs. 56.7%, p=0.56; 72.7% vs. 63.3%, 72.7% vs. 56.3%, 72.7% vs. 56.3%, p=0.25; 80.0% vs. 73.2%, 80.0% vs. 58.6%, 80.0% vs. 58.6%, p=0.36), respectively. No number of prior therapies affected persistence. Retention rate at 2-year was similar in prior TNFi or abatacept groups. Withdrawal reasons were 4 primary or 2 secondary failures, 2 injection site reactions, 1 cardiac failure, and 1 patient preference. [Conclusions] Patients with SAR had lower rate of MTX use and naïve. Modes of action of prior therapies may be important factors related to retention.

## P18-6

### Treatment of rheumatoid arthritis patients with inadequate response to abatacept

Junya Hasegawa<sup>1</sup>, Yuji Hirano<sup>2</sup>, Kyosuke Hattori<sup>1</sup>, Kenji Kishimoto<sup>1</sup>, Yoshifumi Ohashi<sup>1</sup>, Mochihito Suzuki<sup>1</sup>, Kenya Terabe<sup>1</sup>, Shuji Asai<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Shiro Imagama<sup>1</sup>

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Conflict of interest: None

**Objective** This study aims to investigate the effective biologic/molecular targeted DMARD (b/ts DMARD) options for patients with inadequate response to abatacept (ABT) in rheumatoid arthritis. **Methods** Data from Toyohashi RA Database (TRAD) were used. 15 patients who were started on ABT at the Department of Rheumatology, Toyohashi Municipal Hospital between 2011 and 2019 and switched to another b/ts DMARD due to inadequate response were used. The study items included overall patient background at the time of starting b/ts DMARD, treatment results (DAS28-CRP, SDAI, CRP, MMP-3, m-HAQ) for 1 year after changing, and reasons for discontinuation. **Results** There were 12 females and 3 males and mean age of 70.4 years. The b/ts DMARDs were TNF inhibitors in 6 patients, IL-6 inhibitors in 7 patients, and JAK inhibitors in 2 patients. The outcomes (0-3-6-12 months) were as follows: DAS28-CRP 4.7-3.9-3.1-3.2 (0-12 months  $P<0.05$ ), SDAI 26.5-20.6-15.0-15.9 (0-12 months  $P<0.05$ ). The reason for discontinuation was ineffectiveness in 1 case after changing to TNF inhibitor and adverse events in 4 cases after changing to IL-6 inhibitor. **Conclusion** Changing b/ts DMARD due to ineffectiveness of ABT significantly reduced disease activity; IL-6 inhibitors were associated with more adverse event.

## P18-7

### Drug survival rate of 6 biologics in patients with rheumatoid arthritis

Tsutomu Sakuraba<sup>1</sup>, Takeshi Kashiwagura<sup>2</sup>, Hiroki Ito<sup>3</sup>, Moto Kobayashi<sup>1</sup>, Toshiaki Aizawa<sup>4</sup>, Hidekazu Abe<sup>5</sup>, Norio Suzuki<sup>6</sup>, Keiji Kamo<sup>7</sup>, Hiroshi Aonuma<sup>8</sup>, Yusuke Sugimura<sup>9</sup>, Tetsuya Kawano<sup>10</sup>, Yoichi Shimada<sup>2,10</sup>, Naohisa Miyakoshi<sup>10</sup>

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Conflict of interest: Yes

**Background:** Intensive medication with biological disease-modifying antirheumatic drugs (bDMARDs) have caused a paradigm shift in the treatment of rheumatoid arthritis (RA). The Object of this study is to evaluate the retention rates of 7 bDMARDs. **Methods:** Patients with RA were enrolled from a Japanese observational registry: the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) established in 2010. The patients who have experienced treatment for bDMARDs (infliximab IFX: 109 patients, tocilizumab TCZ: 188, adalimumab ADA: 95, abatacept ABT: 107, golimumab GLM: 63, Certolizumab pegol CZP: 30) were assessed and compared the continuation rates of 10 years. **Result:** The retention rate of 6 bDMARDs were ABT 73%, GLM: 71%, TCZ: 66%, ADA: 51%, CZP: 40%, IFX: 21% respectively. **Discussion:** Because even ABT showed a lower risk of hospitalized infection rates and RA-associated interstitial lung disease compared to other bDMARDs in reports, and although ABT have selected as second-switched, or third-switched bDMARDs in our registry, ABT showed highest clinical response.

## P18-8

### Comparison between shortening subcutaneous tocilizumab interval and switching to the other b/tsDMARDs in patients with rheumatoid arthritis who are inadequate to subcutaneous tocilizumab every other week

Toshiyuki Watanabe, Shun Tanimura, Ikuma Nakagawa, Masato Isobe,

Megumi Matsuhashi, Masato Shimizu, Kazuhide Tanimura, Takao Koike  
Hokkaido Medical Center for Rheumatic Diseases

Conflict of interest: None

**[Objective]** To clarify the efficacy of shortening subcutaneous tocilizumab (TCZ-SC) interval in patients with rheumatoid arthritis (RA) who are inadequate to subcutaneous tocilizumab every other week (TCZ-SC q2w), compared with switching to the other b/tsDMARDs. **[Methods]** RA patients who were initiated with TCZ-SC q2w from March 2013 to June 2021 were reviewed. RA patients who discontinued TCZ-SC before the official approval of shortening TCZ-SC interval were excluded. In both shortening and switching groups, the treatment efficacy, persistence, and safety were analyzed. **[Results]** A total of 79 RA patients started with TCZ-SC q2w were recruited. During 16 months (median), 26 patients discontinued TCZ-SC q2w because of the lack of efficacy. In the 26 patients, 17 and 7 were treated with shortening TCZ-SC interval and switching to the other b/tsDMARDs, respectively. At 6 months, 12 patients in the shortening group archived DAS-ESR remission and 2 in the switching group. In the shortening group, 3 patients stopped TCZ-SC therapy during 7.0 months. In the switching group, 4 patients discontinued new b/tsDMARDs during 5.0 months. **[Conclusions]** Shortening TCZ-SC interval strategy can be more effective and tolerable to RA patients insufficient with TCZ-SC q2w than switching strategy.

## P18-9

### Drug Survival of Sarilumab in treatment of RA and Analysis of factors associated with Drug Survival

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St. Luke's International Hospital

Conflict of interest: Yes

**[Objective]** Sarilumab (SAR) is interleukin-6 receptor inhibitor used for treatment of Rheumatoid Arthritis. Here, we report our real world experience at our institution. **[Methods]** This is a retrospective chart review of patients treated with SAR at St. Luke's International Hospital. **[Results]** Total 40 patients were identified (men: women=1:7). The median disease duration was 7 years (3-11). Thirty-one patients (77.5%) were positive for Rheumatoid Factor and 32 (80%) for anti-CCP antibody. Nine (22.5%) had Interstitial Lung Disease. Fifteen used methotrexate concomitantly and 35 (87.5%) used a conventional synthetic DMARD. Nineteen used glucocorticoids. Thirty-six previously had used biologic or targeted synthetic DMARDs and 20 used two or more of them. The median duration of observation was 227.5 days (89.2-401.5). The median dose of prednisone who were on prednisone at baseline was 5 mg/day and 2.5 mg/day at 3 months ( $P=0.005$ ). We analyzed drug survival and factors associated with drug survival using Kaplan-Meier survival curve and log rank test. There was no decreased drug survival rate observed among those previously used two or more biologic/targeted synthetic DMARDs. **[Conclusions]** Sar seems to have relatively good continuation rate. Prednisone dose was decreased significantly at 3 months.

## P18-10

### The efficacy of Tocilizumab therapy in rheumatoid arthritis

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Department of Orthopaedic Surgery, Chuno Kosei Hospital

Conflict of interest: None

**[Objective]** To evaluate the efficacy in tocilizumab therapy with rheumatoid arthritis (RA) and tapering of methotrexate. **[Methods]** This study comprised 45 patients with rheumatoid arthritis intolerant to biologic DMARDs. Patients received tocilizumab therapy with methotrexate for 12 months. The outcomes were assessed with the disease activity during 12 months study period, using the 28-joint Disease Activity Score based on the erythrocyte sedimentation rate (DAS28 ESR) and Clinical Disease Activity Index (CDAI). **[Results]** DAS28ESR (from 3.3 to 1.5) and CDAI (from 4.7 to 0.4) decreased significantly from baseline to Week 52. DAS28ESR Remission achieved in 39 cases at Week 52. Tocilizumab monotherapy was also effective with RA patients of inadequate response to anti-TNF inhibitor therapy. The retention rate of tocilizumab at 52 weeks

was 90%. The average dose of methotrexate tapered from 5.6 mg to 3.2 mg. The average dose of glucocorticoid also tapered from 1.4 mg to 0.1 mg. [Conclusions] These results suggested that tocilizumab therapy is effective in patients with RA of an inadequate response to other biologic DMARDs.

## P18-11

### Investigation of the patients with administration of Sarilumab in Akita Orthopedic Group on Rheumatoid Arthritis registry

Moto Kobayashi<sup>1</sup>, Takeshi Kashiwagura<sup>2</sup>, Tsutomu Sakuraba<sup>1</sup>, Hiroshi Aonuma<sup>3</sup>, Yusuke Sugimura<sup>4</sup>, Masaaki Ogino<sup>5</sup>, Kazuhiro Shoji<sup>6</sup>, Tetsuya Kawano<sup>7</sup>, Naohisa Miyakoshi<sup>7</sup>

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Conflict of interest: None

[Purpose] Sarilumab was the second IL-6 inhibitor released in Japan in 2018, with reported effectiveness. We report cases of sarilumab administration identified from the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry. [Methods] Patient background, treatment details, and disease activity were evaluated in 16 AORA registrants in 2020 who received sarilumab therapy and had available data for analysis. [Results] Three men and 13 women (mean age, 68 y [range, 46-85 y]) were assessed; of these, 5 was naive and 11 were switched from other b/tsDMARDs. Methotrexate 5.0±2.8 mg/wk was used in 5 patients. The sarilumab therapy duration were 1 month to 2 years. At the time of the survey, 3 cases of dropout were due to temporary ineffectiveness, insufficient effect, and the onset of herpes zoster. The mean 28-joint disease activity score for erythrocyte sedimentation rate (DAS28-ESR) was 3.55±1.53 at treatment initiation and significantly improved to 2.50±0.87 at 1 mo. The average was 2.59±0.80 at 3 months and 2.57±0.73 at 6 months. [Conclusion] In clinical practice, sarilumab was often used as a switchover from other b/tsDMARDs, but maintained a significant improvement in DAS28ESR early in administration and subsequent levels of disease activity in remission.

## P18-12

### Administration of sarilumab to elderly patients with rheumatoid arthritis

Yuichi Takahashi  
Yu Family Clinic

Conflict of interest: Yes

[Objective] To investigate the efficacy and safety of sarilumab (SAR) for elderly patients with rheumatoid arthritis (RA). [Subjects and Methods] The subjects were 12 patients with RA and ≥70 years who did not respond well to conventional treatment provided at our outpatient clinic. SAR (200 mg) was administered every 2 weeks, and the outcomes were assessed using DAS28-ESR, The Patient Global VAS, and HAQ-DI. [Results] The DAS28-ESR at 0, 4, 8, and 24 weeks were 3.95, 3.31, 2.88, and 2.56, respectively. Regarding the change in disease activity, remission or low disease activity was observed in 30% of patients at 4 weeks, approximately 50% at 12 weeks, and approximately 80% at 24 weeks. Regarding the patient-reported outcome measures, improvements were observed in terms of both PtVAS and HAQ-DI: 35% and 13%, respectively, at 8 weeks; 68% and 63%, respectively at 24 weeks. Although three patients discontinued SAR due to the lack of improvement in the subjective symptoms, no patient discontinued the drug due to adverse events. [Conclusions] SAR was effective for elderly patients with long-term RA. Improvements were also observed in PtVAS and HAQ-DI following treatment. There were no serious infections or other adverse events, suggesting that SAR is safe for elderly patients with RA.

## P19-1

### Outcomes of rheumatoid arthritis patients who received biologics and JAK inhibitors

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<sup>2</sup>Advanced Diagnostic System Research Laboratory, Fujita Health University Graduate School of Health Sciences

Conflict of interest: None

[Objective] To investigate the outcome of rheumatoid arthritis (RA) cases treated with biologics (BIO) or JAK inhibitor (JAKi). [Methods] We investigated the outcomes of naive cases in which BIO and JAKi were administered from 2003 to 2016. [Results] There were 506 cases with administration of BIO and JAKi. The average age at the start of treatment was 58.1 years. There were 107 males and 399 females (78.9%). The drugs used were infliximab (IFX): 171 cases, etanercept (ETA): 93 cases, tocilizumab (TCZ): 82 cases, adalimumab (ADA): 80 cases, abatacept (ABT): 56 cases, golimumab (GLM): 20 cases, Certolizumab pegol (CPZ): 2 cases, JAKi: 2 cases. 384 patients were transferred to another hospital during treatment. 221 cases (43.7%) were able to confirm the outcome this time. 134 patients were on medication with an average of 9.2 years. 21 cases of discontinuation of remission (1 to 8 years, average of 3.1 years), 54 cases of discontinuation due to adverse events (1 to 15 years, average of 2.5 years), 12 cases of death (malignant tumor, infectious disease, traffic accident, etc.). [Conclusions] Although the usefulness of BIO and JAKi could be confirmed from our own cases, adverse events and ineffective cases appeared at a certain rate, which is a future issue.

## P19-2

### The switch of using disease modifying anti-rheumatic drugs (DMARDs) and disease activities in patients with rheumatoid arthritis using biologic DMARDs in 2010 - TOMORROW study -

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Conflict of interest: None

[Objective] In 2010, using biologic disease modifying anti-rheumatic drugs (BIO) for RA was not common. In this study, we reviewed the changes of patients with treatment by BIO in 2010. [Methods] We analyzed data from the TOMORROW study (UMIN000003876), which is a 10-years prospective cohort for age and sex matched RA (n=208) and volunteers. We evaluated BIO change (switch) and the factors that influence the achievement of low disease activity (LDA) in the DAS28-ESR at the last observation. [Results] There were 111 patients with BIO at 2010 (BL) (infliximab (IFX) 59, adalimumab (ADA) 2, etanercept (ETN) 40 and tocilizumab (TCZ) 10). 33 patients (IFX 13, ADA 1, ETN 15, TCZ 4) remained on their BL BIO during the study period. There were several switches in 52 patients (32 IFX, 0 ADA, 17 ETN, 3 TCZ) and the average number of switches was 1.58. In multivariate analysis, not BIO switches but using dose of prednisolone was significant risk factor for unachieving DAS28-ESR LDA. [Conclusions] About half patients with treatment of BIO experienced BIO switching, but there was no significant association with LDA achievement. In the treatment of patients with RA, switching drugs according to comorbidities and disease activities are considered important for maintaining disease activity.

## P19-3

### An optimal choice of biologics switched from JAK inhibitors for patients with rheumatoid arthritis -single-center retrospective analysis-

Takahiro Seno, Makoto Wada, Masataka Kohno, Kazuki Fujioka, Risa Sagawa, Yu Isoda, Keitaro Saito, Satoshi Omura, Hironori Inoue, Takuya



Inoue, Naoka Kamio, Shunya Kaneshita, Wataru Fujii, Yutaka Kawahito  
Inflammation and Immunology, Graduate School of Medical Science,  
Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Background] Treatment of rheumatoid arthritis (RA) is undergoing rapid development. Five JAK inhibitors (JAKi), in addition to seven biologics, are available in Japan. The opportunity to switch from JAKi to biologics is increasing, but the optimal drug switch regimens have not been established. [Methods] We extracted patients with RA treated with biologics or JAKi in our department from October 2019 to September 2021. And we picked up the patients who switched from JAKi to biologics. Treatment history with biologics or JAK inhibitors, concomitant medications, and disease activities were collected from medical records. [Results] We identified 22 cases of RA who switched from JAKi to biologics. The JAKi used before the switch were tofacitinib in 10, baricitinib in 10, upadacitinib in 1, and peficitinib in 1 case. The biologics after the switch were abatacept in 3, IL-6 inhibitors in 8 (tocilizumab in 6 and sarilumab in 2), and TNF inhibitors in 11 (etanercept in 4, adalimumab in 1, golimumab in 3, and certolizumab pegol in 3 cases). The three patients who switched to TNF inhibitors were eventually switched to IL-6 inhibitors. [Conclusion] Biologics switched from JAKi were mainly TNF inhibitors or IL-6 inhibitors. The continuation rate of IL-6 inhibitors was relatively high.

### P19-5

#### A Case of Rheumatoid Arthritis in which Repair of Joint impairment Was Obtained by Biologics

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Conflict of interest: None

[Objective] Biologics have come to be used in drug therapy for rheumatoid arthritis (RA), and joint space narrowing and bone erosion repair have been occasionally seen in small joints such as fingers and toes. However, repair of impaired joints in large load joints is rare. [Case] A 48-year-old man was referred for the first time in 2009. Anti-CCP antibody 100 IU/ml, RF 40 IU/ml. Mainly left shoulder joint pain, left hip joint pain, and right ankle joint pain. After various tests, methotrexate (MTX) was started at 6 mg/week, but no improvement in symptoms was observed, so infliximab (IFX) was added at 3 mg/kg. At the first visit, XP showed narrowing of the joint space in the left hip joint. Since the left hip pain did not improve even after the introduction of IFX, the dose was increased and the period was shortened. From 2 years later, the dose was 6 mg / kg at 4-week intervals. The MTX was 10 mg / week. After that, CRP became negative and the left hip pain disappeared. Furthermore, on the XP image, the narrowing of the joint space in the left hip joint was repaired. [Conclusions] Improvement of clinical symptoms and restoration of findings on XP images were confirmed. In some cases, IFX administration could delay the performance of artificial joint replacement.

### P19-6

#### The treatment of rheumatoid arthritis (RA) after nontuberculous mycobacteria infection (NTM)

Hirokazu Takaoka

Section of Internal Medicine and Rheumatology, Kumamoto Shinto General Hospital, Kumamoto, Japan

Conflict of interest: None

[Object] The purpose of this study is to examine the optimum treatment method considering the etiology of RA after NTM infection. [Case] No.1 A 65-year-old man diagnosed as RA at 54 ages, had undergone organizing pneumonia. During RA treatment with MTX and ETN, NTM pneumonia was developed, and MAC was detected from sputum culture. Although treated with CAM, RFP, and EB, but RA got worse. Switching from ETN to ABT and adding iguratimod to MTX improved RA, but after a while it worsened, so it changed to adalimumab. However, it was discontinued due to pneumonia. After pneumonia improved ABT was resumed but changed to TCZ due to insufficient control of RA. No.2 A 72-year-old

woman under the treatment of diabetes developed right digital flexor tenosynovitis triggered by a NTM infection. Mycobacterium marinum was detected from the wound culture, then CAM, RFP, and EB was started, but the left hand was swollen 5 months later and it was diagnosed as RA. The addition of MTX and TCZ to prednisolone improved RA activity. [Discussion] NTM are intracellular parasitic pathogens, and in cases of a first NTM infection, innate and adaptive immunity work together to protect against the infection. T cells and NK cell-dependent macrophages are activated, which might be made difficult to control of RA.

### P19-7

#### Patients with biological agency whose disease activity flared up due to interrupting outpatients care under the in-hospital cluster of COVID19

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Rheumatology, Amagasaki Health Co-operative Hospital

Conflict of interest: None

[Objective] A large in-hospital cluster of COVID19 occurred and the effect extended to outpatient care. Some RA patients got worse due to stopping treatment with biological agency. [Methods] Outpatient clinic was closed for 2 months by in-hospital cluster and it was handled by telephone examination. Most patients continued the treatment with biological agency but some of them interrupted the treatment so we evaluate them. [Results] 325 patients were treated with telephone examination and 56 patients including 29 patients who received biological infusion visited the hospital. 62 patients treated with biologics subcutaneous injection and JAK inhibitors continued by telephone examination. 29 patients with biologics infusion expanded the administration period and 4 patients became worse. Case 1: 73 years male using Golimumab for 4.4 years. Case 2: 76 years male using Tocilizumab for 5.4 years. Case 3: 80 years male using Tocilizumab for 5.6 years. Case 4: 90 years male using Tocilizumab for 6.3 years. The background were disease activity before discontinuation couldn't be suppressed sufficiently and using IL-6 receptor antibody. [Conclusions] We should be careful those conditions and tried to continue using biological agency under the in-hospital cluster.

### P19-8

#### Early introduction of biologics for elderly-onset rheumatoid arthritis (EORA) with severe functional disability

Shunsuke Uchiyama<sup>1</sup>, Mitsuhiro Takeno<sup>1,2</sup>, Nobuhito Sasaki<sup>1</sup>, Takahisa Gono<sup>1</sup>, Masataka Kuwana<sup>1</sup>

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Conflict of interest: None

[Objective] To evaluate clinical outcomes of EORA patients with severe functional disability undergoing early introduction of bDMARDs. [Methods] We selected 25 patients with EORA from our RA cohort, based on introduction of bDMARDs within one month after RA diagnosis. Serial CDAI, treatment details, and adverse events were retrospectively collected. Logistic regression analysis was conducted to determine baseline clinical features and initial treatment associated with CDAI remission at one year. [Results] The median age at RA onset was 78 years. The baseline CDAI and HAQ-DI were 30 and 2.0, respectively. The initial treatment included MTX (32%), other csDMARDs (56%), oral glucocorticoids (16%), and intramuscular glucocorticoids (44%). The bDMARDs, including TNF inhibitors (28%), IL-6 inhibitors (40%), abatacept (32%), were started at a median of 8.1 days after RA diagnosis. CDAI remission or low disease activity was achieved at one year in 67% and 95%. Negative RF was identified as a predictor of CDAI remission at one year ( $p=0.028$ ). No serious infection was observed. [Conclusions] Early introduction of bDMARDs is a preferable treatment option for EORA patients with severe functional disability.

### P19-9

#### A Case of Rheumatoid Arthritis with a History of Pulmonary Aspergillosis

Masao Sato<sup>1</sup>, Noriko Iwata<sup>2</sup>

Conflict of interest: None

[Objective] When introducing biologics (BIO) for rheumatoid arthritis (RA), the presence or absence of respiratory infections must be considered. [Case] A 61-year-old woman. In her medical history, she was pointed out with a cavity in her left chest at the age of 6 and was diagnosed with pulmonary aspergillosis at the age of 28. She developed her right wrist joint pain in 2007 and was diagnosed with RA. She was prescribed methotrexate (MTX), and she was first referred in 2009 for the purpose of introducing BIO. After consulting the Department of Respiratory Medicine, she was pointed out that she should not be introduced to BIO or treated with MTX. At the first visit, Aspergillus antigen, Candida antigen,  $\beta$ -D glucan, and KL-6 were all negative. After that, the drug therapy was a combination of 4 drugs, SASP 1000 mg, bucillamine (BUC) 300 mg, mizoribine (MZR) 150 mg, and tacrolimus (TAC) 3 mg. The disease activity did not reach remission. When abatacept (ABT) was introduced by subcutaneous injection in 2014, the disease activity was well controlled. There was no change in chest imaging findings, and no recurrence of pulmonary aspergillosis. [Conclusions] When introducing BIO for cases with a history of pulmonary infections such as pulmonary aspergillosis, it is very troublesome.

### P19-10

#### Complete remission in ultrasound predicts successful discontinuation of biological DMARDs in patients with rheumatoid arthritis

Syuichi Koarada<sup>1,2</sup>, Tetsuhiro Maesaki<sup>2</sup>, Sachiko Soejima<sup>2</sup>, Akihito Maruyama<sup>3</sup>, Mitsunori Komine<sup>4</sup>, Yoshifumi Tada<sup>3</sup>

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Conflict of interest: None

[Objective] To analyze whether complete remission in ultrasound is useful in predicting the successful discontinuation of bDMARDs in patients with rheumatoid arthritis. [Methods] Of a total of the 326 patients with RA who have undergone monthly ultrasound study (US) since the first visit, 46 patients discontinued bDMARDs after remission. Sixteen patients who have achieved PD=0 in US for 6 consecutive months or more are defined as complete remission of US, and 15 patients with PD=1-3 even once as incomplete remission of US. The clinical CDAI remission group without US (n = 15) was control. Survival curve of CDAI remission was examined in these three groups after discontinuation of bDMARDs. [Results] The group of US complete remission had a statistically significantly higher maintenance rate of remission after discontinuation of bDMARDs than the US incomplete remission group and the clinical remission group. Although it is difficult to predict the maintenance of remission after discontinuation of bDMARDs based on clinical examinations alone, US complete remission was useful in predicting the maintenance of remission in patients with RA. [Conclusions] State of US complete remission suggests a deep remission of RA and is useful in predicting maintenance of bDMARD-discontinued remission.

### P19-11

#### Evaluation of SARS-CoV-2 antibody titer after BNT162b mRNA vaccination in patients with rheumatoid arthritis

Kazutoshi Yukawa, Shuntaro Miyoshi, Jiro Yamana, Mitsuhiro Iwahashi, Rie Sasaki, Seizo Yamana  
Division of Arthritis and Collagen Disease, Higashi-Hiroshima Memorial Hospital

Conflict of interest: None

**Objective:** This study aims to investigate the SARS-CoV-2 antibody titer after vaccination. **Methods:** We enrolled 127 patients with RA. SARS-CoV-2 antibody titers were measured at least 2 weeks after two doses of the BNT162b mRNA vaccine using ADVIA Centaur SARS-CoV-2 IgG. **Results:** Out of 127 patients, 26, 21, 29, and 51 were assigned to the TNF- $\alpha$  inhibitor, IL-6 inhibitor, T-cell stimulating modulator, and methotrexate groups, respectively. Patients in the TNF- $\alpha$  inhibitor and metho-

trexate groups received higher doses of methotrexate (median [interquartile range (IQR)]; 8 [6.5-10.0] mg/week, 0 [0-0] mg/week, 0 [0-4] mg/week, and 8 [6-8] mg/week, in the TNF- $\alpha$  inhibitor, IL-6 inhibitor, T-cell stimulating modulator, and methotrexate groups, respectively,  $p < 0.01$ ). The SARS-CoV-2 IgG levels were significantly lower in the T-cell stimulating modulator group (5.5 [2.1-13.4] U/mL, 10.2 [2.7-27.3] U/mL, 1.2 [0.5-4.9] U/mL, and 8.2 [2.1-22.9] U/mL, in the TNF- $\alpha$  inhibitor, IL-6 inhibitor, T-cell stimulating modulator, and methotrexate groups, respectively,  $p < 0.01$ ). **Conclusions:** SARS-CoV-2 IgG titer may be low in patients with RA receiving T-cell stimulating modulator.

### P20-1

#### Treatment pattern of Janus kinase (JAK) inhibitor in rheumatoid arthritis (RA): Data from a Japan large-scale claims database

Yuko Kaneko<sup>1</sup>, Masaya Sakurai<sup>2</sup>, Robert Snijder<sup>2</sup>, Satoshi Kokubo<sup>2</sup>, Daisuke Kato<sup>2</sup>

<sup>1</sup>Keio University, <sup>2</sup>Astellas Pharma Inc.

Conflict of interest: Yes

[Objective] To retrospectively investigate the changes in treatment patterns of major DMARDs, focusing on new drug JAK inhibitor in real-world practice in Japan. [Methods] Subjects were RA patients registered in claims database provided by over 100 health insurance associations, aged 16 years or older and newly prescribed DMARDs between 2016 and 2019. Investigated DMARDs were JAK inhibitor, MTX, csDMARDs, TNF- $\alpha$  inhibitor, CTLA4-Ig, and IL-6 receptor inhibitor. [Results] Data of 10399 patients were analyzed. Major previous drugs prescribed for patients who initiated JAK inhibitors were MTX (30.1%) and biologics (59.0%). Proportions of patients previously treated with MTX before initiation of JAK inhibitor were 21.1% in 2017, 25.3% in 2018, and 33.7% in 2019, while proportions of patients previously treated with biologics were 68.4%, 63.2%, and 54.6%, respectively. MTX was previously prescribed for 62.8% of patients who initiated TNF- $\alpha$  inhibitor. Proportions of patients who initiated JAK inhibitor as monotherapy was 69.1%, and combination therapy with MTX was 15.7% increasing during the study period. [Conclusions] Proportions of patients previously treated with MTX and patients with MTX combination therapy were increased among patients who initiated JAK inhibitors during the study period.

### P20-2

#### Safety of BIO/JAK administration in RA patients over 75 years old

Takaya Sugiura, Tsuyoshi Watanabe  
Orthopaedic, National Center for Geriatrics and Gerontology

Conflict of interest: None

[Objective] To determine whether bDMARDs and tsDMARDs can be used safely in elderly RA patients. [Methods] 35 BIO/JAK patients aged 75 years or older who used them at our hospital from January to September 2021 were included in the study. The safety of the drug was examined in the late elderly based on pulmonary complications, hepatic impairment, renal dysfunction, MTX use rate, and PSL use rate. [Results] The mean age at the start of treatment was  $81.1 \pm 3.79$  years, and BMI was  $21.01 \pm 3.57$ . 13 patients had MTX (4-10 mg, 37.1%) and 18 patients had PSL (3-20 mg, 51.4%). The breakdown of drugs was TNF $\alpha$  inhibitors in 12, non-TNF $\alpha$  inhibitors in 8, and JAK inhibitors in 15. The continuation rates of TNF $\alpha$  inhibitors and non-TNF $\alpha$  inhibitors were equal at 75% and 87% for JAK inhibitors. A total of 26 patients were able to continue. Discontinuations occurred in 9 patients. Excluding the two cases of hospital transfer or self-interruption, there were three cases of interstitial pneumonia, two cases of pancreatic cancer, one case each of infectious lung disease and cerebral hemorrhage. [Conclusions] The continuation rate of DMARDs in the late elderly was equal for TNF-alpha and non-TNF-alpha inhibitors, 75%, and for JAK inhibitors, 87%.

### P20-3

#### Treatment persistence of Janus kinase (JAK) inhibitor in rheumatoid arthritis (RA): Data from a Japan large-scale claims database

Yuko Kaneko<sup>1</sup>, Masaya Sakurai<sup>2</sup>, Robert Snijder<sup>2</sup>, Satoshi Kokubo<sup>2</sup>, Daisuke Kato<sup>2</sup>

Conflict of interest: Yes

[Objective] To retrospectively investigate the treatment persistence for major DMARDs, mainly focusing on new drug JAK inhibitor, and characteristics of patients who initiated DMARDs in real-world practice in Japan. [Methods] Study subjects were RA patients who were registered in claims database provided by over 100 health insurance associations, aged 16 years or older, and newly prescribed DMARDs between 2016 and 2019. Investigated DMARDs were JAK inhibitor, MTX, csDMARDs, TNF- $\alpha$  inhibitor, CTLA4-Ig, and IL-6 receptor inhibitor. Cumulative treatment persistence rate was estimated using Kaplan-Meier curve. [Results] Data of 10399 patients were analyzed. Mean age was highest in patients who initiated CTLA4-Ig (54.1 years), lowest in TNF- $\alpha$  inhibitor (48.1 years), 52.1 years in JAK inhibitor. Female proportion was highest in CTLA4-Ig (82.6%), lowest in MTX (68.5%), and 75.5% in JAK inhibitors. No notable change in patient characteristic during study period was observed in JAK inhibitor. Treatment persistence rate of JAK inhibitor was higher compared with biologics and csDMARDs, similar with MTX, and tended to be higher in older patients with no notable difference by gender. [Conclusions] Treatment persistence rate was suggested to be higher in JAK inhibitor compared with biologics.

## P20-4

### The effectiveness and potential as countermeasure for polypharmacy of JAK inhibitors

Takeo Sato, Kojiro Sato

Division of Rheumatology and Clinical Immunology, Jichi Medical University Hospital

Conflict of interest: None

[Objective] Medications for rheumatoid arthritis (RA) tends to become polypharmacy. JAK inhibitors is effective for RA and this study aims to investigate the effect and impact on medicines associated with RA treatment of JAK inhibitors. [Methods] The disease activity of RA and medicines for RA such as methotrexate (MTX), steroid, NSAID, anti-ulcer medicine, and osteoporosis medicine were retrospectively reviewed in patients treated with upadacitinib or filgotinib. [Results] JAK inhibitors were started in 11 patients (49 to 78 years old, 8 men and 3 women) due to insufficient response to antirheumatic medicine such as salazosulfapyridine, MTX and biologics. After the start of JAK inhibitors, the median of DAS28CRP decreased from 4.21 to 1.39, and the remission rate was 73%. The median of MTX dose decreased from 8 to 0 mg/week, prednisolone dose from 8 to 2 mg/day, and the number of medicines except JAK inhibitors from 3 to 0. Five patients maintained remission with only JAK inhibitors. The adverse events included sudden deafness, liver dysfunction and cough due to MTX. [Conclusions] After the start of JAK inhibitors, 73% of the patients achieved remission, and the dose and number of medicines were reduced. JAK inhibitors may have a potential as a countermeasure for polypharmacy.

## P20-5

### Retention rate and efficacy of JAK inhibitor in elderly patients with rheumatoid arthritis

Takahito Kojima<sup>1</sup>, Tadashi Okano<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Kentaro Inui<sup>5</sup>, Masahiro Tada<sup>4</sup>, Kenji Mamoto<sup>1</sup>, Yutaro Yamada<sup>1</sup>, Kazuki Orita<sup>6</sup>, Koji Mandai<sup>5</sup>, Shohei Anno<sup>1</sup>, Takahiro Iida<sup>7,8</sup>, Hiroaki Nakamura<sup>1</sup>

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Conflict of interest: None

[Objective] The prevalence of elderly rheumatoid arthritis (RA) patient is increasing. We investigated the retention rate and efficacy of JAK

inhibitor (JAK) in elderly RA patients. [Methods] 211 RA patients who started JAK was included. The patients were divided into 65 years or older (ERA group) and under 65 years (YRA group) at the start of JAK. Retention rate and the changes of disease activity were investigated up to 24 weeks. [Results] There were 123 cases in ERA group and 88 cases in YRA group. The average age at the start of JAK was 74.6 years and 52.5 years. Renal function was declined and MTX use was lower (46.3/76.1%) in ERA group. The retention rate of the ERA group up to 24 weeks was 78.0%, while that of the YRA group was 75.0%. In cases who continued up to 24 weeks, the change in DAS28-CRP was 0 w: (4.2, 4.2), 4 w: (3.2, 3.1), 12 w: (2.9, 2.9), 24 w: (2.8, 2.9) and the change in SDAI was 0 w: (21.5, 22.1), 4 w: (13.2, 12.2), 12 w: (10.6, 10.2), 24 w: (10.4, 11.0). [Conclusions] There were no difference in the retention rate and efficacy of JAK inhibitors between ERA and YRA group. Although it is necessary to pay attention to adverse events such as infection, JAK can be an effective option for elderly RA patients.

## P20-6

### Continuation status of RA patients who have changed from biopharmaceuticals to JAK inhibitors for more than 1 year

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Conflict of interest: None

[Purpose] We investigated the continuation status of RA patients who are using biopharmacy and wish to switch to JAK inhibitors, which are oral drugs, one year after administration. [Subjects and methods] The subjects were 40 RA patients, the average age was 66.8 years, and the breakdown of JAK inhibitors was tofacitinib (TOF) 24 patients, baricitinib (BAR) 12 patients, and upadacitinib (UPA). There were 4 cases. The bioforms used before the change were TNF inhibitors in 30 cases, tocilizumab in 4, and abatacept in 5. The continuation status and therapeutic effect were examined for each drug used. [Results] Of the 24 patients who used TOF, 13 patients (54.2%) continued to use TOF, and 8 patients (etanercept 4, adalimumab 2, golimumab 2) requested to switch to the biopharmaceutical before the change. In 12 patients who used BAR, 7 patients (58.3%) continued to use it, and 3 patients (etanercept 2 and adalimumab 1) switched to the biopharmaceutical before the change. The continuation of UPA use in 4 cases was continued in 3 cases (75%), and 1 case was changed to another JAK inhibitor due to an adverse event. [Conclusion] In RA patients who are using biopharmaceuticals, switching to JAK inhibitors may be a useful option in patients with diminished efficacy or desire for oral drugs.

## P20-7

### Case series of rheumatoid arthritis with non-tuberculosis mycobacterium successfully treated with Janus kinase inhibitors

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Conflict of interest: None

Rheumatoid arthritis (RA) patients with nontuberculous mycobacterial (NTM) often have difficulty in RA treatment. We report four cases of active RA in which successful treatment with Janus kinase inhibitor (JAK-i) without worsening of NTM during antimicrobial therapy. The patients were all female in their 60s to 80s with a RA history for years and their BMI below 20. Case 1: NTM flared up after switch from abatacept to TNF inhibitor, small nodular lesion and sputum MAC-PCR positive, NTM subsided after treatment with ethambutol (EB), rifampicin (RFP), and clarithromycin (CAM). Baricitinib was begun, high disease activity went to remission, Case 2: NTM developed during treatment with salazosulfapyridine, lung lesions were fibrocavity, MAC-PCR positive, treated with Gracevit (STFX), RFP, and CAM. However, she became active with knee joint, treated with baricitinib for remission. Case 3: She had been treated with EB RFP CAM at first visit. Her NTM was small nodular type and stable. Baricitinib was begun, her high disease activity to remission. Case 4: NTM (MAC) onset during MTX treatment, on EB, RFP, CAM as NTM



therapy, refractory to ETN treatment, switch to JAK-i, reached remission but no NTM worsening. Clinical Significance): JAK-i may be safe treatment for RA patients with NTM.

## P20-8

### Clinical results of 45 patients with rheumatoid arthritis who switched from biologic DMARDs to JAK inhibitors

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Conflict of interest: None

[Purpose] JAK inhibitors have some effect as a treatment for rheumatoid arthritis (RA). However, there are few reports on the conversion of Biologic DMARDs (Bio) to JAK inhibitors (JAK). We investigated the clinical results of patients who switched their treatment from Bio to JAK. [Methods] From 2013 to 2020, 45 RA patients who switched from Bio to JAK were enrolled in this study. The Twenty patients who switched from TNF inhibitors to JAK were defined as the TNF group, and the 25 patients who switched from non-TNF inhibitors to JAK were defined as the non-TNF group. The time of switching, RA duration, eGFR, the treatment rate of MTX and PSL, the dose of MTX and PSL, the difference of DAS28-CRP ( $\Delta$ DAS28-CRP) were investigated retrospectively. [Results] The average age at the time of change was 64.4 years in the TNF group and 68.4 years in the non-TNF group, and the duration of RA was 13.1/18.9 years (TNF/non-TNF), eGFR 82.0/74.1 (mL/min), and MTX dose 7.6/7.7 (mg/Week), MTX dose rate was 50/48%, PSL dose was 3.6/4.6 (mg), and PSL dose rate was 25/36%.  $\Delta$ DAS28-CRP was 2.8/2.7, each indicating significant improvement, but there was no significant difference between the two groups. [Conclusion] Switching to JAK seems to be effective for both TNF and non-TNF in RA patients receiving Bio.

## P20-9

### Examination of combination therapy of JAK inhibitors and DMARDs

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Conflict of interest: None

[Objective] Examining the effectiveness of the combined use of JAK inhibitors and DMARDs. [Methods] RA patients using our JAK inhibitor were divided into the following 4 groups. JAK inhibitor alone group (n = 5), JAK inhibitor / MTX combination group (n = 20), JAK inhibitor / DMARDs group (n = 8), JAK inhibitor / MTX / DMARDs combination group (n = 9). A comparative study was conducted on the efficacy and continuation rate at 24 weeks. Efficacy assessment used DAS-28CRP [Results] The use of DMARDs was in SASP10, IUG6, Tac1 and BUC2 cases. At 24 weeks, 4 patients in the JAK inhibitor alone group, 19 patients in the MTX combination group, 6 patients in the DMARDs combination group, and 8 patients in the MTX / DMARDs group continued to use JAK inhibitors. Of these, 1, 15, 6, and 4 achieved LDA. Comparing the JAK inhibitor alone group and the MTX combination group, the disease activity at 24 weeks was superior in the MTX combination group (P = 0.03). No superiority was observed in each of the other group comparisons. [Conclusions] JAK inhibitors may increase the therapeutic effect and continuation rate when used in combination with MTX. Cases need to be accumulated for DMARDs.

## P20-10

### A case report of patients with rheumatoid arthritis, maintaining remission after switching from JAK inhibitor to bDMARD

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Conflict of interest: None

[Introduction] JAK inhibitors are useful in a variety of cases, including patients who inadequately responded to treatment with bDMARDs. Although there has been no evidence for switching JAK inhibitor to bD-

MARDs. [Case report] We report a case of a 82-year-old female patient experienced the case of RA who had suffered from RA from 25 years ago. She was inadequate response to treatment with etanercept, abatacept, certolizumab, tocilizumab, and sarilumab. She experienced exacerbation of interstitial pneumonia after treatment with methotrexate. When admitted to our hospital, the examination showed tender joint count 3, swelling joint count 6, VAS 60 mm, ESR 10 mm/hr RF 381 IU/ml, CCP 500 U/ml. We started treatment with baricitinib, then got good response to achieved remission with C-DAI < 3.2. After 20 weeks therapy with baricitinib, revealed she had a lung carcinoma, then we stopped therapy with baricitinib, switched therapy with sarilumab. Thereafter, her remission state was maintained. [Discussion] This case suggested that switching treatment with JAK inhibitors to bDMARDs may be useful.

## P20-11

### Neutrophil count reduction 1 month after initiating JAK inhibitors can not predict clinical remission within 6 months in rheumatoid arthritis patients unlike the IL-6 receptor inhibitors

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Conflict of interest: None

[Background/Object] Nakajima T, et al [doi: 10.1007/s00296-021-04944-x] reported that reduction of neutrophil count initiating tocilizumab predicts clinical remission (CR). JAK inhibitors (JAKi) modulate IL-6 signalling. This study aimed to examine whether neutrophil decrease initiating JAKi predicts CR within 24 weeks. [Method] We reviewed medical records of RA patients initiating JAKi between July 2013 and June 2021 in our hospital. The Simplified Disease Activity Index (SDAI) was evaluated at baseline and 1, 3, and 6 months. CR was defined when SDAI decreased  $\leq 3.3$ . The ratio of neutrophil counts 1 month after initiating JAKi to those at baseline (neutrophil ratio) was also calculated. Neutrophil-lymphocyte ratio [NLR], systemic immune-inflammation index [SII], which are associated with disease activity, were also calculated. Among 142 JAKi-treated patients, 89 patients were enrolled (with median age of 62 years and 74% females). [Result] Univariate analysis showed Biologics/JAKi naïve (odds ratio (OR) 3.58, p = 0.015) as predictors of CR, while neutrophil ratio was not significant. However, a lower SII ratio at 3 months suggested a greater tendency to CR. [Conclusions] In the current study, a neutrophil ratio after starting JAKi did not predict CR within 6 months in RA patients.

## P20-12

### Analysis of efficacy and safety of JAK inhibitor treatment by age

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Conflict of interest: None

[Purpose] In this study, we reported the efficacy and safety of JAK inhibitors (JAKi) treatment by age in our hospital. [Cases and analysis method] Forty RA patients consulting Toho hospital from June 2017 to June 2021 and were verified the effect of JAKi were analyzed. We classified patient into 3 groups: <65, 65-80, and >80 y.o. (Group A, B, and C), and compared the rate of complications, DAS28CRP, HAQ, eGFR, LDL, Hb, lymphocyte count, and CPK at the initial diagnosis and six months after the start of treatment and compared MTX utilization and MTX dose before and after the JAKi treatment. [Results] DAS28CRP and HAQ improved in all 3 groups. After the introduction of JAKi treatment, we could stop using MTX in Groups A and C, and the number of cases using MTX decreased from 13 to 2 in Group B with reduced MTX dose. The eGFR level decreased in all groups, while, LDL, Hb, or lymphocyte count were not changed. The CPK value was higher in Group B. The complication rate of other diseases increased with age. One case of herpes zoster infection in each group, and 3 cases of bacterial infection in Group B were observed. [Conclusion] Our data indicates that JAKi treatment would be effective in patients without MTX and patients with multiple drug resistance, regardless of age.

## P21-1

### Long-term efficacy and safety of Upadacitinib monotherapy in methotrexate-naïve patients with rheumatoid arthritis: 3-year data from the SELECT-EARLY study

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Conflict of interest: Yes

**Objective:** To evaluate the 3-yr efficacy and safety of upadacitinib (UPA) monotherapy in MTX-naïve patients (pts) with RA. **Methods:** Pts were randomized to UPA 7.5 (Japan only), 15, 30 mg, or MTX for 48 wks in a double-blind, and entered an open-label long-term extension study. Pts who met the rescue criteria received UPA+MTX rescue therapy at W26. Efficacy was analyzed for the global and Japanese populations (J-pop), and AEs per 100 pt-yrs were summarized over 156 wks. **Results:** 314, 55, 317, and 314 pts (Japanese: 28, 55, 27, 28) were randomized to MTX, UPA7.5, 15, or 30 mg. At W156, ACR50 was 37, 57 and 57% for MTX, UPA15 and 30 mg, respectively, in the overall pop, and 46, 71 82 and 64% for MTX, UPA7.5, 15 and 30 mg in the J-pop with NRI applied to missing/rescued pts. In the overall safety profile, the incidence of HZ, NMSC, neutropenia, and CPK elevation was higher in UPA compared with MTX group. Although AEs were more frequent with UPA 30 mg overall pop, the incidence of MACE and VTE was similar between the UPA15 mg and MTX groups. In the J-pop, the safety profile was generally consistent with overall pop, except the incidence of HZ in UPA is higher. **Conclusion:** UPA monotherapy maintained improvement of RA for 3 yrs in pts including J-pop, and no new safety risk was identified.

## P21-2

### Highly active rheumatoid arthritis resistant to JAK i, biologics in our clinic A clinical study of the efficacy and safety of UPA at 52 weeks in 20 patients

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Conflict of interest: None

[Purpose] For highly active RA resistant to Bio and JAKi We will examine 52 w efficacy and safety of UPA. [Method] One or more drugs being treated at our clinic from Apr, 2020-Oct, 2021 20 patients with Bio JAK-resistant RA, (Mean) Age 71.4 y M/F1:19 Stage 2.61 Class 1.8 RF189.6 ACPA296.5 MMP300.9 CRP3.66 MTX (Av 6.4 mg) PSL (Av 2.33 mg) Number of Bio JAK used 4.4 agents DAS28-CRP5.27 e-GFR64.6 J-HAQ1.41 UPA15 mg was administered to these patients. DAS28CRP J-HAQ MMP3 GS PD improvement is evaluated from 12 w to 52 w after administration. [Results] DAS28CRP Mean1.84 (P<0.001) after 52 w Significant improvement. MMP3 showed a significant decrease of 46.75 ng (P<0.005) on average 52 w after administration. In US evaluation, average after 52 w Significant improvement was observed with GS1.32 (P<0.03) and PD0.31 (P<0.002). DAS28CRP2.6 below at 52 w post-dose There were 14 cases. There were 2 refractory cases, and 1 case each was discontinued due to vasculitis and atypical mycobacterial infection. [Discussion] A significant improvement was observed in 52 w for the pathophysiology of multidrug-resistant refractory RA. DAS28CRP2.6 Relief was obtained with a high frequency of 68%. Many intractable cases due to UPA in the future We hope that it will be more effective and safer for patients with RA.

## P21-3

### Clinical manifestations of Upadacitinib: Part 2 Short-term efficacy and safety

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Conflict of interest: None

[Objective] We have now conducted a longer-term study of UPA with an increased number of patients. [Methods] Data from 49 patients who were treated with UPA in our hospital after the launch of UPA till October 2021 were analyzed. The assessment items included CDAI, SDAI, morning stiffness (MST), fatigue (FVAS, 0-100 scale), neutrophils real number, lymphocyte count, hemoglobin, platelet, creatinine, creatine kinase, AST and ALT. [Results] CDAI, SDAI, MST, FVAS rapidly improved 1 week after introduction of UPA treatment. Improvement and maintenance in efficacy were also observed during the subsequent courses. As for safety, abnormal decrease in neutrophils real number, lymphocyte count and hemoglobin was not observed, and also abnormal increase in platelets, AST and ALT was not observed. [Discussion] UPA showed efficacy at an early introduction, and it was shown to be effective in patients with insufficient effect even after multiple biologic drugs introduction and multiple JAK inhibitors introduction. UPA 7.5 mg may be one of the options. Post-market survey results suggest that safety may be ensured, but Cr and CK values need attention. [Conclusion] Short-term results suggest that UPA may be guaranteed efficacy and safety.

## P21-4

### Short-term results about 10 RA patients who changed treatment to upadacitinib from tofacitinib, and passed more than three months

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Keiyu Orthopedic Hospital

Conflict of interest: None

[Objective] I change treatment to other JAK inhibitors from the JAK inhibitor which an effect attenuated, and effective experience increases little by little recently. As we experienced 10 RA cases that we change the treatment from tofacitinib to upadacitinib at our hospital and are continuing this time, I report results in the short term. [Methods] 10 RA cases that I change treatment in a continuous administration example to UPA from TOF by July, 2021 from April, 2021 in our hospital. Average age: 72.5 years old, a mean disease duration: 15.9 years, mean antiCCP antibody titer: 926.4 U/mL, mean DAS28ESR: 4.4, MTX combination rate: 30%, PSL combination rate: 20%, RA-ILD rate was 50% by the chest CT reading shadow result. I evaluated the 3-month effectiveness and safety after the dosage about ten objects. [Results] In mean DAS28ESR 3 months after the UPA dosage, 30% reached the remission in 2.9. The average of the number of the lymphocytes after the UPA dosage rose to 1688/μl from 1610/μl a for three months. [Conclusions] Treatment changes from TOF to UPA will hold good. The average of the number of the lymphocytes which are a marker evaluating an easy infection state rises, and it may be slightly advantageous for the infectious disease.

## P21-5

### Efficacy of Upadacitinib in JAK-IR Rheumatoid Arthritis Patients in Clinical Practice

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Conflict of interest: None

[Objective] We evaluated the efficacy of Upadacitinib (UPA) for RA patients with JAK-IR. [Methods] Patients with refractory RA who had received UPA between May and July 2021 and had a history of JAKi use were included in the study. Efficacy was evaluated using PROs such as HAQ-DI in addition to DAS28-ESR at 12 weeks. [Results] There were 20 patients. The mean age at the start of UPA was 77.3 years, the mean disease duration was 21.6 years, the mean number of bDMARDs used was 3.4, JAKi used was 1.4, and the mean DAS28-ESR was 3.77. The survival rate at 12 weeks was 100%. In the DAS28-ESR, 20.0% (4/20) achieved remission and 50.0% (10/20) achieved low disease activity. In the 19 patients who completed the questionnaire, pain VAS was reduced by an average of 42.8%, HAQ-DI remission was 36.8%. [Conclusion] Although JAK inhibitors have been found to be effective in the treatment of refrac-

tory RA regardless of the number of bDMARDs used, there are patients with JAK-IR. UPA was more JAK1-selective than previously approved JAK inhibitors, suggesting that UPA is effective, albeit for a short period of time, regardless of previous use of bDMARDs or JAKi. However, the limitation of the study is the small number of patients and short observation period to validate the efficacy and safety.

## P21-6

### The efficacy and safety of Upadacitinib in resistant rheumatoid arthritis

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Conflict of interest: None

[Objective] We report the efficacy of upadacitinib in resistance rheumatoid arthritis. [Methods] We used Upadacitinib in resistant RA patients (DAS28 > 3.2) despite maximum dose MTX and at least 3 biologics DMARDs and JAK inhibitors, from March 2020 to August 2021. We checked the disease activity at 1, 3 month after the administration. [Results] There were consequence 10 cases. 8 patients achieved low disease activity 1 month. After 3 months, 6 patients reached disease activity. This time, statistical analysis was not proceeded due to retrospective studies and the small number of cases. [Conclusions] Upadacitinib is effective in resistant rheumatoid arthritis. However, there are some cases that show efficacy 1 month after administration but show the disease activity 3 months after administration. We need further investigations.

## P21-7

### Efficacy of Filgotinib in Rheumatoid Arthritis by Age, Body Weight, BMI: Post hoc Subgroup Analysis of Two Phase 3 Trials

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Conflict of interest: Yes

**Objective** We assessed impact of age, body weight (BW) and body mass index (BMI) on the efficacy of filgotinib (FIL), a preferential Janus kinase 1 inhibitor, approved in Japan and Europe for treatment of RA. **Methods** Methotrexate (MTX) inadequate responders (MTX-IR) from FINCH1 (F1, n=1755; NCT02889796) and MTX-naïve pts from FINCH3 (F3, n=1249; NCT02886728) were included. Pts were stratified by age (<65, ≥65 yrs), BW (<60, 60 to <100, ≥100 kg), and BMI (<25, ≥25 kg/m<sup>2</sup>). Efficacy assessments included ACR20, DAS28 (CRP) <2.6, and CDAI ≤2.8. Pts treated with FIL200 mg±MTX were compared vs control arms (F1, placebo+MTX; F3, MTX). Fisher's exact test was used for binary endpoints. P-values were nominal. **Results** FIL200+MTX in MTX-IR pts demonstrated greater efficacy vs placebo+MTX regardless of age, BW, and BMI. FIL200+MTX in MTX-naïve pts demonstrated consistently greater efficacy vs MTX across subgroups, except ≥65 yrs. Rates of treatment-emergent adverse events (TEAEs) were greater in ≥65 vs <65 yrs-safety was comparable in BMI subgroups. In MTX-naïve pts, TEAE rates were higher in pts ≥100 kg vs lower-weight groups. **Conclusion** FIL 200+MTX was efficacious vs controls regardless of subgroup. TEAEs were more common among older (vs younger) and among the highest weight group of MTX-naïve pts.

## P21-8

### Clinical Outcomes of Methotrexate-Naïve Rheumatoid Arthritis Patients on Filgotinib In A Long-term Extension Trial Who Were Initially on Filgotinib or Methotrexate During The FINCH 3 Phase 3 Parent Trial

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Conflict of interest: Yes

**Objective** Filgotinib (FIL) is approved for moderately to severely active RA treatment in Europe and Japan. This analysis assessed long-term FIL ± methotrexate [MTX] efficacy and safety in MTX-naïve pts from the Phase 3 parent study (PS; NCT02886728). **Methods** Pts received FIL 200 mg (FIL200)+MTX, FIL 100 mg (FIL100)+MTX, FIL200 alone or MTX alone for 52 weeks (W) in the PS. In long-term extension (LTE; NCT 03025308), PS FIL-completers maintained their dose and MTX-completers were rerandomised to FIL200 or FIL100; MTX was washed-out at LTE baseline with possible restart at W4. **Results** As of June 1 2020, 439/492 PS FIL200, 144/169 PS FIL100, 131/148 PS MTX to FIL200 and 133/151 PS MTX to FIL100 pts were on study treatment. LTE baseline characteristics were similar between groups. ACR20/50/70 responses from PS FIL arms decreased modestly then stabilized. For PS MTX to LTE FIL, responses remained stable or improved to approach those of PS FIL pts. Safety was largely comparable across groups and did not appear to increase after MTX to FIL switch. **Conclusion** Response rates improved for pts switched from PS MTX to FIL and decreased modestly for PS FIL pts. AESIs rates were low and tended to be higher in pts maintained on FIL from PS. Safety findings were comparable with previous studies.

## P21-9

### Clinical Outcomes up to Week 48 of Filgotinib Treatment in an Ongoing Long-term Extension Trial of RA Patients With Inadequate Response to MTX Initially Treated With Filgotinib or Adalimumab During the Phase 3 Parent Trial

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Conflict of interest: Yes

**Objective** Filgotinib (FIL), a preferential JAK-1 inhibitor, is approved for moderately to severely active RA treatment in Europe and Japan. We assessed FIL efficacy and safety in MTX inadequate responders who completed the Phase 3 FINCH1 trial (NCT02889796) and enrolled in a long-term extension (LTE; NCT03025308; median exposure, 2.2 years). **Methods** Efficacy and safety measures were summarized for 4 treatment groups (all +background MTX): Patients (Pts) who received FIL 200 mg or 100 mg in FINCH1 and continued (FIL200/FIL200, FIL100/FIL100) and adalimumab pts rerandomized to FIL200 or FIL100 (ADA/FIL200, ADA/FIL100). **Results** LTE baseline characteristics were similar between groups. Efficacy responses, including ACR20/50/70, DAS28 (CRP) ≤3.2/<2.6 and CDAI ≤10/≤2.8 were generally maintained from LTE baseline to W48 across all groups. Responses were numerically higher in FIL200 vs FIL100. Treatment emergent adverse events (AEs), serious AEs and AEs Grade ≥3 were largely comparable between groups. Death exposure-adjusted incidence rates were lower for FIL/FIL vs ADA/FIL groups. **Conclusion** During the LTE, response rates were generally maintained for FIL/FIL and ADA/FIL pts. Safety was largely comparable and consistent with previous studies: AE of specific interest rates were low.



## P21-10

### Experience with Filgotinib in patients with RA in clinical practice

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Okuda Orthopedic Clinic

Conflict of interest: None

[Purpose] It has been clarified that the use of JAK inhibitors in RA patients has the same therapeutic effect as biopharmacy. This time, we report the results of use in our hospital for RA patients who used the JAK inhibitor Filgotinib (FIL), which became available from November 2020. [Subjects and methods] Since January 2021, 14 RA patients (3 males and 11 females) who used FIL at our hospital were included. The average age is 73.9 years (61-86 years) and 4 cases have been changed from biologics. The cause was weakening. There were 7 cases of change from other JAK inhibitors, 3 cases of diminished effect, and 3 cases of side effects. The starting dose of FIL was 100 mg in 10 cases and 200 mg in 4 cases. We investigated the short-term continuation status and usefulness of these cases. [Results] Adverse events included 1 case of headache and 1 case of abnormal bleeding, but none of them were serious. Subjective symptoms improved from an early stage after the start of administration, and administration is currently being continued except for 2 cases. [Conclusion] Although it is a short-term use result, the use of FIL is useful for RA patients who use biopharmacy for oral drug use and cases where the effect of other JAK inhibitors is diminished or side effects occur. there were.

## P21-11

### 4 cases in which filgotinib was effective in RA patients with insufficient multidrug effect

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Conflict of interest: None

Recently, a lot of biological agents (BA) and JAK inhibitors (JAKi) has been developed. However, we face several cases with multiple drug resistance (MDR). We report four cases in which selective JAK1 inhibitor filgotinib (FIL) was effective for MDR RA patients. [Case] (1) 68-y.o. F, disease duration (DD) 6 years, no MTX combination (no MTX), treatment history (TH) TOF, BARI. (2) 74-y.o. M, DD: 2 years, complications of dermatomyositis and interstitial pneumonia (IP), no MTX, TH: ABT, BARI, TCZ, TOF, PEFI. (3) 75-y.o. F, DD: 20 years, no MTX, TH: ETN, IFX, TCZ, ABT, GLM, TOF. (4) 80-y.o. M, DD: 22 years, IP complication, no MTX, TH: ABT, TCZ, TOF. [Results] Regarding the transition of activity and complications 6 months after FIL administration, (1) DAS28CRP (before FIL); 3.18 → 1.11, no adverse events. (2) DAS28CRP (before FIL); 7.08 → 4.53, IP tends to improve. (3) DAS28CRP (before FIL); 5.1 → 1.03, no adverse events. (4) DAS28CRP (before FIL); 4.11 → 1.33, IP tends to improve. [Discussion / Conclusion] If the existing treatment is inadequate, the introduction of FIL is an option for MDR elderly patients. In the future, it was considered that the differences of selective JAK1 inhibitor in indications with low-selectivity JAKi and other BA should be investigated in detail.

## P22-1

### Treatment Effect of Baricitinib (BARI) on Fatigue: Mediation Analysis Results from Two Phase 3 trials in patients with rheumatoid arthritis (RA)

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Conflict of interest: Yes

[Objective] To assess BARI's effect on fatigue in RA patients (pt) in phase 3 trials that are dependent on/independent of disease activity (DA). [Methods] Data of BEAM in MTX-IR pts and BEACON in bDMARD-IR pts were used. Fatigue assessed by FACIT-F was used for mediation analysis with RI-CLPM. FACIT-F change from baseline (BL), treatment, CDAI changes from BL were used as dependent, independent, mediator

variables, respectively. The total effect on fatigue over placebo (PBO) that can be accounted for by CDAI changes is the "indirect" or mediation effect; the other is the "direct" effect. [Results] In BEAM, DA-mediated effect accounted for 50-60% of fatigue improvement in both BARI 4-mg and adalimumab (ADA) over PBO. Total and mediation effects of BARI 4-mg over PBO on FACIT-F were numerically greater than that of ADA over PBO from W12 to W24. Direct effect of BARI 4-mg over PBO was significant from W16; that of ADA was not. In BEACON, about 20-30% of effects of BARI 4-mg on FACIT-F were DA independent. Mediation effect change from W12 to W24 reflected CDAI change over time in each study population. [Conclusions] In both trials, BARI 4-mg had DA-independent effects on fatigue. The direct fatigue improvement of BARI 4-mg over PBO was significant from W16, but that of ADA was not.

## P22-2

### Efficacy and safety of baricitinib in patients with rheumatoid arthritis in clinical practice

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Conflict of interest: None

[Objective] To investigate the efficacy and safety of baricitinib for Japanese rheumatoid arthritis (RA) patients in a real-world clinical setting. [Methods] This multicenter retrospective study included 170 RA patients. We analyzed retention rate, number of tender/swollen joints, and patient VAS, CRP, CDAI/SDAI at 0, 4, 12, 24 and 52 weeks. In a subgroup analysis, we compared efficacy and safety between 2-mg and 4-mg doses according to renal function and age. Treatment outcomes for difficult-to-treat RA (D2TRA) non-D2TRA were also compared. [Results] The total retention rate was 68.8%. Adverse events were observed in 20.8% of patients. In the subgroup analysis, there was no statistical difference in continuation rate and CDAI/SDAI at 52 weeks for either renal function or age between the two groups. Comparison of D2TRA and non-D2TRA showed no statistical difference in CDAI/SDAI at 52 weeks. [Conclusions] Efficacy was confirmed even with 2-mg dose administration. Patients aged ≥65 years tended to have an increased risk, including infectious diseases, but efficacy was comparable to that in patients aged <65 years. Effectiveness was also confirmed for D2TRA.

## P22-3

### Comparisons of clinical outcomes between 2mg and 4mg daily of baricitinib in rheumatoid arthritis: Results from the multicenter registry system

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Conflict of interest: Yes

[Objective] Baricitinib (BAR) is usually used at 4 mg/day, but it is sometimes used at 2 mg in cases of renal dysfunction. Using real-world data, we compared the clinical results of BAR between 2 mg and 4 mg. [Methods] From the multicenter study TBCR, we retrospectively analyzed patients who took BAR and were followed for at least 52 weeks. Patient background, changes in disease activity at 0, 4, 12, 24, and 52 weeks, and drug retention rate (Kaplan-Meier method) were compared between the 2 mg (N=68) and the 4 mg group (N=181). Missing data were imputed by LOCF method. [Results] The 2 mg group had older age (72.7 vs 60.3 years) and lower eGFR (64.8 vs 84.3). DAS28-CRP improved significantly from 3.62/3.66 (2 mg/4 mg group) at week 0 to 2.37/2.31 at 52 weeks, with no difference between groups. 52-week drug retention was significantly lower in the 2 mg group (67.1 vs 83.3%). 2 mg group had a higher discontinuation rate due to adverse events (19.7 vs 7.2%). Only when the age was 68 years (median) or older, the discontinuation rate due to adverse events in the 2 mg group was significantly higher (23.5 vs. 8.6%,  $p=0.017$ ). [Conclusions] The 2 mg dose is often used in the elderly patients and is expected to be effective, but careful follow-up considering the patient background is necessary.

## P22-4

### The potential of monotherapy of baricitinib

Masaaki Yoshida

Yoshida Orthopedic Surgery and Rheumatology

Conflict of interest: Yes

[Purpose] The efficacy of biological DMARD (bDMARD) is significantly improved by the combined use of methotrexate (MTX). It has been reported that the efficacy of Janus kinase inhibitors (JAKi) is no significant difference between the MTX combination group and the monotherapy group. [Method] Sixty-seven patients started BAR, 60 females at the age of 63.5 (mean). Disease duration was 15.2 years, and anti-CCP antibody positive rate of 91%. DAS28-CRP was 4.9, SDAI 34.2, and CDAI 32.8. Monotherapy group was 34 cases (50.7%). Thirty-three patients (49.3%) also used MTX, and the average dose was 7.8 mg / week. In the MTX combination group, the dose of MTX was reduced by 2 mg when DAS28-CRP achieved LDA or remission in the evaluation every 4 weeks. [Results] At 12 weeks in the monotherapy group, LDA was 3 cases → 9 cases (26.5%), remission was 0 cases → 17 cases (47.1%), and LDA was 4 cases → 7 cases (21.2%), remission 0 cases → 12 cases (36.4%) in the MTX combination group. Of the 33 patients in the combination group, MTX dose reduction was possible in 9 patients and discontinuation in 10 patients. Eight patients were unable to reduce MTX. [Conclusion] BAR should be started as monotherapy early onset of RA.

## P22-5

### Long-term efficacy and safety after remission-induction of steroids and half-dose baricitinib for seronegative rheumatoid arthritis with over 80 years old onset

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Conflict of interest: None

[Purpose] To investigate the long-term efficacy and safety of remission-induction therapy using prednisolone (PSL) and half dosage of baricitinib (BAR) for seronegative rheumatoid arthritis (RA) with over 80 years old onset. [Method] Five patients aged 80 years or older, diagnosed with seronegative RA at Niigata Rinko Hospital after April 2019, were treated for remission-induction with PSL and BAR 2 mg/day, and followed up to 52 weeks after the initiation of the therapy. [Results] DAS28 (3)-CRP at RA diagnosis averaged  $3.91 \pm 0.77$ , the mean mHAQ was  $2.04 \pm 0.92$ , the mean serum CRP was  $10.4 \pm 5.7$  mg/dl, and the mean dosage of PSL was  $9.6 \pm 6.7$  mg/day, respectively. Two weeks after the start of BAR, data were improved dramatically as the mean DAS28 (3)-CRP  $1.27 \pm 0.51$ , the mean mHAQ  $0.44 \pm 0.11$ , and the mean serum CRP  $0.09 \pm 0.11$  mg/dl. The mean dosage of PSL was also reduced to  $5.5 \pm 3.5$  mg / day. Furthermore, 52 weeks after the start of BAR, the improved status was maintained and PSL

was discontinued in 3 patients. No adverse events were observed during the observation period. [Conclusion] Remission-induction therapy with PSL and BAR half dose can maintain a long-term remission state without any adverse events in patients with super-aged seronegative rheumatoid arthritis.

## P22-6

### The efficacy of baricitinib at 1 year in patients with rheumatoid arthritis in our institution

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Conflict of interest: None

[Objective] To assess the efficacy of baricitinib (BARI) in patients with rheumatoid arthritis. [Methods] Twenty-six RA patients were initiated BARI in our institution from May 2018 to September 2021, and 25 of them were continued BARI over one month. DAS28-CRP and CDAI were assessed at the point of 0, 1, 2, 3, 6, 12 months. [Results] DAS28-CRP / CDAI after initiation of BARI decreased as follows; DAS28-CRP/CDAI 0 month: 4.06/19.14, 0.5 month: 3.13/11.64, 1 month: 2.65/9.60, 2 months: 2.63/7.56, 3 months: 2.38/8.03, 6 months: 2.43/8.05, 12 months: 2.37/6.57 with significant difference (respectively,  $p<0.001/p<0.001$ ) after the two weeks. Remission rate of DAS28-CRP/CDAI was as follows; 0 month: 8%/4%, 3 months: 72%/44%, 6 months: 72%/44%, 1 year: 64%/36% and under low disease activity rate was as follows; 0 month: 16%/24%, 3 months: 72%/72%, 6 months: 72%/72%, 12 months: 68%/84%. Good EULAR response was as follows; 0.5 month: 32%, 1 month: 48%, 3 months: 52%, 6 months: 56%, 12 months: 64% and over moderate EULAR response was as follows; 0.5 month: 52%, 1 month: 68%, 3 months: 80%, 6 months: 76%, 12 months: 72%. [Conclusions] These data indicate that continuation of effectiveness can be expected from BARI therapy from the early phase.

## P22-7

### Double cancer developed after treatment with baricitinib for rheumatoid arthritis

Yoshihiro Hishitani

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Conflict of interest: None

[Case] An 82 years old woman developed RA 8 years and 3 months ago. She has a family history of gastric cancer, breast cancer, and colorectal cancer. After remission with glucocorticoid monotherapy, the disease activity worsened 4 years and 6 months ago. The addition of TAC and IGU was not sufficiently effective, and various biologics such as ABT, GLM, TCZ, and ADA were tried, but none of them was sufficiently effective. Peficitinib was started 1 year and 5 months ago, which showed no efficacy. Then, baricitinib was started 1 year and 3 months ago, resulting in low disease activity. During the course described above, she required hospitalization for diverticular bleeding twice, 2 years and 9 month ago and 1 year and 9 months ago. The CT at that times showed no evidence of tumor. However, when she visited a nearby hospital for frequent urination 1 month ago, CT incidentally indicated ovarian tumor (pathology: clear cell carcinoma) and kidney tumor (pathology: clear cell type renal cell carcinoma). The Uterine and ovarian removal and the right kidney removal was conducted. As a result, eGFR decreased to 29, and baricitinib had to be discontinued. [CLINICAL SIGNIFICANCE] Long term safety of JAK inhibitors remains unclear. This case warns against the easy use of JAK inhibitors.

## P22-8

### Efficacy of Baricitinib Treatment in Patients with Rheumatoid Arthritis in Daily Clinical Practice

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Conflict of interest: Yes

[Objective] Treatment outcomes of Baricitinib (Bari) in RA patients were retrospectively investigated using the data from the Toyohashi RA Database. [Methods] A total of 22 patients with RA treated with Bari from October 2018 to September 2020 were included. Baseline (BL) patients' characteristics, disease activity time-course, MTX and PSL concomitant rates, continuation rates of Bari, and reasons for Bari discontinuation were investigated. [Results] BL characteristics: Mean age was 61.3 years old, females were 86.4%, and RA duration was 158.8 months (m). Ten patients (45.5%) were biologics or JAK-inhibitor naïve. Mean SDAI was significantly decreased as follows: 18.2 at BL, 8.5 at 1 m, 5.7 at 3 m, 4.1 at 6 m and 4.9 at 12 m. SDAI remission rate at 12 m was 44.4%. Mean dose and concomitant rates of PSL were decreased from 1.6 mg/day (27.8%) at BL to 0.4 mg/day (5.6%) at 12 m, whereas the MTX were decreased from 7.8 mg/week (88.9%) at BL to 5.7 mg/day (77.8%) at 12 m. Continuation rates of Bari were 100.0% at 6 m and 100.0% at 12 m. HZ was occurred in 4 cases (18.2%) and Bari was readministered after cure of HZ in all 4 cases. [Conclusions] Bari was initially effective. Although HZ was occurred in 4 cases, continuation rate was excellent.

## P22-9

### Comparisons of clinical outcomes between infliximab BS and baricitinib in patient with rheumatoid arthritis in a routine care

Yutaka Yoshioka

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Conflict of interest: None

[Objectives] Biosimilars (BS) and dose reduction of expensive drugs is economy in the treatment of rheumatoid arthritis (RA). There are a few studies that have compared of clinical outcomes between infliximab BS and baricitinib (BAR) at one-half dose (2 mg) in patient with rheumatoid arthritis in a routine care. In this study, we investigated the efficacy and safety of IFXBS and BAR2 mg in RA patients. [Methods] RA patients treated with IFXBS or BAR2 mg for longer than 52 weeks were included in this study. We retrospectively reviewed the efficacy, discontinuation of therapy and adverse event in IFXBS therapy and BAR2 mg therapy, respectively. [Results] Sixteen (IFXBS group) and ten (BAR group) patients were included in this study. Mean DAS28-ESR was both 4.8 at baseline, and 3.1 and 2.7 at 52 weeks (IFXBS and BA groups, respectively). At 12 weeks, DAS28-ESR in BAR group was significantly lower than in IFXBS group ( $p=0.02$ ). The 52 weeks retention rates were 62.5% and 80% (IFXBS and BA groups, respectively). withdrawal due to adverse events was both two. [Conclusion] BAR2 mg was effective in RA patients in a routine care. This study provides support for the possible use of one-half dose of BAR in RA patients.

## P22-10

### Efficacy and corticosteroid dose reduction effect of baricitinib in patients with rheumatoid arthritis in real clinical practice

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Conflict of interest: None

[Objective] To clarify clinical efficacy and corticosteroid dose reduction effect using baricitinib (BARI) in patients with rheumatoid arthritis (RA) in real clinical practice. [Methods] This retrospective study enrolled RA patients treated with BARI between March and September 2020. The clinical efficacy was examined in MTX-IR group, Bio-IR group, BARI with MTX group, BARI without MTX group. The rate and dose of corticosteroid were also examined. [Results] This study was comprised consecutive 35 patients RA (17 in MTX-IR group, 18 in Bio-IR group, 23 in BARI with MTX group, and 12 in BARI without MTX group). CDAI remission rate at 52 w was 40.0% in MTX-IR, 42.6% in Bio-IR, 50.0% in BARI with MTX group, and 45.5% in BARI without MTX group, respectively. HAQ remission rate in BARI without MTX group was higher at 52 w than the baseline (54.5% vs 16.7%). The rate and dose of corticosteroid were lower at 52 w compared with at the baseline (13/32 (40.6%) vs 26/35 (74.3%), 3.0 mg vs 5.6 mg a day on average). The 50% of patients treated

with corticosteroid could suspend corticosteroid at 52 w after the introduction of BARI. [Conclusions] BARI was effective in the RA patients of MTX-IR, Bio-IR, without MTX. It is possible to treat more safely by reducing the dose of corticosteroid using BARI.

## P22-11

### Exploration of predictive factors for the therapeutic effect of peficitinib (PEF) in patients with rheumatoid arthritis (RA): Post-hoc analysis of phase 3 trial (RAJ3)

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Conflict of interest: Yes

[Objective] Oral Janus kinase inhibitor, PEF demonstrated the efficacy in phase 3 trial in RA patients with inadequate responses to DMARDs (RAJ3), however PEF did not exert therapeutic effect in some patients in this trial. A post-hoc analysis of this phase 3 trial was performed to explore predictive factors for the therapeutic effect of PEF. [Methods] Impact of baseline characteristics on achievement rates of CDAI remission ( $\leq 2.8$ ) were explored by univariate and multivariate analyses. [Results] CDAI remission at Week 52 were achieved in 27.2% (22/81 patients) in the PEF 150 mg group, and 21.1% (15/71 patients) in the PEF 100 mg group. Univariate analysis in the PEF 150 and 100 mg total group (152 patients) indicated that achievement rates of CDAI remission were statistically higher in male patients (41.7% vs female: 19.0%), patients without previous Bio-DMARD (26.7% vs with previous Bio-DMARD: 9.5%), patients without or with lower dose of prednisolone at baseline (no prednisolone: 27.9% vs  $\leq 5$  mg/day: 25.0% vs  $>5$  mg/day: 0%). Multivariate analysis supported these results. [Conclusions] These results suggest male patients, patients without previous Bio-DMARD, and patients without or with lower dose of prednisolone at baseline were possible predictive factors for the therapeutic effect of PEF.

## P22-12

### Relation between the inhibitory effect of peficitinib (PEF) on joint destruction and MMP-3 level in patients with rheumatoid arthritis (RA): Post-hoc analysis of phase 3 trial (RAJ4)

Tsutomu Takeuchi<sup>1</sup>, Yoshiya Tanaka<sup>2</sup>, Yoshiaki Morita<sup>3</sup>, Daisuke Kato<sup>3</sup>, Yuichiro Kaneko<sup>3</sup>, Musashi Fukuda<sup>3</sup>

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Conflict of interest: Yes

[Objective] MMP-3 degrades cartilage components including collagen. In the pathogenesis of RA, it is known that inflammation occurs in synovocytes, and MMP-3 produced from proliferating synovocytes degrades cartilage and subsequently provokes joint destruction. It has been reported that joint destruction rapidly progresses in RA patients with higher MMP-3 levels, and whereas MMP-3 level decreases with disease stabilization by drug therapy. However, it is not known whether MMP-3 level can predict inhibitory effect of joint destruction by drug therapy. In this study, relation between inhibitory effect of joint destruction and MMP-3 levels was investigated based on phase 3 results of PEF, an oral JAK inhibitor. [Methods] Correlations between  $\Delta$ mTSS,  $\Delta$ JSN,  $\Delta$ ES, and MMP-3, CRP levels were investigated based on phase 3 study results of PEF in RA patients with inadequate responses to MTX (RAJ4). [Results] MMP-3 levels at Week 8, 12 and 28 were moderately correlated with  $\Delta$ mTSS and  $\Delta$ JSN at Week 52 (Spearman correlation coefficient:  $\geq 0.35$ ). For CRP levels, moderate correlation was observed between CRP levels (at Week 4 and 8) and  $\Delta$ mTSS at Week 52 only. [Conclusions] These results suggest that MMP-3 level after PEF treatment is a possible predictor of joint destruction.

## P22-13

### Examination of efficacy and safety of peficitinib for rheumatoid arthritis in our department

Masaki Mitsunashi, Kento Ichikawa, Noriko Kojitani, Soichi Ota, Yumiko



Conflict of interest: None

[Objective] Peficitinib (PEF) is the third JAK inhibitor approved for rheumatoid arthritis (RA) in Japan, and many studies have shown its efficacy and safety. We investigated the efficacy and safety of PEF for RA in our hospital. [Methods] For RA patients who treated with PEF from July 2019 to October 2021, the patient's clinical information are described from the medical records. [Results] 37 RA patients were treated with PEF, with an average age of  $76.0 \pm 16.4$  years and an average duration of illness of  $11.5 \pm 11.0$  years. Twelve of them were taking MTX in combination. In addition, 16 patients had eGFR  $<50$  mL / min /  $1.73$  m<sup>2</sup> or less, and the average eGFR was  $59.8 \pm 24.7$  mL / min /  $1.73$  m<sup>2</sup>. Three months after the start of PEF, DAS28-ESR improved significantly ( $5.1 \pm 1.2$  vs  $3.4 \pm 1.1$ ,  $p = 0.026$ ). The 3-month and 1-year continuation rates of PEF were 84.4% and 43.0%, respectively. No onset of herpes zoster or other infectious diseases was observed during the average administration period of  $6.1 \pm 5.1$  months. [Conclusions] At our hospital, PEF showed the efficacy and safety for the relatively elderly RA population.

## P22-14

### Examination of interstitial pneumonia according to the age group in the chest CT reading shadow result of 54 RA patients treated with tofacitinib for 3 years in Keiyo Orthopedic Hospital

Keio Ayabe, Akira Inoue, Wataru Iriyama, Yurina Iwasaki  
Keiyo Orthopedic Hospital

Conflict of interest: None

[Objective] The treatment for the elderly RA patient with ILD is in particular difficult on safety, both sides of the effectiveness. I report a merger of ILD and the progress in three years by 54 RA patients treated with tofacitinib in Keiyo Orthopedic Hospital. [Methods] 54 RA patients treated with tofacitinib for 3 years from December, 2013 to May, 2018 in Keiyo Orthopedic Hospital. We divided an age group into four groups and weighed it about a merger and the progression in three years of ILD, a change of KL-6 from the chest CT reading shadow result by the image diagnostician. [Results] As for the ILD merger rate at the time of the TOF dosage start, the A, B group younger than 75 years was 11.8%, 8.7% each. The C, D group 75 years or older went over 50% together. The progress example of existing ILD was 22.2% only in C group, but there was not the difference with the progress rate according to acpa-positive 568 RA patients in Keiyo Orthopedic Hospital. [Conclusions] The existing ILD progress rate with the continuous administration by TOF was low. It was thought that I could expect TOF for, ILD slight merger RA patient in the effectiveness, the safe both sides.

## P22-15

### A huge shoulder bursitis in patient with rheumatoid arthritis successfully treated with tofacitinib

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Conflict of interest: None

A 85-year-old woman with polymyalgia rheumatica treated with low dose corticosteroid presented with right shoulder arthritis. She was diagnosed with seronegative rheumatoid arthritis (RA) and methotrexate and golimumab (GOL) were sequentially added. However, the swelling of the shoulder increased to the size of a fist. Magnetic resonance imaging showed a huge subacromial and subdeltoid bursitis with rice bodies and bone erosions on the humeral head. Bacterial and mycobacterial cultures of the synovial fluid were negative. We thought that the cause of this huge bursitis was RA. Although incision and drainage of the bursa were performed, a large amount of discharge from bursa continued. After switching from GOL to tofacitinib (TOF), the bursitis improved. There have been case reports of RA complicated with huge subacromial bursitis (Kashid M, et al. JOCR 2019. Joshi PS. Malays Orthop J 2018. Minoru Y, et al. Mod Rheumatol 2001) and iliopsoas synovitis (Tatsumura M, et al. Mod Rheumatol 2008), surgical excision of bursa or synovium improved joint

symptoms. Here we report a case of huge shoulder bursitis in patient with RA successfully treated with TOF.

## P23-1

### Efficacy of switching JAK inhibitors in rheumatoid arthritis

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Conflict of interest: None

[Objective] To clarify the efficacy of JAKi switch for patients with inadequate JAKi effect (JAKi-IR). [Methods] The efficacy of JAKi switch was assessed by DAS28-CRP, SDAI, and patient VAS at 4 and 12 weeks. Changes in blood cytokines (IFN- $\gamma$ , IL-1b, IL-6, TNF- $\alpha$ , IL-15, IL-17A) before and after the JAKi switch were measured using ELISA and examined for association with efficacy. The changes in cytokines were compared with those of bDMARDs to JAKi. [Results] 17 RA patients who switched from JAKi to JAKi were included in the study. Efficacy at 12 weeks after the switch was significantly improved for all disease activity indices: DAS28-CRP, SDAI, and patient VAS (3.88 [3.02-4.39] to 2.15 [1.50-3.03], 14.1 [7.10-21.4] to 6.02 [2.30-7.13], 40 [25 -50] to 20 [13.5-31.0]). Cytokines were measured in 15 patients. Changes in IFN $\gamma$ , IL-15, and TNF- $\alpha$  were different depending on the type of JAKi and the disease background before and after the switch, and were also different from those at the switch from bDMARDs to JAKi. RA patients with marked improvement in disease activity showed an increase in IFN $\gamma$  after the switch. [Conclusions] JAKi switch was considered to be an effective therapeutic strategy. The changes in cytokine profiles suggest that the efficacy and safety of each JAKi may be different.

## P23-2

### Comparison of Effects of Janus Kinase Inhibitors on Rheumatoid Arthritis Fibroblast-like Synoviocytes with Interleukin-6 Stimulation

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Conflict of interest: None

[Objective] Five types of Janus kinase (JAK) inhibitors are available for rheumatoid arthritis (RA), each with different potential effects and side effects depending on their JAK selectivity, but there have been few reports directly comparing JAK inhibitors. In this study, we investigated the effect of each JAK inhibitor on fibroblast-like synoviocytes derived from RA patients (RA-FLSs) with IL-6 to clarify the effect of JAK inhibitors targeting the JAK-STAT pathway by IL-6 involved in the pathogenesis of RA. [Methods] RA-FLS were stimulated with estimated blood concentrations of JAK inhibitors (Tofacitinib 0.3  $\mu$ M, Baricitinib 0.3  $\mu$ M, Peficitinib 1  $\mu$ M, Upadacitinib 0.3  $\mu$ M, Filgotinib 0.01  $\mu$ M), followed by IL-6 (100 ng/ml) and sIL-6R (100 ng/ml). We investigated the mRNA expression of ICAM1, VCAM1, VEGF, MCP1, and MMP1. The relative expression of target transcripts was assessed by qRT-PCR. [Results] ICAM1 and VEGF showed significant differences between groups ( $p=0.027$ ,  $p=0.002$ ). In addition, Upadacitinib, Peficitinib, Baricitinib, Tofacitinib, and Filgotinib tended to suppress the mRNA expression of ICAM1, VCAM1, VEGF, MCP1, and MMP1 in that order. [Conclusions] This study suggests that among the current JAK inhibitors, Upadacitinib and Peficitinib might strongly suppress inflammatory factors.

## P23-3

### Effects of Janus kinase inhibitors on interferon signaling and cytokine production in innate immune cells

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Conflict of interest: None

[Objective] INF- $\gamma$  is overexpressed in the synovium of rheumatoid arthritis (RA) and it has been implicated in the pathogenesis of RA by activating innate immune cells and inducing the production of proinflammatory cytokines. We investigated inhibitory effects of Janus kinase inhibitors (JAKi) upon IFN- $\gamma$  stimulated neutrophils. [Methods] Neutrophils were isolated from the blood of healthy adults and IFN- $\gamma$ -stimulated neutrophils untreated or pretreated with three JAKi: tofacitinib (TOF), baricitinib (BAR) and upadacitinib (UPA). The production of IL-6 and TNF- $\alpha$  was measured by ELISA. The activation of JAK/STAT system induced by IFN- $\gamma$  was analyzed by immunoblotting using antibodies against phospho-specific anti-JAK1/2 and STAT1. [Results] IFN- $\gamma$  induced production of IL-6 and TNF- $\alpha$  through the activation of JAK1, 2 and STAT1 in neutrophils. The activation of JAK/STAT and cytokine production were inhibited by all JAKi. Whereas their inhibitory effects were lower in TOF-pretreated neutrophils compared to those with BAR or UPA under low concentration ( $\leq 100$  nM). [Conclusions] IFN- $\gamma$  may activate innate immune cells which resulting in the rheumatoid synovitis. JAKi inhibits innate immune systems activation and inflammatory cytokine production caused by IFN- $\gamma$ , which can inhibit RA progression.

### P23-4

#### Influence of dosing-time of Tofacitinib on antirheumatic effects in SKG mice

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Conflict of interest: None

[Objective] We investigated influence of dosing-time on antirheumatic effects after Tofacitinib (TOF) was given in SKG mice. [Methods] After Mannan sensitization, TOF was perorally given every day, and arthritis score was recorded. [Results] When TOF (30 mg/kg) was given once a day at 5:00 or 17:00, the 5:00-treated group inhibited 50% of articular increase compared with the control group in mice. Whereas, inhibition rate of arthritis score in the 17:00-treated group remained in 16% relative to the control group. Next, mice were given with one dose as the same amount (15 mg/kg), and TOF was administered once a daily (15 mg/kg/day) at 5:00 or twice daily (30 mg/kg/day) at 5:00 and 17:00. In all during the study period, arthritis score was significantly lower in the once daily 5:00-treated and twice daily groups than the control group ( $P < 0.001$ ). Furthermore arthritic depression effect in the once daily 5:00-treated group (15 mg/kg/day) was equivalent to that in the twice daily group (30 mg/kg/day). [Conclusions] These findings show that to treat TOF once a day considering suitable dosing-time may improve RA symptoms compared with the current standard dosing methods.

### P23-5

#### Effect of CDK6 inhibitor combined with TNF-inhibition on collagen-induced arthritis in mice

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Conflict of interest: None

[Objective] We have reported that SPACIA1 siRNA inhibited the proliferation of TNF $\alpha$ -induced rheumatoid arthritis-synovial fibroblasts (RASFs) via CDK6, a cell cycle regulator at G1 phase. In this study, we investigated effects of CDK6 inhibitor (compound) and/or TNF inhibitor on collagen-induced arthritis (CIA), as a mouse model of human rheumatoid arthritis. [Methods] The CIA model was induced in DBA/1J mice that were administrated CDK6 and/or TNF inhibitor (etanercept) after 2nd injection of type II collagen. CDK6 inhibitor was supplemented in powdered diet in ad libitum-fed and etanercept was given via intraperitoneal injection every 3 days. [Results] As previously reported, etanercept significantly suppressed CIA, compared with negative control. While CDK6 inhibitor (ED50) was considerably suppressed CIA, though the difference was not statistically significant ( $p = 0.053$ ). Using CDK6 inhibitor combined with etanercept, there was a trend of suppression in CIA, compared to treatment with etanercept only ( $p = 0.14$ ). [Conclusions] The results above didn't show the statistically significant suppression of CIA, using CDK6 inhibitor. However, the trend suggested a potential of the CDK6 inhibitor combined with TNF-inhibition for RA treatment.

### P23-6

#### Comparison of angiogenesis-suppressing effects of JAK inhibitors on IL-6-stimulated synovial fibroblasts derived from RA patients

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Conflict of interest: None

[Aim] Angiogenesis is an important target in the treatment of rheumatoid arthritis (RA). Currently, five types of Janus kinase (JAK) inhibitors have been approved for RA, and each JAK is suppressed with different JAK selectivity, but the effect of the difference in JAK selectivity remains unclear. The purpose of this study is to compare the angiogenesis-suppressing effects of each JAK inhibitor on IL-6 stimulation of RA patient-derived synovial fibroblasts (RA-FLS). [Methods] RA-FLS were stimulated with estimated blood concentrations of JAK inhibitors (Tofacitinib 0.3  $\mu$ M, Baricitinib 0.3  $\mu$ M, Peficitinib 1  $\mu$ M, Upadacitinib 0.3  $\mu$ M, Filgotinib 0.01  $\mu$ M), followed by IL-6 (100 ng/ml) and sIL-6R (100 ng/ml). The mRNA expression of VEGF, IL-8 and IL-10 as targets involved in angiogenesis was compared by qRT-PCR. [Results] VEGF showed a significant difference between groups ( $p = 0.002$ ), but IL-8 and IL-10 did not differ significantly. VEGF mRNA expression was suppressed in the order of Upa (46%), Pefi (40%), Bari (30%), Tofa (11%), Filgo (6%). [Conclusion] VEGF plays a major role in RA angiogenesis, and significant differences in VEGF mRNA expression were observed between the groups, suggesting that Upadacitinib may strongly suppress angiogenesis. Further studies are needed for other angiogenic factors.

### P24-1

#### Allograft bone augmentation and wrist arthrodesis for the implant loosening after total wrist arthroplasty: a case report

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Conflict of interest: None

[Objective] We report a case with severe loosening of DARTS total wrist prosthesis that was salvaged by total wrist arthrodesis using block bone allograft. [Case presentation] The case was 69 years old, who suffered from finger dysfunction caused by extensor tendon rupture. We performed tendon reconstruction surgery with total wrist arthroplasty (DARTS total wrist). The range of joint motion was well preserved after surgery (flexion: 40 degrees, extension: 70 degrees). However, we lost the follow up of this case six months after surgery because of a cerebral stroke. We found severe loosening of wrist prosthesis two years after surgery and planned total wrist arthrodesis to avoid further wrist destruction. In revision surgery, both radial and carpal components were easily removed because of complete loosening around bone cement. We applied bone allograft (femoral head) to augment the extensive bone defect after implant removal. The intramedullary nail was used for wrist arthrodesis, which penetrates the grafted bone. Bone union and satisfactory hand function were achieved without any complications. [Clinical importance] Block bone allograft was a viable salvage option to fill and stabilize massive bone defects after removal of total wrist prosthesis.

## P24-2

### Mid- to long-term result of Discovery semi-constrained elbow prosthesis

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Conflict of interest: None

[Purpose] We investigated mid- to long-term results of Discovery semi-constrained Elbow prosthesis. [Methods] We measured the frequency of loosening and radiolucent line around the stem in patients who have undergone TEA with Discovery elbow system for more than 4 years after surgery. All patients were female, mean age 67 (53-81) years old, mean postoperative years 7.0 (4-11) years, 14 cases were primary surgery. [10 rheumatoid arthritis (RA), 4 non-RA], 3 cases were revision (all RA), and 10 cases were trauma. [Results] The loosening of the prosthesis was observed in 3 of 17 cases (18%), all of which were humeral components. 2 of the 3 cases were primary surgery (14%), and 1 case was revision surgery (33%). There was loosening in 1 of 4 non-RA cases (25%), in 2 of 13 RA cases (15%), in 1 of 7 non-trauma cases (14%), and in 2 of 10 trauma cases (20%). The cement fill rate at the tip of the humeral stem was measured to be an average of 42% in the cases with loosening of prosthesis and 86% in the cases without loosening. [Conclusion] The occurrence of loosening of Discovery elbow prosthesis was more observed in revision cases and trauma cases, and radiolucency around the stem was also more common in revision cases.

## P24-3

### Mid-term postoperative results of rheumatoid arthritis patients who underwent linked type total elbow arthroplasty

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Conflict of interest: None

[Objective] We reported the mid-term clinical results of linked type total elbow arthroplasty (TEA) for rheumatoid arthritis (RA). [Methods] Thirty-seven elbows of 33 patients who underwent TEA for RA between 2004 and 2019 at 2 hospitals included in the study. Mean age at the surgery was 69 and a mean follow-up period of 71 months. Range of motion, Japanese Orthopaedic Association elbow treatment performance criteria (JOA score), type of instruments, and postoperative complications were evaluated. [Results] Instruments were Coonrad-Morrey for 11 joints, Discovery for 12 joints, GSB III for 4 joints, and Nexcel for 10 joints. JOA score improved from 41 points before surgery to 74 points at the final follow up, the elbow flexion angle improved from 115 to 131 degrees, and the range of motion from 82 to 105 degrees. Complications included perioperative fracture in 8 cases, infection in 6 cases, and loosening of the peri-implant area in 1 case. [Conclusions] Most of the patients showed improvement in JOA score and elbow flexion range of motion, and the mid-term results showed good results for improvement of the quality of life.

## P24-4

### Clinical results of extensor tendon rupture in rheumatoid hands -reconstruction of the ruptured extensor tendons in the index, middle, ring, and little finger-

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Fujiigekaichouka Seikeigeka

Conflict of interest: None

[Objective] This paper reports the treatment experience of subcutaneous rupture of the extensor tendon of the 4 fingers of rheumatoid arthritis (RA). [Methods] and [Results] Operation method: The indexing finger MP was performed by Swanson implant reconstruction, EPL - EPB cross tendon transfer, volar plate of thumb IP joint was sutured it, four total finger

extension tendons were sutured on the end for the extension tendon, the palm muscle tendon was doubled to the transplanted tendon, and sutured to the near stump. The self-rehabilitation was carried out from the post-operation four week. As of 1 year, the finger tip pinch, side knob, and grip strength have been restored. [Conclusions] Multiple finger ruptures of the extensor tendon in RA are difficult to balance the tendon tension and select the source of force. Reconstruction by bridging tendon transplantation and reconstruction of the rear finger extension mechanism using decompression position taping fixation were obtained. In addition, it was useful as a method of functional reconstruction of RA fingers that the upper limb ADL of the patient was remarkably improved by simultaneous operation of the thumb knob and wrist arthroplasty in a single term.

## P24-5

### A case in which multiple operations were required for two-handed deformity remaining after RA remission with Bio preparation

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Conflict of interest: None

[Case] A 52-year-old woman: After using two Bio-forms, she changed to tocilizumab and became RA remission, but the deformity of both hands progressed, causing problems in daily life and improving appearance and function. The deformity of the right hand were thumb buttonhole deformity, middle finger MP palm ulnar side deformity, and subcutaneous rupture of the extensor (4.5) tendon. In the left hand, the thumb swan neck deformation and the fingers MP joint volar deformity were observed. Resection arthroplasty was performed on the CM joint of the left thumb, and the MP joint of the right thumb was formed using an implant. The MP joint of index, middle finger on the right was formed by soft tissue, and the ring and little finger was subjected to wrist joint formation and tendon transfer. For the finger MP joint, only the index finger implant was used, and the other joints could be preserved. Two years after the final surgery, both hands were highly satisfied with their functions and appearance. [Conclusion] For RA patients who have finger deformity even in clinical remission, finger reconstruction surgery seems to be useful. The destruction of the MP joints, which were deformed after Bio therapy, was minor, and reconstructive surgery was possible while preserving the joints.

## P24-6

### Clinical outcome of the PROSNAP linked elbow prosthesis for the rheumatoid elbows

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Conflict of interest: None

[Object] We investigated the short-term clinical results of total elbow arthroplasty using PROSNAP linked elbow prosthesis for the rheumatoid elbows. [Patients and Methods] We investigated 44 elbows of 48 patients with rheumatoid arthritis. The mean follow-up period was 57.5 (range 12-148) months. Range of motion, Japanese Orthopaedic Association-Japan Elbow Society Elbow Function Score (JOA score), and Mayo Elbow Performance Score (MEPS), and perioperative complications was accessed. [Results] The mean preoperative extension and flexion angle were -35.6 and 108.2 degrees, respectively. The mean preoperative JOA score and MEPS were 46.8 points and 49.2 points, respectively. The mean postoperative extension and flexion range were significantly improved -28.2 degrees and 141.9 degrees. The mean postoperative JOA score and MEPS were also significantly improved 87.8 points and 95.5 points, respectively. Complications included revision in two cases (infection and polyethylene liner breakage), intraoperative fracture in one case, postoperative fracture in three cases. In three cases, soft tissue release was required for postoperative elbow contracture. There was no case of aseptic loosening. [Conclusions] The short term clinical results of PROSNAP for the RA elbows were satisfactory.



## P24-7

### Range-of-motion improvement and complications in total elbow arthroplasty

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Conflict of interest: None

[Objective] The purpose of this study was to investigate changes in range of motion and complications in total elbow arthroplasty (TEA). [Methods] Fourteen elbows in 13 patients who underwent TEA were eligible for inclusion. The mean postoperative follow-up period was 37.1±23.8 months. The range of motion before surgery and at the final follow-up was measured and compared by paired t-test. Intraoperative and postoperative complications were investigated. [Results] The average range of motion before surgery was 105.4 ± 27.3 degrees for flexion and -37.9 ± 17.5 degrees for extension. Postoperative flexion improved to 131.1 ± 13.0 degrees ( $p < 0.001$ ) and extension -27.1 ± 14.4 degrees ( $p = 0.02$ ). During the operation, a fracture of the humerus was observed on one elbow. Postoperatively, 2 elbows showed numbness in the ulnar nerve area, 1 elbow showed triceps dysfunction, and 1 elbow showed loosening of implant. No artificial joint infection was observed. [Conclusions] TEA for rheumatoid arthritis has improved postoperative results with the development of implants. In this study, the range of motion was significantly improved in both flexion and extension. On the other hand, since some complications were observed in 5 of 14 elbows, careful follow-up is necessary.

## P25-1

### Comparison of short-term outcome and function of lesser toe between joint-preserving surgery and resection arthroplasty combined with 1st MTP joint arthrodesis for forefoot deformity due to rheumatoid arthritis

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Conflict of interest: None

[Objective] The purpose of this study was to compare the outcomes of joint-preserving surgery (group P) and resection arthroplasty (group R) combined with 1<sup>st</sup> MTP joint arthrodesis for forefoot deformity due to rheumatoid arthritis (RA). [Methods] We compared the outcomes of 15 cases and 19 feet in which 1<sup>st</sup> MTP joint arthrodesis was performed for forefoot deformity due to RA at our hospital from April 2015 to January 2021, dividing them into a group P (7 cases and 8 feet) and a group R (8 cases and 11 feet). The results of treatment included the JSSF Hallux scale SAFE-Q score, HVA, M1M2 angle, M1M5 angle, Calcaneal pitch angle, Meary's angle. We also measured plantar pressure during walking using Foot scan (RS scan) and paper pull out test. [Results] Whereas JSSF scale was significantly improved, there was no difference all of the SAFE-Q subscales. HVA angle in both groups, M1M2 angle in the group P and M1M5 angle in the group R were significantly improved. There was no significant difference in all parameters between the group P and group R. [Conclusions] As for short-term outcomes, there was no significant difference between joint-preserving surgery and resection arthroplasty combined with 1<sup>st</sup> MTP joint arthrodesis for forefoot deformity due to RA.

## P25-2

### Outcomes of scarf osteotomy with intra-articular stepwise lateral soft tissue release for correcting hallux valgus deformity in rheumatoid arthritis

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Conflict of interest: None

[Objective] This study aimed to investigate the clinical and radiographic outcomes of scarf and Akin osteotomy with intra-articular stepwise lateral soft tissue release for the correction of hallux valgus in patients with rheumatoid arthritis (RA). [Methods] A total of 36 feet in 28 patients with RA who were followed up for a mean duration of 32.0 ± 16.9 months were investigated retrospectively. Clinical outcomes were assessed using the JSSF hallux scale and SAFE-Q. [Results] The procedure resulted in significant HV correction with recurrence rate of 13.9%. JSSF scale and all five SAFE-Q subscale scores significantly improved with no major complications. More than 90% of cases achieved adequate lateral soft tissue release without sacrificing the adductor tendon of the hallux. The foot with recurrent deformity had a larger preoperative deformity than those without. With the cut-off value of preoperative hallux valgus angle of 50.9°, the sensitivity and specificity for the recurrent deformity were 80% and 81%, respectively. [Conclusions] Intra-articular stepwise lateral soft tissue release in combination with scarf and Akin osteotomy provided satisfactory radiographic and patient-reported outcomes for the correction of HV in patients with RA with minimum lateral soft tissue release.

## P25-3

### Comparison of postoperative outcomes for forefoot deformity between rheumatoid arthritis and non-rheumatoid arthritis

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Conflict of interest: None

[Objective] We performed a pre- and postoperative imaging study of hallux valgus (HV) in rheumatoid arthritis (RA) and non-RA patients to evaluate factors involved in HV recurrence. [Methods] Thirty-eight feet (RA: 24 feet, non-RA: 14 feet) that underwent surgery for HV were included in the study. HVA, M1-M2, and M1-M5 were measured preoperatively, postoperatively, and at 1 year postoperatively. [Results] The great toe was subjected to corrective osteotomy proximally or distally, and soft tissue dissection was performed in all cases. The preoperative, postoperative, and 1-year postoperative HVA were 44.1/44.0° ( $P=0.48$ ), 9.9°/7.4° ( $P=0.22$ ), and 22.1/16° ( $P=0.11$ ) in the RA and non-RA groups, respectively. Postoperative recurrence (HVA >20°) was 12 cases/2 cases ( $P<0.05$ ) in the RA group and non-RA group, respectively, and 11 cases/3 cases ( $P<0.05$ ) in the K-wire fixation/plate fixation, with significantly more recurrence in the K-wire fixation and RA group ( $P<0.05$ ). [Conclusions] The recurrence rate was significantly higher in the RA group than in the non-RA group, and there were differences depending on the type of fixation.

## P25-4

### The transition of the patients' characteristics of rheumatoid arthritis undergoing total hip arthroplasty

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Conflict of interest: None

[Objective] We investigate the transition of the characteristics of RA patients who underwent total hip arthroplasty (THA). [Methods] 40 hips underwent THA between 2006 and 2018 are included. From 2006 to 2012 is defined as the early group and after 2012 as the late group. We investigate the type and amounts of drugs as patient background, DAS28-CPR (4) as disease activity, and the percentage of Otto pelvis and acetabular dysplasia (DDH) as radiological evaluation. [Results] 23 hips are classified as the early group and 17 are as the late group. The overall rate of steroid (PSL) use is 50% with an average of 2 mg/day. The amount of PSL significantly decreases in the late group. MTX is administered to 63% of total patients at an average of 5 mg/week with no significant difference.

DAS28-CRP (4) is  $3.00 \pm 0.8$  overall, of which 3 and 7 patients has complete remission, respectively. The percentage of Otto pelvis is 70% and 47% respectively. The percentage of DDH is 13% and 35% respectively. There is no significant difference, but the percentage of Otto pelvis decreases and of DDH tends to increase. [Conclusions] We show the complete remission rate in RA patients undergoing THA is higher than before due to the usage of biologic DMARDs, RA cases with osteoarthritis like features increase.

## P25-5

### Examination of the incidence rates of metatarsal deviation at the osteotomy sites due to the difference in the fixing materials after hallux valgus surgery in patients with rheumatoid arthritis

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Conflict of interest: None

**Object** Proximal rotational closing-wedge osteotomies of the first metatarsal have been performed for hallux valgus deformities in patients with rheumatoid arthritis (RA) at our institute. Osteotomy sites had been fixed by Kirshner wire, but some cases suffered from metatarsal deviations at the osteotomy site. To prevent this complication, we increased the choice of fixing materials. The aim of this study is to compare the incidence rates of metatarsal deviation between the difference of the fixing materials. **Methods** We evaluated 69 RA patients (76 feet) who underwent this procedure between 2017 and 2021. The subjects were divided into two groups: plate fixing (30 feet) and K-wire fixing (46 feet). The incidence rates of metatarsal deviation in each group were evaluated. **Results** The incidence rate of metatarsal deviation in the group who fixed plate (3 feet, 10.0%) was significantly lower than those who fixed K-wire (15 feet, 32.6%) ( $P=0.02$ ). **Conclusions** We found that the incidence rate of metatarsal deviation at the osteotomy sites plate fixing after rheumatoid hallux valgus surgeries was significantly lower than that conducted K-wire fixing.

## P25-6

### Relationship between locomotive syndrome, frailty, and sarcopenia in patients with knee disorders immediately before undergoing TKA

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Conflict of interest: None

[Methods] We evaluated basic attributes, clinical evaluation of knee joint, Dual Energy X-Ray Absorptiometry, locomotive syndrome (LS), frailty, and sarcopenia in all patients with knee disorders scheduled to undergo total knee arthroplasty (TKA) at our hospital from July 2020 to May 2021. [Results] 81 patients (18 males and 63 females) were included. The distribution was as follows: LS stage (no: 0%, 1: 3.7%, 2: 13.6%, 3: 82.7%), frailty (no: 12.5%, pre-frailty: 51.2%, frailty: 36.2%), sarcopenia (no: 92.6%, presence: 4.9%, severe: 2.5%). The incidence of LS stage 3 was high (more than 82%), and the combined incidence of pre-frailty and frailty was high (87%), but the incidence of sarcopenia was low (7.4%). In the LS Stage 3 group, 85% of the patients had pre-frailty or frailty but no sarcopenia. [Conclusions] In patients with knee disorders immediately before undergoing TKA, LS stage 3 patients accounted for more than 82%, and the combined incidence of pre-frailty and frailty patients exceeded 87%, but few patients suffered from sarcopenia. In the LS stage 3 group, 85% of patients had pre-frailty or frailty but no sarcopenia, suggesting that other factors besides skeletal muscle mass loss have a significant effect on the LS of patients with knee disorders.

## P25-7

### Functional reconstructive surgery of the rheumatoid foot results in long-term postoperative decline in physical activity and activities of daily living

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Conflict of interest: None

[Introduction] Functional reconstructive surgeries for the hands and feet are important for improving ADL in long-term affected patients with rheumatoid arthritis. Although the number of surgeries has been increasing, it is still unclear whether they have truly improved the well-being of patients. [Patients and methods] Among 16 patients, 14 patients who were able to be followed up for 6 months were included. Disease-related information was extracted from medical records, and physical activity was calculated using an ultra-small accelerometer. The subjects were followed up for 6 months after surgery and compared between the groups. [Result] The mean age was 66.5 (58-77) years and the mean disease duration was 25.2 (2-49) years. The hand surgery-only group showed an improvement in HAQ and physical activity already 3 months after surgery. In contrast, the group that underwent foot surgery showed a worsening of HAQ and physical activity at 3 months postoperatively. At 6 months after surgery, they finally recovered to the level before surgery. [Discussion] Surgical treatment of the rheumatoid foot was found to force patients to have lower ADL for a long time. It should not be performed merely for relieving pain, but rather, to solve the problem of patients being aware of deterioration.

## P25-8

### Influence of preoperative disease activity on clinical outcomes of total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To investigate whether preoperative disease activity affect the clinical outcomes of TKA in patients with rheumatoid arthritis. [Methods] The study included 41 knees in 36 patients with RA who underwent primary TKA between January 2014 and July 2018 with a minimum of 3-year follow-up. Patients included 4 men and 32 women, with a mean age of 69 years, with a mean disease duration of 12 years. They were classified into two groups (group L: remission + low disease activity, group H: moderate disease activity + high disease activity) by preoperative DAS28ESR. At 12 and 36 months, ROM, KSS (Knee Society Score) and KOOS (Knee injury Osteoarthritis Outcome Score) were compared between the groups. [Results] Both group of patients achieved similar functional ROM at 12 and 36 months. At 12 months, there were no significant differences in KSS, KOOS-S, P, A, but KOOS-QOL of group H was significantly lower than that of L group. At 36 months, there were no significant differences in KSS and KOOS-S, P, A, QOL. [Conclusions] Both group of patients achieved similar functional ROM and reported similar clinical outcomes at 12 and 36 months. But KOOS-QOL of group H was significantly lower than that of group L at 12 months.

## P25-9

### Risk factor for recurrence of hallux valgus deformity after correction surgery for rheumatoid arthritis

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Conflict of interest: None

[Objective] The purpose of this study was to investigate the recurrence rate and factors associated with the recurrence of hallux valgus in rheumatoid arthritis patients 1 year after surgery. [Methods] We reviewed 61 feet in 51 patients (8 men and 43 women, the average age was 67.6 years) with rheumatoid arthritis who underwent hallux valgus correction surgery from 2009 to 2020. 23 feet were operated by the Mitchell method, 20 feet by the modified Mann method, and 18 feet by Swanson arthroplasty. Postoperative recurrence rate, HVA, IMA, DMAA, Hardy classification, lateral sesamoid correction rate were evaluated. [Results] The postoperative recurrence rate was 52.5% (32/61 feet), and one foot required reoperation. The

recurrence rate was not significantly different among the surgical methods. There was no significant difference in recurrence rate between surgical methods. The lateral sesamoid correction rate after surgery was significantly lower in the recurrence group (12.9% vs. 22.6%,  $p=0.037$ ). In the multivariate analysis, the preoperative IMA and lateral sesamoid correction rate were extracted as significant independent factors. [Conclusions] Intraoperative correction of the sesamoid and preoperative IMA may be predictors of recurrence of hallux valgus after surgery.

## P25-10

### Management of patients with rheumatoid arthritis who had concomitant severe joint damage and prominent systemic inflammatory response

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Conflict of interest: None

[Objective] To clarify the desirable management of RA patients with concomitant severe joint destruction and prominent systemic inflammatory response. [Methods] RA patients referred to our department due to concomitant severe weight-bearing joint destruction and prominent inflammatory marker were included in this study. We investigated RA disease activity (SDAI), CRP, physical function (mHAQ), and drug treatment, medical complications before and after TJA. Radiographic joint damage progression during TJA waiting period was also assessed. [Results] Six cases (8 knees, 2 hips) were included. All patients were controlled with medication prior to TJA. Five patients were treated with biologic DMARDs. TJA was performed after an average of 4.9 months, and during the waiting period, the average SDAI, CRP, and mHAQ changed from 23.2 to 9.4, 7.4 to 0.26, and 0.58 to 0.64, respectively, and the ARASHI change score showed progression in 4 joints, improvement in 3 joints, and unchanged in 3 joints. No medical complications during perioperative period were observed. [Conclusions] In RA patients, controlling systemic inflammation prior to TJA improved disease provide desirable outcomes without increasing the risk of perioperative complications.

## P25-11

### Changes in Primary THA for Rheumatoid Arthritis Patients and Treatment Outcomes

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Conflict of interest: None

[Objective] We report about the clinical results of THA for RA patient in 22 years from December in 1997 to December in 2019. [Methods] 39 cases (5.6%) of total 694 THA, were the RA patients. 22 patients were in Stage III, 8 patients in Stage IV. 17 patients were in Class II, 11 patients in III and 2 patients in IV. The average age was 62.1 years old at the time of surgery. Average of preoperative JOA score was 44.8 points. The models used were mainly cementless implants. For the femoral side implant, a fit and fill type (16 joints) was used in the first semester and a taper wedge type stem (21 joints) was used in the second semester. The approach was mainly direct lateral (27 joints) in the first semester and anterior MIS (12 joints) in the second semester. [Results] The postoperative JOA score improved to 83.3 points. There were no complications such as nerve or vascular injury, thrombosis, infection, or dislocation. There were no cases of revision, indicating a good outcome. [Conclusions] The problems of THA for RA include poor bone quality and decreased immunocompetence. However, the frequency of cement use was surprisingly low and there were no threatening infections. With advances in medication, improved implants, and improved techniques, THA is a useful treatment method.

## P25-12

### Changes in walking ability after forefoot reconstruction in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To clarify the changes in walking ability after forefoot reconstruction in patients with rheumatoid arthritis (RA). Methods: Forefoot reconstruction was performed in 185 feet in RA patients at our center. Step size (m), walking speed (m/s), step rate (steps/min), walk ratio (m/steps/min), Pain VAS, Global VAS, and Face Scale were investigated before surgery and one year after surgery. Based on the preoperative disease activity, the remission group was compared with the non-remission group. Results: Overall step rate did not change after the operation, however step size, walking speed, and walk ratio improved significantly. Walk ratio improved significantly in the remission group, but not in the non-remission group. Although there was little change in Pain VAS as a whole, Global VAS and Face Scale improved significantly. Conclusion: Forefoot reconstruction improved walking ability and provided happiness of the patients. It is important to control disease activity as much as possible in order to maximize a favorable effect of surgery.

## P25-13

### Changes in Plantar Pressure Distribution Following Modified Mitchell's Osteotomy and Shortening Oblique Osteotomy for Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] To evaluate changes in plantar pressure after forefoot joint-preserving surgery consisted of modified Mitchell's osteotomy (mMO) and shortening oblique osteotomy (SOO). [Methods] 26 feet in 23 RA patients were evaluated. Background parameters for pain/general health -VAS, DAS28, SDAI, JSSF scale, HVA, M1/2 and M1/5, peak pressure in 9 sections for plantar pressure distribution were measured before surgery and at 1 year after surgery. The percentages in which maximum or minimum peak pressures (MXP or MNP) occurred in each section were also evaluated. [Results] Significant improvement was noted in P/G VAS, JSSF scale, HVA, M1/2 and M1/5. Peak pressure at the 1<sup>st</sup> MTP increased and that at the 2<sup>nd</sup> MTP decreased significantly. Preoperative MXP was observed in 23.1% of feet at the 1<sup>st</sup> MTP and the 3<sup>rd</sup> MTP. Postoperative MXP was observed in 34.6% of feet at the 1<sup>st</sup> MTP, and in 23.1% of feet at the 1<sup>st</sup> IP. Preoperative MNP was observed in 30.8% of feet at the 1<sup>st</sup> MTP and the 5<sup>th</sup> MTP, and in 26.9% of feet at the medial midfoot. Postoperative MNP was observed in 46.2% of feet at the medial midfoot, and in 30.8% of feet at the 5<sup>th</sup> MTP. [Conclusions] The combination of mMO and SOO can be an acceptable option for RA patients in terms of changes in plantar pressure distribution.

## P25-14

### Examination of predictors of postoperative wound healing delay in forefoot surgery for rheumatoid arthritis

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Conflict of interest: None

Background: The purpose of this study was to evaluate postoperative wound healing delay in forefoot surgery of rheumatoid arthritis (RA) patients performed at our hospital and to investigate its predictors. Methods: From January 2004 to December 2020, the number of RA patients who underwent forefoot surgery was 56 and 96 pairs. Age, gender, smoking rate, BMI, RA duration, preoperative blood glucose level, CRP, erythrocyte sedimentation rate, MMP3, RF, ACPA positive rate, MTX, BIO usage



rate, GC usage rate, joint-sparing surgery rate, surgery time, preoperative and postoperative HV (hallux valgus) angle and M1 / 2 (First-second intermetatarsal) angle A regression analysis was performed. Result: Patient background is female: 91 cases (95%), mean age (years): 61.6, duration of illness (years): 21.4, RF: 72 cases (88%), MTX: 63 cases (66%), BIO: 50 cases (55%), operation time (minutes):  $150.9 \pm 55.4$ . Postoperative wound healing delay was observed in 22 of 96 feet (23.8%). Multivariate logistic regression analysis to examine risk factors for postoperative wound healing delays showed males ( $p = 0.025$ ), extended surgery time ( $p = 0.009$ ) was the risk factor. Consideration/Conclusion: Shortening the operation time may lead to a reduction in the incidence of postoperative wound healing delay.

## P26-1

### Bone union rate after prophylactic surgery for incomplete atypical femoral fracture

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Conflict of interest: None

[Objective] Prophylactic surgery to incomplete atypical femoral fracture (AFF) is mostly reported that “fractures healed radiographically or clinically without revision surgery”, although there are scarcely reported by large number of patients. We retrospectively evaluated union rate of incomplete AFF fracture site. Bone union was defined as the disappearance of both beaking and fracture line, and partial bone union was defined as the disappearance of beaking or fracture line. [Methods] Patients of incomplete AFF were performed surgery prophylactically and followed up more than 1 year by plain radiography. [Results] 13 femurs performed surgery by intramedullary nailing and 2 femurs performed by Ender nail. 5 femurs were union and 2 femurs were partially union. Revision surgery needed 2 femurs, which were both used Ender nail. 5 femurs were rheumatic disease patients and only one femur was union, which found out iatrogenic fracture line around proximal screw. 10 femurs were non-rheumatic disease patients and 4 femurs were union and 2 femurs were partially union. [Conclusions] There is possibility that incomplete AFF of rheumatic disease is difficult to achieve bone union, although there is no statistically significant because of still small number of patients.

## P26-2

### Clinical Impact of Low Nutritional Status on Osteopenia of the Lumbar Spine in Elderly Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] This study aimed to investigate the relationship between malnutrition and osteopenia of the lumbar spine in elderly RA patients. [Methods] The authors retrospectively extracted data for RA patients  $\geq 65$  years old. A low nutritional status was defined as a geriatric nutritional risk index of  $<98$ . The patient background data were recorded. The Primary Outcome was osteopenia of the lumbar spine (T score  $<-1.0$ ). Propensity score (PS) matching was performed to adjust the patient background. [Results] A total of 98 patients were enrolled (79.6% female; mean age 67.8 years), and 26 patients (26.5%) had a low nutritional status (81% female; mean 70.8 years). Before PS-matching, there was no significant difference in biologic use (50% vs. 37.5%;  $p = 0.35$ ) and osteopenia (61.5% vs. 38.9%;  $p = 0.065$ ) between the two groups, although patients in the low nutrition group were frequently treated with steroid (64% vs. 39.4%;  $p = 0.039$ ) and showed higher disease activity (DAS28-CRP, 2.7 vs. 2.1;  $p = 0.028$ ). After 1-by-1 PS-matching, the low nutrition group showed higher rate of osteopenia (60% vs. 10%;  $p = 0.002$ ) with odds ratio of 13.5 (95% confidence interval 2.43-74.9;  $p = 0.0029$ ). [Conclusions] Malnutrition in elderly RA patients was associated with osteopenia of the lumbar spine.

## P26-3

### Whether low nutritional status increase the surgical site infection in RA patients?

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Conflict of interest: None

[Objective] We examined whether low nutritional status increase the risk of surgical site infection in RA patients or not. [Methods] We evaluated 749 patients data who was performed orthopaedic surgery in 2017-2018 (Rheumatoid arthritis (RA): 162; others: 587). We evaluated weight, height, sex, duration of operation, implant use, type of surgery, total volume of bleeding, use of MTX, biologics, prednisolone, blood albumin, CRP, total protein, cholesterol, lymphocyte, and nutritional status using Geriatric nutritional risk index and Controlling Nutrition Status. [Results] Seventeen patients affect surgical site infection, 5 patients was RA and 12 patients were others. There was no statistical differences of rate of surgical site infection between RA patients and others. Only male, higher height, and longer duration of operation time increased the rate of surgical site infection in all patients. Geriatric nutritional risk index showed that low nutritional status increased the rate of surgical site infection in RA patients. [Conclusions] Our findings showed that only in RA patients, low nutritional status increased the risk of SSI. Improvement of nutritional status is more important in RA patients before operation.

## P26-4

### Impact of the change of drug therapy on the patient background in surgical cases of rheumatoid arthritis

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Conflict of interest: None

[Objective] We examined how the changes in drug therapy for rheumatoid arthritis affected the background of surgery cases. [Methods] 1020 RA patients were examined. The age of the patients was categorized as Group A (before MTX approval: 1990~1998), Group B (after MTX approval but before Bio approval: 1999~2002), Group C (after Bio approval but before JAK-I approval: 2003~2010), and Group D (after JAK-I approval: 2011~2020). [Results] The mean age at surgery was 60.9 years in Group A, 61.7 years in Group B, 64.2 years in Group C, and 66.3 years in Group D. The PSL use rate was 49.0% in Group A, 61.1% in Group B, 50.0% in Group C, and 20.9% in Group D. The MTX use rate was 64.4% in group B, 75.0% in group C, and 59.2% in group D. The Bio use rate was 1.9% in group C and 33.5% in group D, and the JAK-I use rate was 0.7% in group D. Preoperative CRP (mg/dl) was 4.1 in group A, 2.1 in group B, 1.6 in group C, and 0.6 in group D. Preoperative ESR (mm/h) was 68.0 in group A, 55.8 in group B, 54.0 in group C, and 33.0 in group D, and decreased significantly with age. [Conclusions] With the introduction of new medications, the use of NSAIDs and PSLs and preoperative inflammatory values have decreased, and it has become possible to perform surgery with good preoperative disease control.

## P26-5

### Trend of number and commodities of lower extremity surgery among the patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Surgical procedures in rheumatoid arthritis (RA) is reduced due to the biologics but the trend since 2010, when “Treat-to-Target” was proposed, is unclear. In this study, we investigated the trend of RA-related lower extremity surgery at our hospital since 2010. [Methods]

We retrospectively investigated the surgical sites, medications, clinical scores and comorbidities from the medical records of patients underwent RA-related lower extremity surgery from 2010. [Results] 274 surgeries underwent in 10 years and there was no drastic decrease in each site, each year. The mean age at surgery was around 65, and more than 80% were women. DAS28-ESR was around 4, and mHAQ was around 1. About 30% of patients had respiratory disease, and there was a trend of obstructive dysfunction. Wound infections occurred in 7.6% of patients, 42.8% of whom were on biologics. Deep vein thrombosis (DVT) occurred in about 20% of THA and TKA. [Conclusions] There was no drastic decrease of surgery from 2010, as there was when biologics were launched. For RA patients, we should pay attention to inflammatory anemia, infection due to immunosuppressive drugs, and DVT in prostheses. Perioperative management becomes more important due to increase in late onset RA and the aging of RA patients.

## P26-6

### Survey of patients with rheumatoid arthritis performed surgery in a regional core hospital

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Conflict of interest: None

[Purpose] To verify the characteristics of rheumatoid arthritis (RA) patients who received surgical treatment at our hospital that is a regional core hospital. [Method] We analyzed RA patients performed surgery in our hospital's orthopedic department from January 2015 to February 2021. Furthermore, we included only those who could obtain their clinical parameters. [Results] The average value was 70.6 years of age, BMI 23.0, the duration period was 22.9 years, the preoperative Larsen Grade was 3.75. The rate of ACPA positive patients, joint replacement surgery, small joint surgery, and spinal surgery were 61.3%, 48.4%, 35.4% and 16.1%. The average improvement values of CRP, MMP-3, and RF before and after surgery were 0.55 mg / L, 36.1 ng / mL, and 26.7 IU/mL. The reduction of MTX and PSL were 0.65 mg / week and 0.66 mg / day. Small joint surgery had a significantly lower reduction of PSL than joint replacement surgery. [Conclusion] Most of patients performed surgery at our hospital have relatively long duration period and ACPA. Their inflammation and disease activity might be suppressed after surgery, and it seems that the dose of oral medication has been reduced. Moreover, joint replacement surgery might reduce steroid dose in RA-patients.

## P26-7

### The risk factor related to life prognosis after cervical spine surgery in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] The risk factor related to life prognosis after cervical spine surgery in patients with rheumatoid arthritis (RA) was analyzed. [Methods] 138 patients with RA who underwent first cervical spine surgery from 2001 to 2020 were investigated retrospectively. Survival time analysis and risk factor analysis for life prognosis after surgery were done by Kaplan-Meier plots and cox regression analysis. Investigated factor was age, surgery time and bleeding volume, American Society of Anesthesiologists-Physical Status, Charlson Comorbidity index, body mass index, drug used, serum CRP and albumin (sAlb), and types of cervical spine lesion (CSL). [Results] 53 patients died. Median survival after surgery was 12.3 years. In univariate analysis, elderly, low level of sAlb, subaxial subluxation (SAS), high intake of prednisolone (PSL), no or low intake of methotrexate were detected the risk factor of short prognosis. In multivariate analysis, high intake of PSL, low level of sAlb and SAS remained as the risk factor. [Conclusions] Elderly and undernutrition were relevant to prognosis of patients with RA requiring cervical spine surgery. In addition, progressive CSL and high intake of PSL were suggested to shorter lifetime

of the patients with RA after cervical spine surgery.

## P26-8

### Tuberculous arthritis of the rheumatoid knee treated with two-stage total knee arthroplasty

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Conflict of interest: None

[Case] A 80-year-old woman treated for rheumatoid arthritis with Etanercept presented with severe pain and swelling of the knee. A diagnosis of miliary tuberculosis with tuberculous arthritis of knee was made by culture of sputum and joint fluid, and anti tuberculous chemotherapy was started, which successfully improve her chest symptom. However, the patient became disabled by knee pain, thus, through synovectomy and debridement was performed under arthroscopically. Although no sign of recurrence of the arthritis postoperatively, she still required a wheel chair for mobility due to knee pain and total knee arthroplasty (TKA) was indicated. Postoperatively, the range of motion was increased from -30/100 degree to 0/120 degree and the patient was able to walk with a single cane. 8 month after the TKA, the patient remained free of systemic and local infection with no evidence of recurrent tuberculosis. [Conclusions] Longer follow-up period might be necessary to clarify the prognosis of the disease and the safety of the TKA.

## P27-1

### Clinical effect of guselkumab on Pustulotic arthro-osteitis (PAO)

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Conflict of interest: None

[Purpose] To investigate the therapeutic effect of guselkumab on palmo-plantar pustulosis osteoarthritis METHODS: Human anti-human IL-23p19 monoclonal antibody (guselkumab) against patients with pustulotic arthro-osteitis (PAO) who are visiting our department between March 2019 and December 2020.) Will be examined in 10 cases. All females had an average age of 55.3 ± 9.9 years, an average age of PPP onset 48.7 ± 12.8 years, an average age of PAO onset 50.8 ± 11.9 years, and an average observation period of 20.3 ± 10.2 months. As an evaluation method, ASDAS and the degree of improvement of ASDAS were evaluated as disease activity evaluation. Results: ASDAS showed a significant improvement after 6 months of administration, with an average of 2.8 ± 1.3 before administration, an average of 1.8 ± 0.9 after 6 months, an average of 1.5 ± 0.9 after 12 months, and 1.3 ± 0.9 after 24 months. The ASAS improvement was 50% clinical improvement at 6 months and 50% significant improvement at 12 and 24 months. [Conclusion] The clinical effect of guselkumab on PAO was 50% for clinical improvement up to 6 months, but after 12 months, it was all inactive and low disease activity, so it was judged as a therapeutic effect. Requires a follow-up period of 6 months or more.

## P27-2

### Efficacy of Guselkumab Across BASDAI Components in Treating Axial-related Symptoms of Psoriatic Arthritis: Results From Two Phase 3, Randomized, Placebo-controlled Studies

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Conflict of interest: Yes

[Objective] To evaluate the efficacy of guselkumab (GUS) on components of the BASDAI in improving symptoms of axial manifestations of active psoriatic arthritis (PsA) patients (pts) using pooled data from DISCOVER-1&2. [Methods] Pts were randomized to GUS 100 mg every 4 weeks (Q4W); GUS 100 mg at Week (W)0, 4, and Q8W; or PBO Q4W W0-20, then GUS 100 mg Q4W from W24; data are presented for Q8W and PBO. These analyses included pts identified by the investigator as having axial symptoms and sacroiliitis (based on prior X-ray or MRI or screening X-ray). [Results] Among 209 pts with axial disease (91 GUS Q8W, 118 PBO), mean total BASDAI scores at W0 were 6.5 and 6.6, respectively. This subgroup had a higher mean CRP level at BL and a higher proportion with enthesitis and included a slightly higher proportion of males versus the total population. Mean scores for all six BASDAI components, including spinal pain, decreased through W24 in GUS-treated pts, with separation from PBO as early as W8; improvements were maintained at W52. [Conclusions] Among PsA pts with axial symptoms and sacroiliitis, GUS treatment resulted in lower mean scores for all six BASDAI components compared with PBO as early as W8 and through W24, with mean scores maintained at W52.

### P27-3

#### Guselkumab Treatment Shows Rapid Onset of Effect on Components of American College of Rheumatology Response Criteria: Results of 2 Randomized Phase 3 Trials

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Conflict of interest: Yes

[Objective] To assess the effects of guselkumab (GUS) across individual components of ACR response in psoriatic arthritis (PsA) patients (pts) in DISCOVER-1&2. [Methods] In DISCOVER-1&2, pts were randomized and treated with GUS 100 mg Q4W (N=373); GUS 100 mg at Week (W)0 and W4, then Q8W (N=375); or placebo (PBO; N=372); Q8W data are presented. ACR20 response is defined as  $\geq 20\%$  improvement from baseline in tender joint count (0-68 [TJC68]) and swollen joint count (0-66 [SJC66]), and  $\geq 20\%$  improvement from baseline in  $\geq 3$  of 5 assessments: Patient Assessment of Pain [Pt Pain], Patient Assessment of Global Disease Activity (arthritis) [PtGA], Physician Assessment of Global Disease Activity [PGA], Health Assessment Questionnaire Disability Index (HAQ-DI), and CRP. [Results] Median time to response for all components occurred earlier with GUS than PBO. 46.1-59.7% of GUS-treated pts had  $\geq 20\%$  improvement in CRP and TJC68/SJC66/PGA at W4, and 43.5-49.9% in HAQ-DI, PtGA, and Pt Pain by W8. By W24, >78% of GUS-treated pts had  $\geq 20\%$  improvement in SJC66/TJC68/PGA, 61.1-63.7% in PtGA, CRP, and Pt Pain, and 52.5% in HAQ-DI. [Conclusions] GUS 100 mg Q8W pts demonstrated ACR20 improvements with separation from PBO in ACR components as early as W4.

### P27-4

#### Tonsillitis-related arthritis: a report of 2 cases whose arthritis disappeared after tonsillectomy

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Conflict of interest: Yes

[Objective] Our case demonstrates that tonsillectomy is effective for the treatment of tonsillitis-related arthritis to eradicate the bacterial infection in the tonsils. [Methods] A 49-year-old man developed acute aseptic arthritis of the nonmigratory and asymmetrical type in his knee, ankle, and bilateral metatarsal joints 13 days posttreatment with antibiotics for acute tonsillitis. He was diagnosed with tonsillitis-related arthritis after other rheumatic diseases were ruled out. Treatment with salazosulfapyridine, methotrexate, and methylprednisolone for 3 months did not completely improve. Then, tonsillectomy was undertaken and that arthritis rapidly improved. [Results] *Finexgoldia magna* (previously *Peptostreptococcus magnus*) was cultured from the microabscesses of the resected tonsils. After outpatient follows, the patient did not experience a relapse of arthritis for more than 2 years without any treatment. [Conclusions] It is noted that tonsillectomy is necessary to remove the tonsillar microabscesses and eradicate bacterial infection of the tonsils, especially for patients with a prolonged and/or recurrent course of PSRA and/or tonsillitis-related arthritis.

### P27-5

#### Effectiveness of tooth extraction in pustulotic arthro-osteitis patients with odontogenic focal infection

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Conflict of interest: None

[Objective] To evaluate the effectiveness of tooth extraction in pustulotic arthro-osteitis (PAO) patients with odontogenic focal infection. [Methods] We conducted retrospective observation study. 8 PAO patients with odontogenic focal infection, who had experienced tooth extraction at National Hospital Organization Osaka Minami Medical Center between December 2018 and April 2021, were investigated. ASDAS was used to evaluate the disease activity of PAO. [Results] ASDAS was 2.20 $\pm$ 1.24 (n=8) before tooth extraction, 1.54 $\pm$ 0.65 (n=8) 6 months after tooth extraction, 1.17 $\pm$ 0.44 (n=6) 12 months after, 1.58 $\pm$ 0.62 (n=4) at the final follow-up. Compared between improved group (n=5; lower ASDAS at the final follow-up than before tooth extraction) and non-improved (n=3), PAO onset age was 62.2 $\pm$ 12.0 years (n=5) vs 51.0 $\pm$ 10.7 years (n=3); current smoker ratio was 25.0% (n=4) vs 66.7% (n=3); ASDAS before tooth extraction was 2.46 $\pm$ 1.45 (n=5) vs 1.79 $\pm$ 0.55 (n=3). ACPA, RF, and HLA-B27 were negative in 7 cases (unknown in 1 non-improved case). [Conclusions] This study suggests that tooth extraction treatment is effective in PAO patients with odontogenic focal infection. However, there are some non-improved cases. This may be related to some factors such as smoking, early age of PAO onset, and low disease activity before the treatment.

### P27-6

#### Clinical features, treatment methods and therapeutic effects of SAPHO syndrome

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Conflict of interest: None

[Objective] To review the clinical features and treatment of SAPHO syndrome [Methods] An retrospective study was performed on patients diagnosed as SAPHO syndrome who visited our hospital between 2002



and September 2021. [Results and Conclusions] 28 patients were included. Of the 28 patients, mean age was 54.3 years old, 39.3% had metal allergy, 57.1% had smoking history, 53.6% were CRP positive. Cutaneous symptoms were observed in 25 patients, and the types were as follows. 23 patients had palmoplantar pustulosis alone, 1 patient had acne alone, and 1 patient had both of palmoplantar pustulosis and acne. The onset of these 25 patients were as below, 16 patients were skin predominant type, 7 patients were coincidental type and 2 patients were joint predominant type. Of the 28 patients, the sites of arthritis were as below, 23 patients were sternoclavicular arthritis, 9 patients were axial spondyloarthritis-related changes, 16 patients were peripheral arthritis. The most recent treatment were as below. No treatment were 3, Biotin were 12, NSAIDs were 14, bisphosphonate were 2, immunomodulators were 7, MTX were 9, bDMARDs were 3, PSL was 1, and chemotherapy was 1. Almost all patients showed improvement. We report the details the subsequent clinical course.

## P27-7

### Denosumab treatment affect relief of inflammation and pain of sternocostoclavicular hyperostosis: a case report

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Conflict of interest: None

[Background] Sternocostoclavicular hyperostosis (SCCH) is treated with Nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (cDMARDs), bisphosphonates and biologics, but there is no standardized treatment. In this study, we report a case in which denosumab treatment was effective in SCCH patient who did not respond well to NSAIDs and cDMARDs. [Case presentation] A 70-year-old female patient had been suffering from swelling and pain around the right clavicular for more than 10 years. She was referred to our department, and some examinations were performed. Laboratory results showed elevated inflammatory marker. MRI showed intramedullary speckled change, sclerosis and thickening of the sternocostoclavicular region. Bone scintigraphy showed uptake strongly in the same area. Clinical and imaging findings were confirmed the diagnosis of SCCH. The patient was treated with salazosulphapyridine and methotrexate but symptoms did not improve. The patient refused to biopsy of clavicular, so denosumab was administered instead of biologics. Swelling and pain improved immediately after denosumab administration. Laboratory results showed a marked decrease inflammatory marker. The patient should be carefully monitored for recurrence of clinical symptoms of SCCH.

## P27-8

### Successful treatment of a human anti- IL-17 monoclonal antibody to a young girl with axial spondyloarthritis

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Conflict of interest: None

[Introduction] Axial spondyloarthritis (axSpA) is infrequent in the children and is difficult to diagnose because the appearance of those axial joint disorders may be delayed. In this report, we describe a case of a girl with axSpA unresponsive to anti-TNF $\alpha$  inhibitors and improved with anti-IL-17A monoclonal antibody. [Case] The patient showed polyarticular pain at 7 years old and was treated for poly-articular juvenile idiopathic arthritis. She was unable to take methotrexate orally due to lack of cooperation, and anti-TNF- $\alpha$  inhibitors were first administered subcutaneously. However, adequate remission wasn't obtained. Subsequently, symptoms of atlantoaxial rotatory fixation became apparent, and lumbar MRI at the age of 17 showed sacroiliac arthritis, leading to the diagnosis of JSpA. Since anti-TNF $\alpha$  inhibitor therapy did not resolve her symptoms, subcutaneous injection of an anti-IL-17A monoclonal antibody was introduced at this time and it showed improvement in her symptoms. [Discussion] In recent years, spondyloarthritis has become a concern in the adult rheuma-

tology, as a result, it has been warned not to be overlooked in children. In this study, treatment targeting IL-17 seemed to be an option for JSpA with poor response to treatment.

## P28-1

### Examination of osteoporosis/osteopenia and obesity in psoriatic arthritis

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Conflict of interest: None

[Purpose] To investigate osteoporosis/osteopenia and obesity in psoriatic arthritis. [Method] Bone mineral density measurement and DXA (Dual Energy X-ray Absorptiometry) were performed on patients with psoriatic arthritis (PsA) who were visiting our department from January 2019 to December 2020. Body composition was measured. The number of cases was 275, 160 males, 115 females, average age  $56.2 \pm 10.8$  years, and average BMI  $24.4 \pm 3.9$ . The YAM value and T-score of the lumbar spine and femur were measured. As body composition values, body fat percentage (%) and android/gynoid (A/G ratio) were measured. In addition, a history of fractures of the lumbar spine and proximal femur was confirmed to determine fragile fractures. (Results) Osteoporosis was found in 21 cases (7.64%) and osteopenia was found in 33 cases (12.0%). In DXA, the mean T-score was lumbar spine  $-0.053 \pm 1.627$  and femur  $-0.120 \pm 1.254$ . As for the body composition results, the average body fat percentage was  $31.1 \pm 8.31$  and the A / G ratio was  $1.19 \pm 0.24$ . [Conclusion] The rate of osteoporosis and osteopenia in PsA is as high as 19.6%, so screening is considered necessary. In addition, The A / G ratio is 1.19, and screening for comorbidities and guidance on proper diet and exercise are more necessary.

## P28-2

### Initial symptom of axial spondylitis

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Conflict of interest: None

[Objective] To examine initial symptom sites with axial spondyloarthritis (axSpA) by onset age. [Methods] This study examined initial symptom sites and onset ages in 69 patients with axSpA between January 2004 and June 2021. We analyzed whether initial symptom sites with axSpA were axial joint or peripheral joint by onset age. [Results] 69 patients (mean onset age 29.5 years), 75% men, 62% human leucocyte antigen B27 positive, 91% ankylosis spondylitis were included. Initial symptom sites were low backs (23 patients), hips (20 patients), buttocks (11 patients), knees (11 patients), necks (7 patients), fingers (5 patients) and shoulders (3 patients). 49% patients had only axial joints with initial symptom and 45% patients had only peripheral joints. For patients with onset age less than 16 years, 33% patients had only axial joints with initial symptom and 66% patients had only peripheral joints. [Conclusions] About half of the patients with axSpA had only peripheral joints with initial symptom. In particular, many juvenile onset axSpA had only peripheral joints with initial symptom.

## P28-3

### Clinical outcome for osteoporotic vertebral fracture with ankylosing spinal hyperostosis

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Conflict of interest: None

[Objective] The osteoporotic vertebral fracture is increase one of a major issue in Japan within a super-aging society. As for the body of vertebra fracture due to ankylosing vertebral hyperostosis, bone union is not

often obtained by conservative treatment, many cases need to surgical treatment. [Methods] We investigated 7 men, 7 women patients at our hospital from November 30, 2018 to November 30, 2020. We examined an injury level, a cause of injury, a period to treatment and methods for surgery cases. [Results] The conservative treatment was two patients due to poor general condition. Nine patients underwent posterior surgery and 3 patients underwent anterior-posterior surgery. Periods from injury to a hospital visit were from one day to 2 weeks, and there were 5 patients which they visited a hospital after 7 days from the injury. [Conclusions] An osteoporotic vertebral fracture with ankylosing vertebral hyperostosis may occur after the minor trauma. Many cases are hard to diagnose using only X-rays. Most cases are surgical treatment is necessary, and some cases need to consider that spinal reconstruction both an anterior and posterior column of spine.

## P28-4

### Evaluation of enthesis by ultrasonography (which is the best evaluation site?)

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Conflict of interest: None

[Objective] In rheumatism such as spondyloarthritis, it is important to examine which site is the most suitable enthesis site in ultrasonography, clinically. [Methods] The subjects were 55 males and 255 females with suspected or confirmed rheumatic diseases who underwent joint ultrasonography from November 2020 to August 2021, and were  $59.8 \pm 17$  years old. Lesions found at the enthesis of the elbows, knees, and heels were analyzed by site and age. Swelling, loss of tendon fibrillary pattern and bursitis were classified as inflammatory signs, and bone erosion, calcification, bone cortex irregularities, and osteophytes were classified as structural changes. [Results] The rate of either inflammatory signs or structural changes, the rate of structural changes only, and the Power Doppler (PD) signal rate were 38.7%, 20.5%, and 12.5% for the triceps tendon, tibial tubercle 16.5%, 8.5%, 0%, patellar tendon inferior pole 8.8%, 1.8%, 0.7%, patellar quadriceps tendon 51.1%, 26.5%, 3.5%, Achilles tendon 61.1%, 35.7%, 10.3%, the plantar fascia was 13.3%, 8.3%, and 1.3%, respectively. Structural changes tended to increase with age. [Conclusions] From this result, in ultrasonography, the enthesis sites with high significance are maybe the triceps tendon and the Achilles tendon.

## P28-5

### A case of elderly-onset spondyloarthritis mimicking polymyalgia rheumatica

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Conflict of interest: None

A 77-year-old Japanese woman presented because of the posterior neck and lower leg pain with CRP elevation. NSAIDs failed to improve her symptoms, but 10 mg of prednisolone (PSL) rescued them. When the dose of PSL was decreased, her pain worsened, spread throughout her body, and made her difficult to walk. Under the temporary diagnosis of polymyalgia rheumatica (PMR), she was given 20 mg of PSL that resolved her symptoms. For further evaluation of her condition, she was referred to our hospital. On physical examination revealed back tenderness and swelling of the right knee joint. Laboratory examination showed serum CRP elevation, but autoantibodies and infection-related tests were all negative. At sacroiliac joints, particularly right-sided, radiography, MRI, and bone scintigraphy showed joint space narrowing, high-signal area (STIR), and increased accumulation, respectively. The patient was diagnosed with spondylarthritis (SpA). Golimumab was administered, which was effective and the dose of PSL was tapered without flare. This case indicates that SpA should be considered as a differential diagnosis when a patient complains of joint/muscle pain suggesting PMR because elderly-onset SpA had severe systemic symptoms such as fever, weight loss, and high inflammatory responses.

## P28-6

### A case of peripheral spondyloarthritis with single joint lesion

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Conflict of interest: None

[Introduction] Spondyloarthritis (SpA) is a systemic disease that causes characteristic bone and joint change due to enthesitis. We report a case of peripheral SpA that developed only in a single MCP joint. [Case] A woman in her 70s visited our hospital because of persistent pain in her fingers, toes, and knee joints. She is negative for both RF and ACPA. She was diagnosed with osteoarthritis of the DIP of finger and knee joints and hallux valgus by X-ray and joint ultrasonography. And osteophytes, erosions, and extensor tendinitis were found in the right 4th MCP joint. Enthesitis were also observed on the right fingernail beds. Synovitis was not found in the wrist, fingers, or toes joints. HR-pQCT examination of the fingers was performed for the purpose of close examination. In the right 4th MCP, joint space narrowing and pencil in cup deformity with osteophytes and erosions was observed. The DIP joints were not found except for age-related deformation. Based on the above, a diagnosis of peripheral SpA of the right 4th MCP joint was made. [Conclusions] We experienced peripheral spondyloarthritis that developed only in a single joint. It is possible that the enthesitis of nail bed spread to the extensor tendons.

## P28-7

### A case report: severe ankylosing spondylitis in patient with psoriatic arthritis

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Conflict of interest: None

39 years old male [Chief complaint] ankylosing spondyloarthritis [Present history] The disease psoriatic was on set in 2008. After 1 year, cyclosporine was medicated for psoriatic, but was not useful. Joint pain was controlled by NSAIDs. After 3 years, Uveitis, cataract and tongue cancer was occurred. After 10 years from onset, ankylosing spondylitis was shown in X ray. [Complication] Uveitis, cataract and tongue cancer [disease treatment] cyclosporine was failed etretinate and liniment [clinical findings] The thoracic vertebra is straightforward in 30 degree of flexion. He can't look forward with ankylosing spin. Elevation of a joint of both shoulders admits. Joint effusion was in bilateral knees. CRP 11.88 mg/dl and MMP-3 were 1468 ng/ml and a high value without RF and ACPA elevation. HLA-B27 was negative. [Consideration] Ankylosing spondyloarthritis was doubted, but it was negative for underlying disease. We diagnosed the rare case of axial SpA.

## P28-8

### A case that spondyloarthritis became apparent after receiving COVID-19 vaccine

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Conflict of interest: None

[Presentation of case] A 32-year-old man got COVID-19 vaccine. A fever appeared just after the second vaccine, and it was relieved in several days. Two weeks after the second vaccination, he got a fever again. Fur-

thermore, joint pain at elbows, lower back, hip, and knees, and chest pain on the left side occurred. He visited internal medicine, and oral prednisolone (PSL) 30 mg/day was started. The day after starting PSL, both joint and chest pain were diminished. He took PSL for a week and finished, at which time the symptoms did not recur. One month after finishing PSL, neck and back pain occurred, and left chest pain became active again. These symptoms diminished immediately with PSL 15 mg/day but flared up again after stopping. Hip MRI showed high intensity at both sacroiliac joints on fat-suppressed T2-weighted image. HLA-B27 was positive, thus we considered his clinical conditions related to spondyloarthritis (SpA). The pain was relieved without medication, but it was still there. We started Adalimumab as SpA treatment. [Clinical significance] Hip X-ray showed osteosclerosis slightly at the right sacroiliac joint. It is unlikely that osteosclerosis occurred in several months. Hence, we suggest he had SpA-like pathophysiology potentially and it became apparent after vaccination.

## P28-9

### Psoriatic arthritis development during pembrolizumab administration in a patient with lung cancer: case report

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Conflict of interest: None

We report a 59-year-old man with lung cancer recurrence in the mediastinal lymph nodes after lobectomy. Programmed death-ligand 1 tumor proportion score was 70% so four courses of carboplatin + pemetrexed + pembrolizumab and pembrolizumab maintenance therapy were performed. After 10 courses, psoriasis-like rashes, polyarthritis and dactylitis appeared. MRI showed no sacroiliitis, but showed knee-joint enthesitis and finger tendonitis/arthritis. The patient was diagnosed with psoriatic arthritis with a negative blood test for rheumatoid factor and a total of 4 points according to CASPAR classification. Pembrolizumab was discontinued because of these immune-related adverse events (irAE) but no improvement was observed. Topical steroids for rashes and prednisolone (PSL) 5 mg + methotrexate (MTX) 6 mg/week were started. But arthritis persisted, so PSL was increased to 20 mg and symptoms improved significantly. MTX was gradually increased to 10 mg/week, PSL was gradually reduced to 10 mg, and the arthritis and eruptions remained in remission. No progression of the lung cancer has been observed without any treatments. Cases of psoriatic arthritis as irAE during immune checkpoint inhibitor administration are extremely rare and will be reported with a review of the literature.

## P28-10

### A case of SAPHO syndrome diagnosed after non-traumatic clavicle fracture

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Conflict of interest: None

[Case] A 46-year-old woman presented with pain from the clavicle to the anterior chest since her 30s. Four years before presentation, she broke her left clavicle without any trauma. Three months later, she developed left clavicle fracture again without any triggers. She was referred to our hospital because of the pain in right clavicle and shoulder. At the presentation, she had a pustular skin rash on the sole of her foot and tenderness in the right clavicle and right sternoclavicular joint. Bone scintigraphy showed accumulation in bilateral sternoclavicular joints, first sternal rib joint, bilateral costal cartilages, and left clavicle. We diagnosed SAPHO syndrome because of a history of palmoplantar pustulosis (PPP) and the result of bone scintigraphy. Non-traumatic clavicle fracture is rare, because clavicle fractures are usually caused by a fall onto the shoulder from traffic accidents or sports, direct trauma to the clavicle, or indirect trauma from falls onto an outstretched hand. Since our patient had clavicle pain and PPP before the fracture, it was considered that osteitis caused by SAPHO syn-

drome affected the non-traumatic fracture. [Clinical significance] When we see the patients with non-traumatic clavicle fracture, we should suspect the osteitis due to SAPHO syndrome.

## P28-11

### A case of an elderly man with systemic scleroderma whose hyper-CRPemia was caused by ankylosing spondylitis

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Conflict of interest: None

[Case] 68 years old, male [Current medical history] The patient was diagnosed with bilateral Raynaud's phenomenon in X-3 year, with stiffness, edema, and arthralgia of the fingers upon waking in the early morning since X year. He visited our department in August, and skin sclerosis was observed on the fingers, toes, and face. CRP 5.6 mg/dL, KL-6 1,161 U/mL, RF 9 U/mL, anti-Scl-70 antibody >850 U/mL, PR3-ANCA 26.5 U/mL. He was diagnosed with diffuse scleroderma systemic scleroderma. Joint echocardiography showed no synovitis, and chest CT showed bilateral inferior dorsal frosted shadows. The cause of hyper-CRPemia was unknown. He had back pain since his late 30s, and he had tenderness in the lumbar spinous process and sacroiliac joint. MRI showed high signal areas in the bilateral sacroiliac joints and faint signal elevation in the lumbar corners with T2 fat suppression. He was diagnosed ankylosing spondylitis, he took NSAIDs, and CRP was decreased. [Discussion] A close examination of hyper-CRPemia, which cannot be explained by systemic scleroderma, diagnosed hyperPR3-ANCAemia, and initially suspected small vasculitis, but reassessment of medical history and physical findings revealed ankylosing spondylitis.

## P28-12

### A case of chronic recurrent multifocal osteomyelitis diagnosed by repeated osteitis of the jaw and systemic imaging findings

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Conflict of interest: None

A 24-year-old man had a tooth extracted one and a half years ago. 8 months ago, he developed osteomyelitis of the right jaw and was started on antibacterial medication, but did not get better. 2 months before, he had back pain and came to see us. The patient had mild inflammation, but PCT was negative, WBC was not elevated, and two sets of blood cultures were negative, so there was no obvious suspicion of infection. Lumbar MRI showed high signal on STIR and diffusion-weighted images at L4 and L5, suggesting the possibility of osteomyelitis. Additional bone scintigraphy showed moderate-to-severe accumulation in the mandible, bilateral sternoclavicular joints, and sternal body, as well as moderate accumulation in Th7 and the limbic region of L3-5 vertebrae, consistent with polyosteoitis and osteomyelitis. So we diagnosed him Chronic Recurrent Multifocal Osteomyelitis: CRMO. He was treated with NSAIDs, but his pain did not improve and now he was treated with TNF inhibitors. CRMO is a rare disease that has been reported in less than 100 patients in Japan, and it takes time to diagnose. We believe that systemic evaluation with MRI and bone scintigraphy was useful for diagnosis.

## P29-1

### Association between disease activity and presence of vertebral fractures in rheumatoid arthritis

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Conflict of interest: None



[Objectives] To investigate the prevalence and risk factors for vertebral fractures (VFs) in patients with rheumatoid arthritis (RA) during an era of tight control. [Methods] We analyzed 107 RA patients. We assessed the DAS28, the history of medication, the number and location of VFs, and the bone mineral density (BMD). [Results] The average age, disease duration, and DAS28 were 67.9 years, 14.9 years, and 2.8, respectively. VFs were found in 33 patients and 84.8% of patients with VFs were treated with active vitamin D3, bisphosphonate, and/or denosumab. RA patients with VFs had significantly higher DAS28, a higher rate of patients with a history of glucocorticoid use, and lower BMD in comparison to those without VFs ( $p = 0.009$ ,  $p = 0.004$ , and  $p = 0.01$ , respectively). Logistic regression analysis showed DAS28 ( $p = 0.038$ ) and BMD ( $p = 0.004$ ) were independent factors associated with the presence of VFs. The ordered logistic regression analysis also showed DAS28 ( $p = 0.043$ ) and BMD ( $p = 0.024$ ) were independent factors that explained the number of VFs. [Conclusions] VFs were frequently observed in RA patients, even when treated with the recommended anti-osteoporotic agents. High disease activity and low BMD were associated with the presence and number of VFs in RA patients.

## P29-2

### New insights into the pathogenesis of glucocorticoid-induced avascular necrosis

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Conflict of interest: None

[Objective] Glucocorticoid (GC) usage is the most common non-traumatic cause of avascular osteonecrosis (AVN). However, the mechanism of GC induced AVN remains to be elucidated. To identify the mechanisms for pathogenesis of GC induced AVN in patients with systemic lupus erythematosus (SLE). [Methods] 25 SLE patients using GC were enrolled, of which 18 patients had AVN and 7 patients did not have AVN. We compared the rate of change in osteoclasts produced in cells treated with GC. We performed RNA sequencing to investigate the transcriptomic analysis of osteoclasts. Circulating immune cells were defined by cell surface markers and measured by FACS analysis. [Results] Cells from SLE AVN patients differentiated into osteoclasts and showed reduced sensitivity to the GC. Our transcriptomic analysis revealed that AVN osteoclasts exhibited a high interferon signature. Accordingly, we found that serum CXCL10 was significantly higher in the SLE AVN patients compared to those with SLE but without AVN. We found that the CD4/CD8 T cell ratio was significantly lower in SLE AVN patients. [Conclusions] Our findings indicate that there are transcriptomic differences between SLE patients with and without AVN, suggesting that such changes may lead to the differential responses of osteoclasts to GC.

## P29-3

### Study of proximal femoral (hip) structural analysis (HSA) using DXA and 3D-SHAPER in patients administrated with Romosozumab

Yusuke Suzuki<sup>1</sup>, Shigenori Tamaki<sup>1</sup>, Takashi Kato<sup>2</sup>, Motokazu Kai<sup>3</sup>, Kunikazu Ogawa<sup>3</sup>, Ryosuke Hibi<sup>1</sup>, Hidenao Imada<sup>1</sup>, Hitomi Nagasaka<sup>1</sup>, Hiroaki Mizuno<sup>1</sup>, Hisaji Oshima<sup>4</sup>, Ikuko Tanaka<sup>1</sup>

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Conflict of interest: None

[Objective] In this study, the structural rigidity and strength of the proximal femur of patients who administrated Romosozumab were examined by hip structural analysis (HSA) obtained by 3D-SHAPER (3DS). [Methods] The results of DXA measurements of the proximal femur of 45 patients who administrated Romosozumab once a month for 12 months were used. Changes in BMD of DXA and HSA after 12 months were examined. [Results] The BMD of DXA significantly increased by about 1.6% in the proximal femur and by about 2.6% in the femur neck 12

months after. In HSA of 3DS, the cross sectional area, the cross sectional moment of inertia, and the section modulus significantly increased by about 3.2% after 12 months in both the neck and intertrochanter. The buckling ratio significantly decreased by about 1.1% after 12 months. The predictors of the change in HSA were examined by principal component analysis based on the results of 3DS. In the femur neck, vBMD, trabecular vBMD, lateral cortical thickness were extracted. In the intertrochanter, vBMD, trabecular vBMD, lateral cortical thickness were extracted. [Conclusions] It was clarified that Romosozumab increased the bone mineral density in the proximal femur and also improves the structural rigidity and strength.

## P29-4

### Examination of bone structure related to changes in the proximal femur before and after treatment with Romosozumab measured by 3D-SHAPER ~ HR-pQCT Study ~

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Conflict of interest: None

[Objective] 3D-SHAPER (3DS) reconstructs the 2D data of the proximal femur obtained by DXA into 3D, and can measure cortical (Ct.) bone and trabecular (Tb.) bone. Romosozumab (ROMO) was administered to severe osteoporosis patients, and the bone structure by HR-pQCT associated with changes in the proximal femur before and after administration were examined. [Methods] The subjects were 48 patients (73 ± 8 years old) who received ROMO once a month for 12 months. The amount of change in Ct. and Tb. bone mineral density (BMD), Ct. bone thickness (Ct. Th), and Ct. bone surface density (Ct. sBMD) between before and 12 months after were calculated using 3DS. Before administration, bone structure measured by HR-pQCT in the distal radius. [Results] All 3DS measurements showed a significant increase 12 months after administration. The amount of change in Ct. BMD was not correlated with all HR-pQCT measurements. Changes in Tb. BMD and Ct. Th were negatively correlated with Tb. thickness (Tb. Th). The amount of change in Ct. sBMD was positively correlated with Tb. number (Tb. N) and negatively correlated with Tb. Th. [Conclusions] In the severe osteoporosis cases, Tb. N decreased and the Tb. Th increased compensatory. ROMO administration should be considered when the trabecular structure is maintained.

## P29-5

### Romosozumab increase the bone mineral density at lumbar and femoral irrespective of preosteoporosis treatment and history of fragility fracture

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Conflict of interest: None

[Objective] We evaluated the BMD and BMM change in osteoporosis patients treated with Romosozumab, and assessed the effect of preosteoporosis treatment and history of fragility fracture. [Methods] This study included 141 osteoporosis patients treated with Romosozumab. BMD using DXA and PINP were evaluated at 0, 4, 6 and 12 months after treatment. [Results] BMD change were 5.2% ( $p < 0.01$ ), 9.2% ( $p < 0.01$ ), 10.8% ( $p < 0.01$ ) at lumbar spine (LS), 1.3% ( $p = 0.02$ ), 2.8% ( $p < 0.01$ ), 4.5% ( $p < 0.01$ ) at proximal femoral (PF), 2.0% ( $p = 0.03$ ), 2.7% ( $p = 0.06$ ), 5.0% ( $p = 0.01$ ) at femoral neck (FN), -1.5% ( $p < 0.01$ ), -0.8% ( $p = 0.17$ ), -1.0% ( $p = 0.13$ ) at radius and PINP change were 63% ( $p < 0.01$ ), 6.4% ( $p = 0.55$ ),

-2.3% ( $p=0.2$ ) at 4, 8, 12 months after treatment. There were no differences in 1 year improvement ratio of BMD at LS, PF and FN between 38 patients with pretreatment of osteoporosis and 54 patients without pretreatment of osteoporosis (13.5 vs 9.5%:  $p=0.1$ , 4.9 vs 4.4%:  $p=0.7$ , 6.1 vs 4.6%:  $p=0.67$ ), between 33 patients with a history of fragility fracture and 59 patients without a history of fragility fracture (7.3 vs 11.7%:  $p=0.42$ , 0.8 vs 5.5%:  $p=0.08$ , -0.7 vs 6.6%:  $p=0.14$ ). [Conclusions] Romosozumab improved BMD at lumbar and femoral independently regardless of preosteoporosis treatment and history of fragility fracture.

## P29-6

### Efficacy and safety of romosozumab in rheumatic diseases

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Conflict of interest: None

[Objective] To clarify the efficacy and safety of romosozumab for osteoporosis associated with rheumatic diseases. [Methods] Patient characteristics, efficacy, retention rate, and safety were evaluated in 28 patients who started romosozumab between December 2019 and August 2021. [Results] Patient characteristics: age 75.4 years, 28 females, body weight 45.8 kg, BMI 21.1 kg/m<sup>2</sup>, steroid use 16, prednisolone equivalent dose 4.7 mg/day, underlying disease: RA 20, SLE 4, MCTD, SSc, SjS, MPA 1 each. The previous treatment was bisphosphonate in 6 patients, denosumab in 8 patients, teriparatide in 2 patients, vitamin D alone in 3 patients, and no medication in 9 patients. Lumbar spine (L2-4) bone mineral density (BMD) 0.800 g/cm<sup>2</sup>, cervical BMD 0.579 g/cm<sup>2</sup>. The median duration of treatment was 11.5 months with a retention rate of 92.4%, one patient discontinued due to hepatic dysfunction and the other due to patient request. 2 patients developed fractures of the right femoral neck. In a study of 10 patients who had BMD assessed after 12 months, lumbar spine (L2-4) BMD 0.938 g/cm<sup>2</sup> improved significantly ( $p<0.02$ ), and femoral neck BMD 0.600 g/cm<sup>2</sup> tended to improve ( $p=0.06$ ). [Conclusions] Although two patients had fragility fractures, romosozumab significantly improved BMD in rheumatic diseases.

## P29-7

### Comparative efficacy of romosozumab treatment in patients with rheumatoid arthritis and primary osteoporosis

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Conflict of interest: None

[Objectives] The purpose of this study was to compare the efficacy of romosozumab in patients with secondary osteoporosis associated with rheumatoid arthritis and in patients with primary osteoporosis. [Methods] Among 140 patients who received romosozumab at our hospital until August 2021, 60 patients who could be assessed for bone mineral density before and 1 year after treatment were included in the study. Two males and 58 females. The mean age was 76 years, 34 patients had concomitant VtD, and 42 patients had a history of fragility fracture. There were 32 patients in the primary osteoporosis group (P group) and 28 patients in the secondary osteoporosis associated with rheumatoid arthritis (R group). The treatment effects were compared between the two groups. [Results] In the R group, lumbar spine BMD increased from 63.4% to 73.9% in YAM, and proximal femur from 56.1% to 58.9% in YAM; the P group also increased from 80.7% to 84.8% and from 60.9% to 63.3% in YAM, respectively. The P group also showed an increase from 80.7% to 84.8%, and from 60.9% to 63.3%, respectively. [Conclusion] Romosozumab may be useful in the treatment of secondary osteoporosis associated with rheumatoid arthritis.

## P29-8

### Investigation of longitudinal changes of carotid artery wall thickening and cardiac function by ultrasonography at baseline and 12 months after romosozumab induction

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Conflict of interest: None

[Objective] We investigated longitudinal changes of the carotid artery wall thickening and cardiac function using cervical and cardiac ultrasonography before and after ROMO administration. [Methods] 8 patients with osteoporosis administered ROMO from June to October 2020 (all females; average age 76 years; average T-Score lumbar spine (LS) -2.4, total hip (TH) -2.7). We evaluated the maximum intima-media thickness (max-IMT) of common carotid artery (CCA) and carotid artery bulb (Bif), the presence of new plaques, and the left ventricular ejection fraction (LVEF) by ultrasonography. [Results] From baseline → 12 months, LS and TH BMD changes were 16.4% and 2.68%, the max-IMT changes were 0.94 → 0.84 mm for right CCA, 1.65 → 1.80 mm for right Bif, 0.88 → 1.07 mm for left CCA, 1.68 → 1.75 mm for left Bif, and the LVEF changes were 68.6 → 71.8%. There were no significant differences in all cases ( $p>0.05$ ). A new plaque appeared in 1 case (71-year-old woman, BMI 11.5, history of respiratory disease). Adverse events were injection site pain in 1 case, hypercalcemia in 1 case, and new fracture in 1 case (Humerus fracture). [Conclusions] There were no significant differences in changes of the max-IMT and LVEF between the baseline and 12 months. A new plaque appeared in 1 case / 8 cases.

## P29-9

### Therapeutic effects of romosozumab in osteoporotic patients with histories of cancers

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Conflict of interest: None

[Objective] We had examined therapeutic effects of romosozumab (RMAB) in osteoporosis patients with histories of cancers. [Methods] 33 patients (9 men, 24 women, average 75.8 years old) had been diagnosed at great high risks of several fractures and treated with RMAB more than 12 months. [Results] Cancer origins were lung: 8 cases, breast: 7 cases, colon: 6 cases, gastric: 5 cases, prostate: 4 cases, kidney: 2 cases, and others: 4 cases (overlapped). 23 of them had surgery histories of cancers at 25 times. Their cancer conditions were 13 remission, 8 follow-up, 10 during chemotherapy, 2 palliative treatments. 61% of them had been treated with osteoporotic drugs. The bone density increased rates of lumbar vertebrae were average 8% at 6 months, 10.6% at 12 months, and of proximal femur were average 2.8% at 6 months, 4.1% at 12 months from the baseline. P1NP were increased 26% and TRACP-5b were inhibited 15% at 3 months from the baseline. We had used combination therapeutic drugs with RMAB in 70%. 79% of patients had been completed for 12 months, and there were no cases of new fragile fracture onset and no fatal cases by cancers. [Conclusions] RMAB had been able to get good therapeutic effects in osteoporosis patients with histories of cancers.

## P29-10

### Efficacy of romosozumab in severe osteoporosis patients with no effect of prior treatments

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Conflict of interest: None

[Objective] Efficacy of romosozumab in severe osteoporosis patients with no effect of prior treatments was investigated. [Methods] A total of 40

severe osteoporosis patients with no effect of prior treatments were enrolled in this study. These patients were treated with romosozumab and were observed for more than 12 months. Changes from baseline of bone mineral density in lumbar spine and femoral neck, and changes from baseline of serum bone turnover markers, TRACP-5b and P1NP, were evaluated. [Results] Mean age was 72 years, and 36 patients were completed treatment with romosozumab for 12 months. Changes of bone mineral density from baseline at 6 and 12 months were +7.6% and +10.8% in lumbar spine and +3.7% and +5.3% in femoral neck, respectively. Change of serum turnover markers from baseline at 6 and 12 months were -20% and -31% in TRACP-5b and +60% and +23% in P1NP. There was no serious adverse event in all patients. [Conclusions] Romosozumab was effective in severe osteoporosis patients with no effect of prior treatments.

## P29-11

### Investigation for disease activity of rheumatoid arthritis (RA) and therapeutic effect of osteoporosis in rheumatoid arthritis patients combined with osteoporosis treated by Romosozumab (ROMO)

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Conflict of interest: None

[Objective] It has been reported that inhibition of sclerostin promotes TNF-dependent inflammatory joint destruction in basic research. We investigated the disease activity of RA and the therapeutic effect of osteoporosis in RA patients combined with osteoporosis treated by ROMO. [Methods] 42 followed up for 12 months after the administration of ROMO at our hospital were included. Disease activity and bone mineral density (BMD) were investigated before and 12 months after ROMO administration. [Results] Of the 42 cases (2 male, 40 female, average age 75.2 years), 8 were in the TNF group, and 21 were in the non-TNF group, 13 were in the non-bio group. The mean values of (DAS28-CRP, DAS28-ESR, CDAI) in the TNF group were (1.75, 3.32, 4.25) before administration and (1.49, 2.79, 3.11) after administration. Those in the non-TNF group were (2.04, 2.77, 5.81), and (1.85, 2.63, 5.10). Those in the non-bio group were (2.25, 3.12, 5.23) and (2.08, 3.12, 4.89). Disease activity of RA was improved in the TNF group. The rate of change in BMD was 9.48% in the lumbar spine, 3.08% in the total hip, and 4.93% in the femoral neck. [Conclusions] 12 months after ROMO administration, the disease activity of RA in the TNF group was significantly improved, and BMD also improved significantly in all.

## P29-12

### Four cases of rheumatoid arthritis with atypical femoral fractures

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Conflict of interest: None

[Introduction] RA is a typical disease that causes osteoporosis, and bisphosphonate (BP) are often administered. Here, we report four RA cases that developed atypical femur fracture (AFF) at a single institution since April 2017. [Case 1] The case was a 71-year-old female patient who developed RA in the year X-13. She started using alendronate (ALN) in the year X-8. She developed AFF in October X while being treated with prednisolone (PSL) and tocilizumab. [Case 2] The case was a 62-year-old female patient who developed RA in the year X-7. She started using ALN in the year X-5. The patient developed AFF in May X while being treated with PSL and upadacitinib. [Case 3] The case was a 70-year-old female patient who developed RA in the year X-22. She started using ALN in the year X-5. The patient developed AFF in March X while being treated with PSL, tacrolimus and abatacept. [Case 4] The case was a 77-year-old female patient who developed RA in the year X-37. Denosumab (Dmab) administration was initiated in the year X-2. The patient developed AFF in March X while being treated with PSL and golimumab. [Conclusions] In all the cases, a long-term administration of PSL, BP or Dmab was observed. AFF

risk should be considered for patients with RA who have received BP or corticosteroid.

## P30-1

### Risk factors for dropping out of treatment with denosumab in patients with postmenopausal osteoporosis

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Conflict of interest: None

[Objective] Although discontinuation of denosumab without any sequential treatment can cause multiple vertebral fractures, some patients with postmenopausal osteoporosis (PMO) drop out of treatment with denosumab. We investigated risk factors for dropping out of treatment with denosumab in PMO patients. [Methods] Patients divided into two groups according to whether patients continued or dropped out of treatment with denosumab (defined as Continue group and Dropout group) were compared. Cox proportional hazard model was performed using factors which were significantly different between two groups to confirm risk factors for dropping out of treatment with denosumab. [Results] Patients in Continue group was younger than those in Dropout group, and weight, bone mineral density (BMI) and albumin were greater in Continue group than in Dropout group. Cox proportional hazard model confirmed that low BMI was a risk factor for dropping out of treatment with denosumab. [Conclusions] Low BMI was a risk factor for dropping out of treatment with denosumab in PMO patients. Treatment with other agents than denosumab in PMO patients with low BMI could be considered to avoid multiple vertebral fractures caused by dropping out of treatment with denosumab.

## P30-2

### Low serum albumin concentration is associated with increased risk of osteoporosis in postmenopausal patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To identify the correlation between serum albumin and the prevalence of osteoporosis in postmenopausal patients with RA. [Methods] This study enrolled 197 patients who underwent DXA without osteoporosis treatment. Patients were classified into 2 groups: osteoporosis (121 patients), and non-osteoporosis (76 patients). Groups were then matched by propensity score using clinical backgrounds affecting bone metabolism. [Results] In non-matched model, serum albumin concentration was significantly associated with osteoporosis-related factors. Multivariate logistic regression revealed that serum albumin concentration was independently and significantly associated with osteoporosis risk (odds ratio = 0.22,  $p = 0.0033$ ). After propensity score matching, 57 patients for each group showed that serum albumin concentrations ( $p = 0.01$ ) remained lower in the osteoporosis group compared to non-osteoporosis group. ROC analysis in non-matched model revealed that when cut-off value of serum albumin concentration for indicating osteoporosis was set at 4.2 g/dl, AUC was 0.69, sensitivity 0.74, and specificity 0.58. [Conclusions] Low serum albumin concentration was significantly and independently associated with the prevalence of osteoporosis in postmenopausal patients with RA.

## P30-3

### Risk factors in patients with new vertebral compression fractures using dual-energy X-ray absorptiometry and Fracture Risk Assessment Tool

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Conflict of interest: None

[Objective] To evaluate the fracture risk in patients with new vertebral compression fractures (VCF) by DXA and FRAX, and to compare them with non-VCF patients. [Methods] We compared 30 patients in the VCF group with 60 patients in the control group (group C). Fracture risk by FRAX and T-scores in the lumbar spine (L), total hip (TH), and femoral neck (FN) of each patient were investigated. T-score, BMI, fracture risk according to the FRAX, and the type of osteoporosis (OP) treatment were investigated and compared between groups. [Results] The T-scores of the VCF and C groups were -1.7 and 0.7 for L ( $p<0.001$ ), -2.4 and -1.8 for TH ( $p=0.04$ ), and -3.2 and -2.7 for FN ( $p=0.03$ ), respectively. BMI was lower in the VCF group than in the C group ( $p=0.02$ ). The fracture risk due to FRAX in the VCF and C groups was 31% and 24% for major fractures ( $p=0.04$ ) and 16% and 11% for hip fractures ( $p=0.04$ ). The rate of bisphosphonate, denosumab, and teriparatide (BP, DMAB, and TPTD) treatment intervention was lower in the VCF group ( $p=0.01$ ). [Conclusions] T-scores of the VCF group was lower than that of the C group, and new VCF patients tended to have low BMI and were not medicated for OP.

### P30-4

#### Relationship between efficacy of teriparatide and nutritional status in postmenopausal rheumatoid arthritis patients

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Conflict of interest: None

[Objective] The aim of this study is to clarify the influences of nutritional status for efficacy of TPTD in postmenopausal RA patients. [Methods] We evaluated the bone mineral density (BMD) of the proximal femur and lumbar spine by the DXA method in 35 postmenopausal female RA patients who continued TPTD for 2 years. The clinical background including the nutritional status (Prognostic Nutritional Index: PNI) in the effective and the non-effective group divided by the BMD change rate (2 years later / start time ratio) was compared. [Results] The median BMD change rate at 2 years after the TPTD initiation was significantly improved in lumbar spine (1.035) and proximal femur (1.098) ( $P<0.05$ ). The effective group in the lumbar spine had higher PNI and albumin levels and lower initial BMD than the non-effective group. As a result of ROC analysis and multivariate analysis, low PNI ( $<45$ ) (OR: 15.67, 95% CI: 1.597-153.6) and low BMD ( $<0.6$  g/cm<sup>2</sup>) (OR: 16.59, 95% CI: 1.235-222.9) at the TPTD initiation were influential factor on the effectiveness of that. There was no difference in the femur between the two groups. [Discussion] Postmenopausal female RA patients are prone to malnutrition. It is important to manage to maintain good nutritional status for obtaining the full effect of TPTD.

### P30-5

#### Investigation of prevalence of osteoporosis and evaluation of factors affecting femoral YAM value in patients undergoing primary total knee arthroplasty at our institution

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Conflict of interest: None

[Objective] We conducted a study to investigate the prevalence of osteoporosis in patients underwent total knee arthroplasty (TKA). We also investigated the factors that affect femoral YAM value. [Methods] Patients with osteoarthritis of the knee who underwent primary TKA at our institution between July 2020 and May 2021 and who underwent preoperative osteoporosis screening were included. The prevalence of osteoporosis and therapeutic intervention were evaluated. Femoral YAM value was the objective variable, and age, gender, BMI, 25 (OH)D, TRACP-5b, P1NP, and

presence of therapeutic intervention were the explanatory variables, which were evaluated by Spearman correlation analysis and multiple regression analysis. [Results] The mean age was 75.0 years, 18 males and 63 females, and the mean BMI was 25.5 kg/m<sup>2</sup>. Osteoporosis was 42%, of which 55.9% were untreated. Spearman correlation analysis showed that older age, women, lower BMI, and lower 25 (OH)D were associated with lower femoral YAM values. Multiple regression analysis showed that gender and BMI had a significant effect on the results. [Conclusions] Patients with knee arthritis preoperative TKA had a higher prevalence and untreated rate of osteoporosis, and femoral YAM values were associated with age, gender, BMI, and 25 (OH)D.

### P30-6

#### Very low bone mineral density is a risk factor for exceed the T-score of osteoporosis diagnostic criteria after an average of 4.5 years of denosumab treatment

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Conflict of interest: None

[Objective] To reveal the factors that influence the improvement of T-score of bone mineral density by denosumab (DMAB) treatment. [Methods] We analyzed the data of 106 patients who were able to follow up for more than 3 years after initiation of DMAB for osteoporosis. We measured T-score at three sites (lumbar spine (L), proximal femur (TH), and femoral neck (FN)) at baseline (BL) and every six months. We evaluated achievement of T-score  $>-2.5$  during the follow-up period and time to its achievement. [Results] Of 106 patients, 60 were with RA. The mean follow-up period was  $4.47\pm1.3$  years. The rates of T-score  $>-2.5$  achievement were L 44.0%, TH 43.5%, and FN 16.3%. Cox proportional hazard analysis identified not incidence of RA and use of GC but high T-score at BL as a significant factor for T-score  $>-2.5$  achievement. Cutoff values of BL T-score determined by ROC analysis were L -3.23 (AUC 0.87), TH -2.98 (AUC 0.94), and FN -2.90 (AUC 0.89) T score. [Conclusions] In this study, an average of 4.5 years of DMAB treatment for osteoporotic patients with very low T-score makes it difficult to exceed the T-score of osteoporosis diagnostic criteria. For patients with a very low T-score at initiation of osteoporosis treatment, the use of bone-forming agents might be considered.

### P30-7

#### Comparison of risk factors affecting osteoporosis, sarcopenia and osteosarcopenia in patient with rheumatoid arthritis

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Conflict of interest: None

[Objective] Rheumatoid arthritis (RA) patients are likely to develop osteoporosis and sarcopenia, and combined cases osteoporosis and sarcopenia are diagnosed osteosarcopenia. Osteosarcopenia is well known in its frailty. We checked their differences in the factors of osteoporosis, sarcopenia, and osteosarcopenia. [Methods] Bone density was measured, YAM 70% or less was osteoporosis. Skeletal muscle was measured, SMI 5.7 kg/m<sup>2</sup> or less was sarcopenia. Combined osteoporosis and sarcopenia are osteosarcopenia. Group with osteoporosis only was O group, group with sarcopenia only was S group, and group with osteosarcopenia was OS group. We compared age, duration of RA, height, weight, BMI, Steinbrocker Class (Class), Steinbrocker Stage (Stage), PSL use history, and biologics (Bio) use history among the three groups. Age, duration of RA, height, weight, BMI, Class and Stage were tested by Anova, PSL use history and Bio use history was tested by Fisher accurate test. [Results] 10 in O group, 9 in S group, 14 in OS group. Weight was low in OS group, Stage was high in OS group. PSL use history was high in O and OS group, Bio use history was low in the OS group. [Conclusions] In underweight, wrist

deformity, PSL use history, and no Bio use history cases, we should consider the drug to be used.

### P30-8

#### The effect of measurement sites choice in bone densitometry in the proximal femur on judging the criteria for the initiation of drug treatments for osteoporosis

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Conflict of interest: None

[Objective] To evaluate the effect of measurement sites choice in the proximal femur on judging the criteria for the initiation of drug treatments for osteoporosis (OP) by dual-energy X-ray absorptiometry (DXA). [Methods] A total of 242 patients without fragility fractures who underwent bone densitometry using ALPHYS LF (Hitachi, Ltd.) were enrolled. We compared T-Score (TS) at the lumbar spine (LUM), total hip (TH), and femoral neck (FN). We compared the TH method; which uses TS of LUM and TH, and the FN method; which uses that of LUM and FN, in terms of judging the criteria for the initiation of drug treatments for OP according to the 2015 Guidelines for Prevention and Treatment of OP ("the criteria"). [Results] The mean TS of LUM, TH, and FN were 0.84, -1.25, and -2.14, respectively ( $p < 0.001$ ). More patients met the criteria by the FN method (103/42.6%) than by the TH method (43/17.8%) ( $p < 0.001$ ). Of the 199 patients who did not meet the criteria by the TH method, 61 patients (30.1%) met the criteria by the FN method. Of the 139 patients who did not meet the criteria by the FN method, only one patient (0.71%) met the criteria by the TH method. [Conclusions] TS by DXA tended to be lower in FN. When evaluating TS in the proximal femur, it was suggested that we should check TS of FN.

### P30-9

#### Current status of osteoporosis treatment for elderly patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] We investigated the current status of osteoporosis treatment for elderly RA patients at our hospital and examined issues for future treatment intervention. [Methods] Of the 176 patients treated with RA between April 2020 and March 2021, 108 patients aged 65 years or older (26 males, 82 females, average age 77.9 years) were included. Of the 108 patients, 58 patients who underwent DXA were group A, and 50 patients who did not undergo DXA were group B. In groups A and B, osteoporosis treatment rate, fracture history, gender ratio, and early-stage elderly The ratio, bDMARDs, tDMARDs usage rate, and steroid usage rate were investigated. [Results] The treatment rate for osteoporosis was 81% in group A, 4% in group B, the history of fracture was 50% in group A, 14% in group B, the proportion of men was 10% in group A, 40% in group B, and the proportion of early-stage elderly. The usage rates of bDMARDs and tDMARDs were 36% in group A and 26% in group B, and the steroid usage rates were 21% in group A and 10% in group B. [Conclusions] The treatment of osteoporosis for elderly RA patients at our hospital was highly intervened in the cases where DXA was performed, but the treatment intervention was rarely performed in the cases where DXA was not performed.

### P30-10

#### The relation between osteoporotic insufficiency vertebral body fracture and 25-question geriatric locomotive function scale

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Conflict of interest: None

[Objective] To indicate the severity of locomotive syndrome, "Locomo" grade is used. In this study, we evaluated the relation between "Locomo" grade 3 and insufficiency vertebral fracture. [Methods] 257 female outpatients over 65 years diagnosed osteoporosis were enrolled. We evaluated radiographic lateral image of thoracic and lumbar spine, bone mineral density, and geriatric locomotive function scale 25 (GLFS-25). [Results] Of 257, 208 patients have undergone radiographic examination within the past year. Patients who were not diagnosed locomotive syndrome were 41 cases, and diagnosed "Locomo" grade 1, 2, and 3 were 42, 36, and 89 respectively. Further the patients with radiographic vertebral fracture were 8, 12, 9, and 34 cases. The significance for the findings rate was detected between the cases without locomotive syndrome and cases of "Locomo" grade 3 ( $P = 0.03$ ). We could not find significance between every group for bone mineral density of lumbar spine and proximal femur. Moreover, average GLFS-25 were 29.6 points in the patients with radiographic vertebral body fracture (62 cases) and 22.6 points in other 146 cases ( $P = 0.02$ ). [Conclusions] In the patients with osteoporosis, who diagnosed "Locomo" grade 3 have to been considered to accompany radiographic vertebral body fracture.

### P30-11

#### Evaluation of denosumab continuity and reasons for discontinuation

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Conflict of interest: None

[Objective] There are various drugs for osteoporosis treatment, among them, denosumab is a highly effective drug. We evaluated the adverse events and continuity of patients who used denosumab. [Methods] We evaluated the continuity and reasons for discontinuation, adverse events, who were initially introduced to denosumab at our hospital. Statistical analysis was performed by Wilcoxon rank sum test. [Results] The subjects were 81 patients (9 males and 72 females), and the average age was  $79.8 \pm 7.4$  years. The average duration was  $29.9 \pm 17.9$  months, and 44 cases were discontinued. The reasons for discontinuation at our hospital were 19 cases (mean 79.8 years old) associated with changing doctors, followed by 13 cases (mean 83.3 years old) whose details were unknown in the medical record. The unknown had a clearly higher average age than other reasons for discontinuation and was significantly older than the continuous average age. ( $P = 0.016$ ) [Conclusions] More than half of them were suspended, and most of them were for reasons such as changing doctors or unknowns. Since the average age of the unknown group is high, it may be difficult to go to the hospital due to old age.

### P31-1

#### Serum peptides as candidate biomarkers for relapsing polychondritis

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Conflict of interest: None

[Objective] We tried to find useful serum biomarker candidates for relapsing polychondritis (RP). [Methods] Serum peptides were comprehensively analyzed by mass spectrometry. [Results] 160 peptides were detected in a cohort (19 RP, 17 healthy controls [HC], 21 rheumatoid arthritis [RA]). In the RP group, 27, 9, and 9 peptides showed ion intensity at least 1.2-fold higher or lower in comparison to the HC, RA, and HC+RA (non-RP) groups, respectively ( $p < 0.05$ ). Selecting 11, 9, and 14 peptides by multivariate analysis, we completely discriminated the RP group from those groups, respectively (AUROC, 1.000). 19 out of the above peptides were identified, almost all of which were derived from proteins associated with coagulation. Selecting any 1-4 out of 10 identified peptides used in the discriminant model between the RP and non-RP groups, we generated 4 RP/nonRP-discriminant models with 4 peptides which provided both sensitivity and specificity of 70.0% or more in another cohort (18 RP, 18 HC, 21 RA, 7 granulomatosis with polyangiitis; AUROC, 0.779-0.815). Notably, one of the models provided sensitivity of 83.3% and specificity of 71.7% (AUROC, 0.802). [Conclusions] Serum peptide profiles provided useful RP biomarker candidates and may be implicated in the pathophysiology of the disease.

### P31-2

#### Factors related to walking speed in patients with end-stage knee joint disorder scheduled for total knee arthroplasty

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Conflict of interest: None

[Background and purpose] Various factors are assumed for the decrease in walking speed. Therefore, the purpose of this study was to measure the walking speed of patients scheduled to undergo initial total knee arthroplasty (TKA) and to investigate the factors that most correlate with this. [Subjects and methods] Among patients with end-stage knee joint disorders who underwent the first TKA at our hospital from July 2020 to May 2021, the subjects whose walking speed was measured preoperatively. We investigated the relationship for age and gender at the time of the survey, pain VAS during walking, knee joint function clinical evaluation (KSS), skeletal muscle mass of both lower limbs (DXA method), quadriceps femoris muscle strength, range of motion. [Results] The subjects were 81. Multivariate analysis was performed with walking speed as the objective variable and the dependent variables as age, gender, pain during walking VAS, KSS, muscle mass of both lower limbs, thigh quadruple muscle strength, and range of motion. As a result, age and range of motion (flexion) were significantly independently associated with walking speed ( $P = 0.01, 0.03$ ). [Conclusion] It was found that age has the greatest correlation with walking speed, and walking speed decreases with age.

### P31-3

#### Evaluation of physical function in elderly patients over 85 years old who required Total Knee Arthroplasty

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Conflict of interest: None

[Objective] In this study, we investigated the preoperative physical function and muscle strength of patients aged 85 years or older who underwent TKA at our department, and compared them with patients aged less than 85 years, including locomotive syndrome (LS) and sarcopenia. [Methods] Eighty-two patients with TKA performed in our department between July 2020 and May 2021 were included in the study. There were 9 patients who were 85 years old or older at the time of surgery (85+ group), 52 patients who were 70 to 85 years old at the time of surgery (70-84 group), and 21 patients who were younger than 70 years old (<70 group). The preoperative evaluation were JOA score, Knee Society Score (KSS), quadriceps muscle strength, and LS stage. [Results] In the 85+ group, 8 (out of 9) patients were classified as LS stage 3, but there was no significant difference in the distribution compared to the other groups. The grip strength and skeletal muscle mass of the 85+ group were significantly lower than those of the <70 group, but did not differ significantly from

those of the 70-84 group. [Conclusions] Osteoarthritis of the knee is thought to be particularly related to LS, and the results of this study showed that the majority of patients with osteoarthritis of the knee have LS.

### P31-4

#### Two cases report of rheumatoid arthritis of knee treated with high tibial osteotomy after complete remission

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Conflict of interest: None

Purpose: Osteotomy is basically not indicated for rheumatoid arthritis (RA), some reports showed good postoperative results. We report our experience with two cases of high tibial osteotomy (HTO) for knee joint disorder in patients achieved complete remission of RA. Case 1: A 73-year-old woman, Stein Brocker Steage II, Class 2. She was treated with methotrexate (MTX) and infliximab for 6 years, and the DAS28 was 2.26. During the course of treatment, she got knee pain at the medial joint space with varus deformity on X ray film. HTO was performed and FTA improved to 167°. After three years since the surgery, but she does not have the left knee pain. Case 2: 64-year-old female, Stein Brocker Stage II, Class 2. During 4 years of treatment with MTX, abatacept, salazosulfapyridine, and busiramineshe was added and her DAS28 was 2. At the same time, she started to get left knee pain of medial joint space and was diagnosed as osteonecrosis of the medial condyle of the tibia. HTO was performed and FTA improved to 168°. The patient has been doing well since then, and is doing well at 1 year and 7 months postoperatively. Conclusion: HTO could be a treatment for rheumatoid arthritis of knee with varus deformity if patients achieved complete remission of RA.

### P31-5

#### Significance Of serum MMP-3 for varus and valgus knee osteoarthritis patients

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Conflict of interest: None

[Objective] OA is commonly believed to be caused mainly by mechanical stress, but partly by immunogenic mechanism possibly. MMP-3 reflects synovitis in RA and is considered to be a marker of disease activity, but few is known in OA mechanism. We investigate relation between MMP-3 and parameter of OA patients and contribution of MMP-3 for the mechanism of OA. [Methods] From January 2019 to September 2021, 196 (165 varus 31 valgus) OA female patients who were scheduled to receive primary knee arthroplasty were included and serum MMP-3 was measured. We distinguished them into two groups, varus and valgus knee OA according to FTA. BMI, serum CRP, total FTA, Range of motion, extension lag, examination of degree of synovitis and amount of joint fluid, cell count and presence of CPPD of joint fluid, Knee Society Score (KSS), Heberden nodule on hand X-ray were statistically analyzed in two groups. [Results] In varus and valgus group, mean age was (75.4/73.2) years old, serum MMP-3 level was significantly high in varus group (73.2/58.3). Cell count and CPPD positivity and KKS was significantly different. Positive relation was observed between serum MMP-3 and FTA in varus group. [Conclusions] MMP-3 may contribute joint destruction and clinical symptom worsening in OA.

### P32-1

#### A Report on the Satisfaction with the Operation of Auto-Injectors: The Effect of Disease Duration and Grip Strength

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Conflict of interest: None



**Objective** Since the advent of biologics, various types of autoinjectors (AI) have been developed, and we report on the factors that influence satisfaction with AI operation. **Methods** Forty-four patients with rheumatoid arthritis admitted to our hospital who could use AI were classified into three groups: early group (<1 year), middle group (<10 years), and long-term group (>10 years). Patient background, hand function factors, and daily living function factors were evaluated, and the relationship between the three groups and patient satisfaction in performing each AI operation was statistically verified. **Results** In the intergroup comparison, there was no difference in the satisfaction with the execution of the operation in all AIs, but there was a significant difference in the duration of the disease and grip strength ( $P<0.05$ ). In the intra-group comparison, there were differences between ETN and CZP and SAR, and between GLM and CZP and SAR only in the long-term group ( $P<0.01$ ). **Discussion** In this study, it was suggested that the AI operation satisfaction was affected by the decline of grip strength due to the prolonged illness. Therefore, it is desirable to take into account the state of hand function of the subject and the shape of the AI when using AI for drug selection.

## P32-2

### Evaluation for the correlation between “Locomo” grade and the muscular strength of lower extremity using Locomoscan®2

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Conflict of interest: None

[Objective] Locomoscan®2 can measure the muscular strength of lower extremity; considered to be able to assess for the severity of locomotive syndrome; however to date few studies have shown the correlation for them. In this study, we evaluated the correlation between specific measurement of Locomoscan®2 and “Locomo” grade. [Methods] 71 patients performed total knee arthroplasty due to osteoarthritis in our institute in 2020 were included. Of 71, 36 patients approved to be enrolled to this study; 6 males and 30 females. Mean age was 75.4 years. We evaluated the muscular strength of lower extremity using Locomoscan®2 and “Locomo” grade using 2 step test, preoperatively. [Results] Mean of the maximum muscular strength of lower extremity was 25.1 kgf. In 3 cases, 2 step test could not be performed due to gait disturbance. In other cases, 9 cases were diagnosed “Locomo” grade 1, 9 were 2, and 12 were 3. The sum of the muscular strength of bilateral lower extremity/body weight were 1.39 in the patients who were not diagnosed locomotive syndrome, 0.97 in the patients did “Locomo” grade 1, 0.89 in grade 2, 0.67 in grade 3, and 0.36 in the patients who could not perform 2 step tests. [Conclusions] The correlation between the specific measurement of Locomoscan®2 and “Locomo” grade was found.

## P32-3

### Two improved cases of dysphagia in polymyositis and dermatomyositis after long-term rehabilitation

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Conflict of interest: None

Dysphagia is a relatively rare complication of polymyositis (PM) and dermatomyositis (DM), but it often persists even after clinical remission is achieved. In this session, we report two cases of severe dysphagia that improved by long-term rehabilitation. 1, a 74-year-old man with PM, anti-ARS antibody (+), CK 4621, and had severe dysphagia (Dysphagia Severity Scale (DSS)2, Penetration-Aspiration Scale (PAS)7) and lung cancer. After remission with steroid pulse and PSL, CK normalized on the 18th day, but dysphagia was still severe (DSS 2). He continued rehabilitation with radiotherapy for cancer, started eating on the 55th day, and achieved code-4 diet on the 67th day (DSS 5, PAS 3). 2, a 49-year-old man

with DM, aldolase (+), CK 18931, and had severe dysphagia (DSS 1, PAS 8) and bladder cancer. After remission with IVIg and PSL, CK normalized on the 44th day, but dysphagia was still severe (DSS 2). He continued rehabilitation with chemotherapy for cancer, started eating on the 193rd day and achieved a normal diet on the 208th day (DSS 6, PAS 1). In these cases, their dysphagia eventually improved during swallowing rehabilitation, which included functional training as well as chin down swallowing. We believe that it is important to continue rehabilitation even after clinical remission.

## P32-4

### Grip strength affect postoperative upper limb function of total elbow arthroplasty for patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To explore the confounding factors which affect the upper limb function after total elbow arthroplasty (TEA) for the rheumatoid elbow. [Methods] We retrospectively reviewed 72 rheumatoid arthritis (RA) cases who performed TEA (82 elbows). Age, disease duration of RA, DAS28-CRP, range of elbow motion (ROM), elbow pain (NRS 0-10), and grip strength were investigated. We analyzed the correlation between these factors and Disability of the Arm Shoulder and Hand Questionnaire (DASH) score. In addition, the total Larsen score of wrist and finger joints was calculated (total hand LS), and its correlation with grip strength was evaluated. [Results] DASH score was improved from  $49.6\pm 20.7$  to  $36.9\pm 21.9$  postoperatively. DASH score didn't correlate with elbow ROM, but with grip strength (preoperative;  $r=-0.56$ /postoperative;  $r=-0.67$ /change;  $r=0.52$ ) and elbow pain ( $r=0.32$ / $r=0.22$ / $r=0.41$ ) significantly. Furthermore, post operative grip strength correlated with disease duration ( $r=-0.35$ ) and total hand LS ( $r=-0.53$ ). [Conclusions] The postoperative upper limb function of TEA was significantly affected by grip strength. Because long-standing RA patients with hand/wrist joint destructions have lower grip strength, their postoperative therapy should be planned considering their grip weakness.

## P32-5

### Second attempt of online music therapy for patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We have reported that active music therapy improves general health (GH) condition and moods of patients with RA. However, under COVID-19 pandemic, we have switched the activity from onsite to online since 2020. Therefore, in this study, we investigated the effects of second attempt of online music therapy. [Methods] Zoom online meeting system was recruited. Eight songs were sung with a piano accompaniment and 2 were played with CUPS. GH condition was evaluated by 0-10 NRS, pain by face scale, positive and negative moods, and emotional relaxation were surveyed by self-rating questionnaire including NRS, face pain rating scale, PANAS, and ERS. [Results] Seven female patients were participated. mHAQ was  $0.64\pm 0.54$  (0-1.38). The sound was delayed online meeting system and the synchronization of music was very difficult. The results of before/after the activity were; GH 2.0/2.3, pain 4.3/3.7, and positive affect of PANAS 24.6/20.9, negative affect of PANAS 22.6/20.6. Four subscales of ERS were 7.6, 10.0, 9.3, 8.9 respectively. Arthralgia was not induced by CUPS. [Conclusions] On line active music therapy can be

applied for patients with RA under COVID-19 pandemic with several limitations.

### P33-1

#### **A case of lupus nephritis in an elderly patient, suspended dialysis**

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Conflict of interest: None

A 80-year-old male patient who diagnosed as pulmonary MAC disease. He had fever, chest pain and pleural effusion. He was transferred from A hospital to our hospital to examine. He recovered to the outpatient to observe weakly positive for anti-ds-DNA antibodies. On November 11, he began to have respiratory distress and leg edema, and his body weight increased to 9 kg/month. He was admitted to the A hospital on November 19 with suspected heart failure. He was treated with diuretics, but did not improve. He transferred to our hospital. He had nephrotic syndrome and was suspected to have lupus nephritis with low complement and mildly positive anti-ds-DNA antibody. One thousand mg of mPSL was administered for 3 days from December 4, and 30 mg of PSL was followed as post-treatment. Later, the diagnosis of lupus nephritis was confirmed by renal biopsy (ISN/RPS III+V). MMF 1000 mg, HCQ 200/400 mg, and CyA 100 mg were started with carefully followig pulmonary MAC disease. He had introduced to dialysis because of development to severe uremia. He could be suspended dialysis on January 27. The patient was discharged from the hospital on February 17, next year. We experienced a elderly patient with lupus nephritis who was suspending dialysis during early treatment of lupus nephritis.

### P33-2

#### **A Case of Nephritis with MPO-ANA positivity has manifestations of both Systemic Lupus Erythematosus and Antineutrophil Cytoplasmic Antibodies-Associated Vasculitis**

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Conflict of interest: None

[Case Report] The patient was a 79 years old female who was admitted to the hospital on suspicion of heart failure due to bilateral pleural effusion in March 2021. Since exudative pleural effusion was revealed, the exists of serositis was suggested. Laboratory results showed acute kidney injury, lymphopenia, positivity of both ANA and anti-DNA antibody, therefore she was diagnosed with SLE. In addition, overlap syndrome with SLE and ANCA-associated vasculitis was suspected because CRP and MPO-ANCA levels were high. After steroid semi-pulse therapy administered for 3 days and a commencement of post therapy with PSL 50 mg, renal biopsy was performed with the aim of diagnosis and decision on therapeutic strategy. From the result which showed crescentic/necrosis glomerulus and pauci-immune glomerulus, she was diagnosed with ANCA-associated glomerulonephritis. Accordingly, a treatment regime consisting of azathioprine and hydroxychloroquine started, so that renal function has recovered and pleural effusion, CRP, anti-DNA antibody and MPO-ANCA were decreased. [Clinical Significance] It is predicted that SLE in the elderly which has vasculitis characteristics is increased in the aging society. We report the significance of the positivity of MPO-ANCA with bibliographic considerations.

### P33-3

#### **A case of systemic lupus erythematosus; SLE with varicella during treatment for nephrotic syndrome associated with lupus nephritis**

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Conflict of interest: None

27 years-old female In X-11, she was diagnosed with SLE at another hospital and treated at 30 mg/day of prednisolone; PSL and gradually reduced to 5 mg. From around the summer of X-3, urinary protein and occult blood were positive and renal biopsy showed lupus nephritis type V. Tacrolimus; TAC was added on. In October X-1, urinary protein increased, and in January X, facial and lower legs edema appeared. The test showed urinary protein (5 g/day) and hypoproteinemia (4.5 g/dl), so she was diagnosed with nephrotic syndrome and transferred to our hospital in March for continuing treatment. We increased the dose of PSL to 40 mg and changed TAC to mycophenolate mofetil; MMF. Clinically, edema occurred, serum protein levels tended to rise gradually, but urinary protein did not change. She was followed up as an outpatient from the end of April, but in May she developed sore throat and rash in the mouth, face and her back. She was readmitted to our hospital because of positive varicella by the Dermaquick method. Virus-associated hemophagocytic syndrome, DIC and varicella pneumonia were complicated, so we treated with steroid pulse therapy and thrombomodulin alfa in addition to acyclovir. We report a severe infection during immunosuppressive treatment.

### P33-4

#### **Two cases of anti-ds-DNA antibody-negative lupus nephritis Class V associated with Sjögren's syndrome for which Belimumab was effective**

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Conflict of interest: None

[Background] Belimumab has been shown to be effective against SLE in the BLISS trial, but not indicated in SjS. We examined two cases of belimumab for anti-ds-DNA antibody-negative SLE that had a history of SjS and newly developed lupus nephritis (LN) Class V. [Case 1] A 45-year-old woman. She visited for proteinuria. The 2016 ACR/EULAR classification criteria for SjS was 8 points, and it could be classified as SLE from the 2012 SLICC classification criteria, but the specific antibody was negative. Renal biopsy revealed membranous nephropathy. Moderate steroids, mycophenolate mofetil, and hydroxychloroquine (HCQ) were started as LN Class V, but Belimumab was introduced without success. [Case 2] A 48-year-old woman. She visited for eyelid edema and joint pain. The 2016 ACR/EULAR classification criteria for SjS was 3 points, but she was diagnosed with SjS based on dryness and positive specific antibodies. She could be classified as SLE from the 2012 SLICC classification criteria, but was negative for specific antibodies. Renal biopsy revealed membranous nephropathy. Treatment with moderate steroids, tacrolimus, and HCQ was started as LN Class V, but Belimumab was introduced without success. [Conclusion] Belimumab may be effective in LN with various immune abnormalities such as SjS.

### P33-5

#### **A case of systemic lupus erythematosus with exacerbation of lupus nephritis during maintenance therapy and belimumab introduced after reinduction therapy**

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Conflict of interest: None

[Case] 46-year-old man [Chief complaint] None [Clinical Course] Butterfly rash appeared in X-20, and systemic lupus erythematosus (SLE) was diagnosed by skin biopsy. Lupus nephritis (LN) type V was diagnosed in X-18. SLE relapsed in X-11, then PSL and cyclosporine (CsA) was used in combination. Renal function deteriorated in X-2, and CsA was changed to mycophenolate mofetil (MMF), and in X-1, tacrolimus (Tac) was used in combination. However, exacerbation of LN was observed with urinary

protein/urinary Cre 3.32 g/gCre and serum Cre 1.61 mg/dL under the use of MMF2000 mg+Tac1.5 mg+PSL10 mg. Renal biopsy was re-performed in May X. A diagnosis of LN type IV-G (A) was made, and PSL was increased to 65 mg (1 mg/kg) and cyclophosphamide infusion (IVCY) 500 mg/2 weeks was performed 6 times. After remission, subcutaneous injection of belimumab (BEL) was introduced as maintenance therapy. PSL gradually decreased and MMF was resumed. Currently, BEL 200 mg/week+MMF1000 mg+PSL8 mg, and there is no recurrence of LN. [Discussion] For the worsening of LN, after reinduction therapy by IVCY, maintenance therapy was performed by combining BEL and MMF. Remission was successfully maintained and the dose of PSL was reduced. We report the effectiveness of BEL on LN with a review of literature.

### P33-6

#### A case of refractory lupus nephritis treated with rituximab as induction and maintenance treatment

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Conflict of interest: None

[Case] Thirty-eight-year-old female [Chief complaint] Renal dysfunction [History of present illness] Ten years ago, she was diagnosed as systemic lupus erythematosus and treated with steroid pulse therapy followed by prednisolone (PSL) 40 mg/day because of the central nervous system involvement. Her symptoms were improved and the dose of PSL was gradually reduced. Six years ago, renal dysfunction was newly appeared and renal biopsy showed Class IV by ISN/RPS 2018 classification. PSL was increased up to 40 mg/day and intermittent intravenous cyclophosphamide was added (total 7 g). Concomitant immunosuppressants such as mizoribine, tacrolimus, cyclosporine, or mycophenolate mofetil were used as maintenance therapies. But the disease activity was still remained. Then, she re-admitted to our hospital due to decreased renal function. Because of the resistance to the previous treatment, RTX plus PSL was selected as an induction therapy. Renal function and urinary findings were improved. Also, RTX was continued as a maintenance therapy and she is still free from relapse. [Consideration] We experienced the case of refractory lupus nephritis treated with RTX as induction and maintenance treatment. RTX might be one of options for the treatment of refractory lupus nephritis.

### P33-7

#### A case of lupus nephritis that developed NPSLE during administration of mycophenolate mofetil

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Conflict of interest: None

A 49-year-old woman developed loop nephritis at the age of 32 and was treated for a long time with CsA and prednisolone (PSL). Nephritis was suspected, and it was difficult to reduce the dose to 7 mg or less with PSL. Therefore, the immunosuppressant was changed from CsA to MMF in September X-1. Since NPSLE was suspected serologically and image-wise, steroid pulse and plasma exchange were performed, but the patient was almost in a coma. After being transferred to another hospital and undergoing a brain biopsy, he was re-transferred to our hospital. Although he was treated with PSL alone at the transfer destination, his consciousness level gradually improved after the biopsy, and he improved even after he was re-transferred to our hospital. Continuing, the progress of physical and language rehabilitation was good, and he was discharged from the hospital. Currently, he can go to the hospital and shop alone. Brain biopsy results show only nonspecific inflammation, which is consistent with NPSLE. MMF is an important drug in the treatment of SLE, but in the case reports registered with PMDA, 3 cases were reported in which the primary disease was SLE and the suspected drug MMF was NPSLE as an adverse

event. It should be noted that NPSLE can develop.

### P33-8

#### Belimumab (BEL) efficacy in Japanese patients (pts) with a history of active lupus nephritis (LN): A design of post-Marketed effectiveness of BEL coHorT and Japan Lupus nationwide reGistry (LUNA) coHorT (MOONLIGHT) study

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Conflict of interest: Yes

[Objective] Although the add-on effect of BEL during induction phase in active LN was shown in the BLISS-LN trial (GSK Study BEL114054), this treatment strategy is rare in Japan. By using the post-marketing and LUNA data, the MOONLIGHT study will evaluate the effectiveness of BEL in pts with LN who are not in induction phase, by examining renal relapse risk reduction, steroid tapering, and systemic responsiveness after 3 years of treatment. [Methods] In this multicenter, retrospective, observational study (GSK Study 214710), pts with systemic lupus erythematosus (SLE) and a history of active LN will be enrolled into 1 of 2 groups (N=200/group): a 3-year medical record of BEL + standard therapy (ST; BEL group: post-marketing data) or ST (comparative group: data from LUNA). Primary endpoint: occurrence of renal flare. BEL efficacy will be estimated by adjusting time-dependent confounding factors and intermediate factors using a peripheral structural model. Data on pt background, disease activity/chronic disability score, serum/urine test, treatment, and hospitalization will be collected. [Conclusions] MOONLIGHT will provide valuable data on BEL effect on renal outcomes in pts with SLE and LN, and useful evidence in the management of SLE and LN treatment. **Funding:** GSK

### P33-9

#### Electron microscopic remission on repeat biopsy predicts good outcomes at 5-year for patients with lupus nephritis

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Conflict of interest: None

[Objective] To clarify the significance of repeat biopsy in predicting long-term outcomes for patients with lupus nephritis [Methods] Of 36 lupus patients, 24 underwent repeat biopsy, and 23 with glomerular counts of 10 or higher were included. The relationship between renal histological findings and clinical data was examined. [Results] 2nd biopsies were performed at an average of 29 months after the start of treatment. At the time of 2nd biopsy, proteinuria 0.18 (0.4)/day, Cr 0.80 (0.3) mg/dl, SLEDAI=2.0 (4.2), PSL 6.5 (2.3) mg/day. Activity index (AI)=0 was observed in 57% of cases in light microscopy. Resolution of immune complexes (electron microscopic remission: ER) was observed in 39% of cases in electron microscopy. "SLEDAI=0 and PSL≤5 mg/day at 5-year" correlated with ER (p=0.07), higher C3 levels (p=0.017) and higher lymphocyte counts (p=0.015). "Normal Cr levels at 5-year" correlated with ER (p=0.054). "Proteinuria ≤0.2 g/day at 5-year" correlated with baseline Cr levels (p=0.013) and AI=0 (p=0.055). ER was predicted by "SLEDAI=0 and PSL≤5 mg/day at 2nd biopsy". [Conclusions] In repeat biopsies, ER and AI=0, but not by fluorescence findings, predicted good outcomes at 5-year. Recalibration of therapy based on the results of repeat biopsy may lead to improved long-term outcomes.



### P34-1

#### **A case of systemic lupus erythematosus complicated by concurrent Evans' syndrome and acquired ADAMTS13-deficient thrombotic thrombocytopenic purpura**

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Conflict of interest: None

A 18-year-old woman was diagnosed with systemic lupus erythematosus based on butterfly rash, hair loss, thrombocytopenia and the presence of anti-dsDNA antibodies and anti-Sm antibodies eight years ago. She had been treated with high-dose prednisolone (PSL) and mycophenolate mofetil, and PSL had been tapering off by two months ago. Two weeks before admission, she was suffered from shortness of breath, headache, hemolytic anemia and purpura due to thrombocytopenia. Since the blood test showed a positive direct Coombs' test and the presence of anti-GPIIb/IIIa antibodies, she was diagnosed with Evans' syndrome (ES). She had been treated with methylprednisolone pulse followed by PSL 45 mg/day, however, her thrombocytopenia had not been improved. Based on a low ADAMTS-13 activity level and a high ADAMTS-13 inhibitor level, the diagnosis of acquired thrombotic thrombocytopenic purpura (TTP) was made. She had undergone daily plasma exchange therapy for six days, and her platelet count had recovered rapidly. Acquired TTP has been reported to be rarely complicated by ES. However, this case suggested that it is important to suspect concomitant acquired TTP especially when refractory to PSL, as PE is the first choice of treatment for acquired TTP.

### P34-2

#### **Three cases of systemic lupus erythematosus and thrombotic thrombocytopenic purpura with deficient ADAMTS13 activity**

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Conflict of interest: None

[Objective] Thrombotic thrombocytopenic purpura (TTP) is rare in patients with systemic lupus erythematosus (SLE). We report 3 cases with SLE-TTP. [Cases] Case 1: A 39-yr-old woman presented with bleeding tendency. Plt, 8,000 / $\mu$ L; Hb, 8.0 g/dL; LD, 1,212 IU/L. Methylprednisolone (mPSL) pulse was immediately started, followed by daily plasma exchange (PEX) on the 2nd day, but she died on the 6th day. Case 2: A 53-yr-old woman presented with bleeding tendency. Plt, 8,000 / $\mu$ L; Hb, 9.9 g/dL; LD, 1,266 IU/L. Pulsed mPSL was immediately started, followed by daily PEX on the 2nd day, but she died on the 6th day. Case 3: A 43-yr-old man presented with malaise and dyspnea. Plt, 7,000 / $\mu$ L; Hb, 6.4 g/dL; LD, 2,386 IU/L. Pulsed mPSL and weekly rituximab (RTX) was immediately started, followed by daily PEX on the 4th day. Treatment was successful, and he was discharged on the 27th day. ADAMTS13 activity was deficient (<1%) in all the patients. [Conclusions] In acquired TTP, RTX is considered in PEX-resistant cases. However, our 2 patients died, despite immediate induction of PEX. Therefore, RTX should be administered immediately when SLE-TTP was diagnosed.

### P34-3

#### **A case of SLE complicated by non-autoimmune coagulation factor 13 deficiency**

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Conflict of interest: None

We have experienced a case of SLE with non-autoimmune coagulation factor 13 deficiency, which was detected by prolonged bleeding time. [Case] The patient was a 17-year-old female. She came to our hospital because of fever for about 3 weeks, skin rash, finally leading to the diagnosis of SLE. There were no abnormalities in PT/APTT levels, but prolonged

bleeding time was observed. We suspected acquired factor XIII deficiency because the coagulation factor XIII activity was 48% and the coagulation factor XIII antigen was 59. Due to the appearance of irregular organ bleeding, the patient was supplemented with a coagulation factor 13 preparation. Based on the negative result of coagulation factor 13 inhibitor, the diagnosis of non-autoimmune coagulation factor 13 deficiency was made; it was thought that the coagulation factor was consumed due to the increased disease activity of SLE. On admission SLEDAI was 15, and LL-DAS was achieved with 2 courses of steroid pulse followed by PSL 1 mg/kg/day, MMF 2 g/day, and BLM. [Conclusions] The bleeding time test is a useful test to suspect coagulation factor 13 deficiency before bleeding tendency appears. Acquired coagulation factor 13 deficiency has been increasingly reported in recent years, and is a disease that requires attention.

### P34-4

#### **A case of SLE that has been followed up for a long time as pancytopenia of unknown cause**

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Conflict of interest: None

[Case] 71 years old, male. In April X-3, he found a mass in his right parotid gland and visited our otorhinolaryngology, his parotid gland was biopsied and he was diagnosed with Warthin's tumor. We suggested surgical treatment, but he didn't want to do surgery. May X-2, he became aware of dyspnea, so visited a local doctor. A laboratory test revealed myelocytes and metamyelocytes and progressive anemia, they suspected myelodysplastic syndromes. In June X-2, he visited a hematology and bone marrow biopsy was performed, but blood disorders were negative. They suspected IgG4-related disease, but it didn't meet IgG4-related disease's criteria. In August X, he visited our department. He had 160 times more antinuclear antibodies. He also had pancytopenia, anti-ds-DNA IgG antibody, renal dysfunction such as urinary protein, so he met the 2019 EULAR/ACR SLE classification criteria. We performed renal biopsy and then started treatment with prednisolone (PSL) 30 mg/day (0.5 mg/kg equivalent) to improve pancytopenia and renal dysfunction. [Consideration] He had been followed up in hematology for pancytopenia. In this case, he visited our hospital because of the positive antinuclear antibody, and we diagnosed him as SLE. If pancytopenia is observed, it is necessary to consider collagen diseases.

### P34-5

#### **A case of systemic lupus erythematosus during the onset of aplastic anemia**

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Conflict of interest: None

An 84-year-old woman was admitted to our hospital suffering from shortness of breath. A peripheral blood test revealed the following: white blood cell count, 1800/ $\mu$ L; neutrophil count, 810/ $\mu$ L; lymphocyte count, 846/ $\mu$ L; hemoglobin, 7.2 g/dL; reticulocyte count, 68820/ $\mu$ L; and platelet count, 4000/ $\mu$ L. Her bone marrow was hypocellular with no increased dysplasia or blasts, but a chromosomal analysis revealed a 13q deletion. In addition, a high-sensitivity PNH blood cell test revealed that 0.068% of red blood cells and 1.364% of granulocytes were positive. She was diagnosed with aplastic anemia (stage 3) with an immunological condition. At the same time, laboratory findings showed elevated antinuclear antibody and anti-dsDNA antibody values. She was diagnosed with systemic lupus erythematosus (SLE) based on the SLICC classification criteria. We started the administration of cyclosporine as immunosuppressive therapy. Aplastic anemia is extremely rare as a complication of SLE. Immunosuppressive therapy is often performed for such cases, however, since there are refractory cases, it is necessary to examine the treatment methods selected for each case.

### P34-6

#### Hodgkin's lymphoma in a 9-year-old patient with systemic lupus erythematosus

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Conflict of interest: None

The risk of malignant lymphoma is elevated in systemic lupus erythematosus (SLE) and Hodgkin's lymphoma (HL) is a relatively rare subtype. We report herein a case of HL complicated with childhood SLE. A 9-year-old, female patient received the diagnosis of SLE at age 6 years after presenting with fever, rashes, cytopenia, proteinuria, hypocomplementemia, and positivity for autoantibodies. She had a history of concomitant Sjogren's syndrome with recurrent parotitis and a sublingual gland cyst. She also had lupus nephritis but no history of cyclophosphamide use. Her disease activity was controlled with mycophenolate mofetil, hydroxychloroquine, and belimumab. One month prior to admission, she began experiencing severe fatigue, low-grade fever, and chest and back pain. A chest X-ray revealed an anterosuperior mediastinal mass. Laboratory data demonstrated nothing remarkable except elevated inflammatory indices. Subsequently, the tumor was removed, and histopathology produced findings indicating HL. Hematological malignancies complicated with SLE are estimated to have a three-fold risk ratio and should be considered in cases of lupus presenting with persistent, non-specific symptoms. To our knowledge, the present patient was the youngest to have HL complicated with SLE.

### P34-7

#### Successful use of belimumab to treat refractory autoimmune hemolytic anaemia associated with juvenile systemic lupus erythematosus

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Conflict of interest: None

[Introduction] There are no clear treatment plan for refractory autoimmune refractory hemolytic anemia (AIHA). We present a case of SLE-related AIHA who was refractory to treatment with PSL, MMF, and RTX, but successfully treated with belimumab. [Case] The is 8-year-old girl with epilepsy and psychomotor retardation. Her laboratory data showed low hemoglobin and haptoglobin levels, and high reticulocyte counts and indirect bilirubin level. Because of the positive result of direct Coombs test, AIHA was diagnosed. Physical findings were normal except for conjunctival anemia. SLE was diagnosed because antinuclear antibody and anti-dsDNA antibody were positive with low complement levels and nephritis. mPSL pulse and high-dose PSL therapy were started but ineffective for her AIHA. Therefore, RTX and MMF were added. Although RTX depleted B lymphocytes to 0.1% of all lymphocytes, anemia persisted. MMF was stopped due to recurrent UTIs. After oral hydroxychloroquine and intravenous belimumab therapy were started, hemoglobin level became normal and proteinuria diminished. [Discussion] Because of her recurrent UTIs, we selected a biologic therapy rather than immunosuppressants. This is the first case with pediatric SLE-related AIHA for which belimumab has been significantly effective.

### P34-8

#### Two cases in which remission of arthritis and thrombocytopenia was maintained by induction / maintenance therapy with rituximab for "rhus syndrome" complicated with thrombotic thrombocytopenic purpura

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Conflict of interest: None

[Cases 1] A 70-year-old woman with a history of RA was referred to our department because of thrombocytopenia. As a result, we found anemia with schistocytes, AKI and complement reduction. Also, it was found that anti-ds-DNA antibody, anti-RNP antibody were positive. ADAMST13 activity was reduced and ADAMST13 inhibitor was positive. Therefore, TTP with SLE was diagnosed. High-dose steroid and RTX were administered, and plasma exchange were performed and continued RTX maintained remission. [Cases 2] A 75-year-old man was referred to our department because of fever, polyarthritis, and petechiae. Thrombocytopenia, AKI, anemia with schistocytes, high titers of anti-nuclear antibody and complement reduction were found. It was also found that RF, anti-CCP antibody were positive. Finally, "rhus syndrome" with TTP was diagnosed due to ADAMST13 activity reduction and inhibitor positivity. RTX maintains remission of these conditions. [Clinical significance] Reports of TTP associated with "rhus syndrome" are rare, and there are few reports of administration of RTX with maintenance therapy for TTP with SLE. For "rhus syndrome", which can cause joint destruction with TTP, maintenance administration of RTX was performed, and it was possible to maintain remission for a long period of time.

### P35-1

#### A case of acute disseminated encephalomyelitis-like neuropsychiatric SLE complicated by varicella zoster virus meningoencephalitis

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Conflict of interest: None

A 65-year-old woman with a 30 years history of SLE presented with a fever, headache and disorientation. Elevated cell counts and protein levels in cerebrospinal fluid (CSF) were found. Brain MRI showed multifocal lesions including cerebral hemispheres, cerebellum and pons, suggesting the possibility of infectious meningoencephalitis, neuropsychiatric SLE (NPSLE) and acute disseminated encephalomyelitis (ADEM). She was initially treated with antibiotics, acyclovir and high-dose glucocorticoids. Varicella zoster virus (VZV) meningoencephalitis was confirmed based on the detection of VZV DNA in CSF. Although her neurological symptoms were temporarily improved, she newly developed limb weakness and bladder bowel dysfunction on the 13<sup>th</sup> hospital day, followed by worsening altered mental status. Nerve conduction study showed multiple mononeuropathy pattern, and spinal MRI showed T2 hyperintensity lesions in both cervical and thoracic cord. Serum anti-AQP4 and anti-MOG antibodies were not detected, whereas VZV DNA in CSF turned negative. She was diagnosed with ADEM-like NPSLE and intravenous cyclophosphamide (IVCY) was added, which resulted in improvement. We herein report a rare case of SLE which developed ADEM-like multifocal neurologic deficits triggered by VZV meningoencephalitis.

### P35-2

#### A case of neuropsychiatric systemic lupus erythematosus with multiple cerebral infarctions caused by vertebral artery dissection

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Conflict of interest: None

[Case report] A 36-year-old Japanese female, diagnosed with mixed connective tissue disease (MCTD) 11 years ago and systemic lupus ery-

thematosis (SLE) 7 years ago, was admitted to our hospital because of nephrotic syndrome. A renal biopsy revealed lupus nephritis (class V). Prednisolone 30 mg and tacrolimus 3 mg were started on the third hospital day. On the other hand, MRI showed white matter lesions in the frontal lobe, and cerebrospinal fluid (CSF) examination showed a slight elevation of IL-6 (7.5 pg/mL), suggesting central nervous system (CNS) manifestation. During hospitalization, headache in the back of the left orbit, left posterior neck pain and marked hypertension were observed. Her MRI showed a left vertebral artery dissection and new multiple cerebral infarctions, and CSF examination showed further increase of IL-6 (23.1 pg/mL), suggesting that the vertebral artery dissection was caused by vasculitis. Mycophenolate mofetil (MMF) was added, and the headache symptoms disappeared. Although atherosclerosis, Ribman-Sachs endocarditis and antiphospholipid antibody syndrome are common causes of cerebral infarction in SLE patients, this is a rare case of vertebral artery dissection caused by CNS vasculitis leading to embolization.

### P35-3

#### **A case of SLE with various neuropsychiatric involvements mimicking to bacterial meningitis**

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Conflict of interest: None

[Case] A 61-year-old woman presented with dizziness and fever. She had arthritis, Raynaud's phenomenon and sclerodactyly for 14 years. Since her brain MRI showed multiple cerebral infarctions, aspirin was initiated. She showed lymphopenia, hypocomplementemia, positive ANA, anti-Sm and anti-dsDNA antibodies. She was diagnosed as having SLE and systemic sclerosis and admitted to our hospital. Lupus nephritis was suspected due to proteinuria and hematuria. On the tenth hospital day, she developed left occipital subcortical hemorrhage, and underwent craniotomy for hematoma evacuation. She developed fever and headache after surgery. Bacterial meningitis was suspected owing to leukocytosis, hypoglycemia and markedly elevated level of IL-6 in cerebrospinal fluid (CSF) and treated with meropenem. Persisting headache and fever, progressing cognitive impairment led to the diagnosis of neuropsychiatric SLE (NPSLE). High dose of corticosteroids and intravenous cyclophosphamide therapy successfully improved her symptoms. [Discussion] Leukocytosis and high level of IL-6 in CSF can be seen in both bacterial meningitis and NPSLE. Reporting this case is meaningful in that close monitoring for her various neuropsychiatric symptoms led to the accurate diagnosis of NPSLE.

### P35-4

#### **A case of systemic lupus erythematosus with limbic encephalitis**

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Conflict of interest: None

[Case presentation] A 39-years-old woman was diagnosed with systemic lupus erythematosus (SLE) 11 years ago and SLE was stable with the treatment of prednisolone and tacrolimus. She had an emergency hospitalization due to a headache, changing disturbance in consciousness, retrograde amnesia and memory loss. There were no abnormal findings on the brain MRI. CSF analysis indicated normal other than elevated IL-6 levels. The pulses of intravenous methylprednisolone and cyclophosphamide were administered under the presumptive diagnosis of neuropsychiatric SLE (NPSLE), but a light headache and short-term memory loss remained. MRI demonstrated a new signal hyperintensity in the left amygdala after 8 days. Suspecting an autoimmune limbic encephalitis, we started an intravenous immunoglobulin and her symptoms were improved remarkably. Because anti-NMDAR antibody was negative and anti-NR2 antibody was positive in the CSF, limbic encephalitis with SLE was sus-

pected. [Discussion] There are only 12 case reports MRI indicated abnormal signal in limbic system in the patients with NPSLE and no reports described about anti-NMDAR antibody and anti-NR2 antibody. This is the first case of SLE with limbic encephalitis focused to autoantibodies that are thought to be associated with NPSLE.

### P35-5

#### **A case of anti-centromere antibody positive lupus nephritis resulting in central nervous system lupus**

Keitaro Saito, Shunya Kaneshita, Yu Isoda, Risa Sagawa, Naoka Kamio, Takuya Inoue, Kazuki Fujioka, Wataru Fujii, Takahiro Seno, Makoto Wada, Masataka Kohno, Yutaka Kawahito

Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Conflict of interest: None

[Case] 73-year-old female [Medical history] Limited systemic sclerosis Cytomegalovirus enteritis Herpes zoster [Complaint] Disorder of consciousness [History of current illness] An anti-centromere antibody-positive lupus nephritis patient had been treated with corticosteroid and mycophenolate mofetil for a year. The patient had disorientation and followed by convulsions, and was transferred to our hospital. Head MRI showed hyperintense on DWI and FLAIR in the left medial hindbrain to the lateral thalamus and vast area of the corpus callosum, but no significant stenosis on MR angiography. Spinal fluid examination showed no evidence of bacterial meningitis, HSV-1/2, VZV, or JC virus, and prednisolone was continued for central nervous system lupus. She was discharged from the hospital one month later after a gradual reduction of steroids in combination with IVCY. [Clinical significance] Anti-centromere antibodies have been reported to be positive in scleroderma, Sjogren's syndrome, and primary biliary cirrhosis, and are also found to be positive in some forms of SLE. However, there is no report of NPSLE, and we consider this case to be a valuable one and report it with a discussion of the literature.

### P35-6

#### **A case report of an intravenous cyclophosphamide-resistant cerebral lupus vasculitis successfully treated with rituximab**

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Conflict of interest: None

The case is 52-year-old female with systemic lupus erythematosus (SLE), who was diagnosed with class V lupus nephritis, and attained remission with hydroxychloroquine (HCQ), prednisolone (PSL), and mycophenolate mofetil. At age 51, she had two cerebral infarctions that resulted in complete recovery of the symptoms on the day after. A head MRA revealed multiple stenoses and aneurysms of peripheral cerebral arteries. A diagnosis of cerebral vasculitis due to SLE was made based on the cerebrospinal fluid (CSF) profile: elevated leukocytes, proteins, and IL-6. High-dose PSL and intravenous cyclophosphamide (IVCY) were started as remission induction. While CSF proteins and leukocyte decreased, subarachnoid hemorrhage and recurrence of subacute cerebral infarction occurred during the treatment course. Furthermore, CSF IL-6 levels gradually increased and new cerebral aneurysms appeared on MRA. Remission induction was re-attempted with rituximab (RTX) plus PSL, leading to improved CSF profile and disappearance of some aneurysms. This is a rare case in which SLE lesions were exclusively localized in the central nervous system without any serological changes suggestive of SLE. Our case suggests that RTX may be effective in IVCY-resistant SLE localized in the cerebrovascular system.

### P35-7

#### **A case of NPSLE that was thought to be mild aseptic meningitis at the onset, but was difficult to treat and responded to plasma exchange (PE) therapy**

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Itami City Hospital



Conflict of interest: None

A 17-year-old woman who presented with fever and headache was diagnosed with SLE on the basis of malar rash, antinuclear antibodies and anti-dsDNA antibodies positive, hemolytic anemia and hypocomplementemia. Antiphospholipid syndrome (APS) was suspected due to anti-CL- $\beta$ 2GPI antibodies, LA and prolonged APTT. The cerebrospinal fluid (CSF) showed only mild albuminocytologic dissociation. She was treated with mPSL pulses and then with PSL 1 mg/kg/day, which resulted in improvement of fever, anemia and hypocomplementemia. However, the headache gradually flared up despite addition of treatments. Suddenly consciousness disorder appeared. Subarachnoid hemorrhage due to disruption of microvessels in the subarachnoid space was suspected from images. The CSF showed increased cell count and elevated protein. We thought that the severe inflammation and spasm of microvessels or microthrombosis and vascular damage associated with potential APS caused the consciousness disorder. We started PE, IVCY and mPSL pulses and the treatments were successful. Later, IL-6 in the CSF on admission revealed markedly high. The CSF showed only mild albuminocytologic dissociation despite high IL-6 level. PE would correct the severe inflammation reflected by the high IL-6 level or break down APS condition.

### P35-8

#### **A case of systemic lupus erythematosus thought to be complicated by autoimmune autonomic ganglionopathy**

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Conflict of interest: None

Recently, the association of anti-autonomic ganglion acetylcholine receptor antibody (anti-gAChR antibody) in autoimmune autonomic ganglionopathy (AAG) has been reported. A woman in her 40s was continuously treated with prednisolone (PSL) 5 mg/day for SLE (pancytopenia, polyarthritis). She was admitted to the hospital because of thrombocytopenia and relapse due to nephritis (type V). Imaging studies showed bilateral hydronephrosis, bilateral ureteral dilatation over the entire length of the ureters, bladder dilatation, and decreased peristalsis and marked dilatation of the intestinal tract. There was no obstructive origin of the urinary tract. There was also no evidence of transverse myelitis. In response to SLE flare-up, IVIG and steroid pulse therapy were started, and then MMF, Tac, and belimumab were added to the steroid therapy, and hydronephrosis, ureteral dilatation, and intestinal dilatation improved along with platelet count and nephritis. During the course of the disease, we suspected AAG and measured anti-gAChR antibody, which was positive for anti-gAChR $\alpha$ 3 antibody, suggesting that the urinary tract and intestinal tract lesions were caused by AAG. The possibility that dysuria and decreased intestinal peristalsis in SLE patients may be caused by AAG should be considered.

### P36-1

#### **Three cases of organizing pneumonia in patients with systemic lupus erythematosus**

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Center for Rheumatic Diseases, Mie University Hospital

Conflict of interest: None

[Cases] Case 1: A 34-year-old woman who had immunogenetic thrombocytopenic purpura for 21 years presented with cough, dyspnea, fever, discoid rash, and lymphocytopenia with positive antinuclear antibodies. Systemic lupus erythematosus (SLE) was diagnosed. Chest CT revealed organizing pneumonia (OP). PSL and tacrolimus (TAC) improved OP and other symptoms. Case 2: A 74-year-old woman who was diagnosed as SLE 12 months before and had been treated with PSL, TAC, MMF and belimumab. She newly presented with fever, arthralgia, pleuritis and lupus nephritis and OP. PSL and repeated intravenous cyclophosphamide therapy improved SLE manifestations including OP. Case 3: A 35-year-old woman presented with fever, cough, dyspnea, arthralgia and butterfly rash. Chest CT revealed OP and lupus nephritis developed later. Methyl-PSL pulse

therapy followed by PSL, TAC improved OP along with other manifestations. [Discussion] OP rarely occurs in SLE, however, 18 cases have been reported including our 3 cases. When OP developed, active extrapulmonary lesions of SLE simultaneously presented in all cases. Therefore, OP was considered to be a manifestation of SLE. [Conclusion] Reporting these three cases is meaningful in proposing that OP is considered to be one of the pulmonary manifestations of SLE.

### P36-2

#### **Prophylaxis of pneumocystis pneumonia in patients with systemic lupus erythematosus and its relationship to glucocorticoid dose: a cross-sectional study from lupus registry of nationwide institutions (LUNA)**

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Conflict of interest: None

[Purpose] The purpose of this study is to describe the practice of pneumocystis pneumonia (PCP) prophylaxis in patients with systemic lupus erythematosus (SLE) and evaluate its relationship to glucocorticoid (GC) dose. [Method] We evaluated the relationship between prednisolone (PSL) dose and PCP prophylaxis cross-sectionally using data from multicenter registry, excluding pregnant patients, patients without a history of GC treatment, and patients with missing data. [Results] Mean age of the 1453 patients was 47 years, mean duration of the disease was 179 months, and mean PSL dose was 7.2 mg/day. PCP prophylaxis was performed in 310 patients (21%), and the medications included trimethoprim/sulfamethoxazole in 281, atovaquone in 25, and pentamidine in 4. Proportion of PCP prophylaxis decreased by PSL dosage: PSL  $\geq$  30 mg, 24/32 (75%); 20-30 mg, 30/47 (64%); 15-20 mg, 23/46 (50%); 10-15 mg, 62/182 (33%); 7.5-10 mg, 49/181 (27%); 5-7.5 mg, 98/534 (18%); <5 mg, 24/428 (5.6%). After adjusting confounding factors in 970 patients without missing values using multivariate analysis, PSL was still related to PSL dose significantly (odds ratio per 5 mg reduction: 0.57 [95% confidence interval: 0.49-0.65]). [Conclusion] PCP prophylaxis is performed according to GC dose in patients with SLE.

### P36-3

#### **A case of systemic lupus erythematosus which developed severe course of lupus myocarditis after drug-induced lupus improvement**

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Conflict of interest: None

[Rationale] In drug-induced lupus, symptoms similar to systemic lupus erythematosus (SLE) usually resolve after discontinuation of offending drug. Further, it usually lacks major SLE complications. [Case presentation] A 41 year-old-woman with a history of ulcerative colitis who had been in remission by mesalazine presented with polyarthritis, myositis and was positive for anti-dsDNA antibody. After discontinuation of mesalazine, the symptoms resolved and the antibody titer decreased. She was diagnosed with drug-induced lupus. Half a year later, however, she developed lupus myocarditis with distinct histological evidence. Though her initial state was so severe as indicated by extremely low Ejection Fraction (EF) (20%) and global hypokinesia, after treatments with glucocorticoid, cyclophosphamide, intravenous immunoglobulin and intra-aortic balloon pump (IABP), she showed dramatic improvement, and was discharged without any mechanical support on the 42nd day of her admission. [Conclusions] Life-threatening systemic disorders of SLE can occur in drug-induced lupus even after resolution of the symptoms through stopping the drug. Our case suggests that some drug-induced lupus cases should be offered careful observation and should be given intensive treatments as SLE when needed.

### P36-4

#### **A case of systemic lupus erythematosus complicated by severe heart failure due to lupus myocarditis**

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Izumi City General Hospital

Conflict of interest: None

Case: A 42-year-old female was referred because of the lower leg edema, high fever and pleural effusion from 2 months ago. Lupus nephritis was diagnosed because of high proteinuria, antinuclear antibody 640-fold positive, anti-DNA antibody positive, anti-Sm antibody positive and hypocomplementemia. From the day of hospitalization, dyspnea, anorexia and pleural effusion worsened. Echocardiography showed a decrease in ejection fraction (EF) to 34% and severe diffuse hypokinesia. Acute heart failure due to lupus myocarditis was diagnosed. After renal biopsy, High-dose methylprednisolone, prednisolone 50 mg/day, mycophenolic acid 2 g/day and belimumab were administered. However, one week after the start of treatment, the EF decreased to 18%. Hemodialysis was performed and cardioprotective drugs were administered in the intensive care unit. Improvement of cardiac function and proteinuria was gradually observed, and hemodialysis and cardioprotective drugs were withdrawn on the 32nd hospital day. On the 92nd day of illness, the EF improved to 45%. Lupus myocarditis is a rare manifestation of SLE. There is limited evidence of the optimal treatment and the prognosis. We report a valuable case of lupus myocarditis with severe heart failure as an initial symptom, with a review of the literature.

### P36-5

#### **HFpEF associated with atrial fibrillation in a patient with systemic lupus erythematosus**

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Conflict of interest: None

[Background] Heart failure with preserved ejection fraction (HFpEF) is a well-known condition that is often associated with atrial fibrillation (Af). The recent study suggested that systemic lupus erythematosus (SLE) was a risk factor for Af (Lim SY.2019). I report a case of SLE complicated with HFpEF and Af. [Case] An 83-year-old woman had a history of SLE and hypertension. She was referred to another hospital because of her mal-

aise and foot edema. Laboratory tests and an echocardiography showed elevated BNP and normal EF, which was compatible to HFpEF. An electrocardiogram (ECG) showed Af rhythm. Despite diuretics, mineral corticoid receptor antagonist, beta blocker, calcium channel blocker, angiotensin II receptor blocker (ARB), and direct-acting oral anticoagulant (DOAC) resolved the edema, malaise and dyspnea developed due to hypotension. When she was admitted to our hospital, a chest radiograph demonstrated the absence of HF and ECG showed sinus rhythm. Her blood pressure was elevated and malaise was resolved after discontinuation of medication except ARB and DOAC. She was discharged from our hospital on foot. [Clinical significance] The study also showed that mortality rate was greater in SLE group with Af. Af should be treated in patients with SLE complicated with HFpEF.

### P36-6

#### **Systemic lupus erythematosus with cardiac tamponade one week after hospitalization**

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Conflict of interest: None

The patient is a 20 years old woman. She has had lower limb myalgia since May 20XX and was hospitalized on June 15 with suspected collagen tissue disease. She was diagnosed with systemic lupus erythematosus (SLE) based on fever, proteinuria, hypocomplementemia, positive of antinuclear antibodies, anti-DNA antibodies, and anti-Sm antibodies. Renal biopsy and muscle biopsy were considered for further investigation, but due to persistent fever and myalgia, treatment with prednisolone (PSL) 55 mg/day was started on day 6. The chest CT scan on admission showed small amounts of pericardial effusion, but echocardiography on day 8 showed massive pericardial effusion. After that, she was hypotensive and tachycardiac, and pericardial drainage was performed. Colchicine was started on the same day, and the drain tube was removed on day 13. She could not continue mycophenolate mofetil due to drug-induced arthritis and was finally treated with PSL 37.5 mg/day, hydroxychloroquine and tacrolimus without relapse and was discharged on day 76. This case was SLE with rapidly massive pericardial effusion. Of the SLE patients admitted to our hospital from 2013 to 2021, 7 cases were diagnosed with cardiac tamponade. We report the clinical characteristics of SLE patients with cardiac tamponade.

### P36-7

#### **A case of systemic lupus erythematosus (SLE) of elderly male complicated with pericardial fluid as an initial symptom**

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Conflict of interest: None

A case of systemic lupus erythematosus (SLE) of elderly male complicated with pericardial fluid as an initial symptom. Fukuda Natsuko, Ito Naoko, Kuboyama Tomohiko, Konma Junichi, Fujiki Youhei Department of Rheumatology, Yodogawa Christian Hospital, Osaka, Japan A 80-year-old man was admitted to the hospital for cardiac tamponade in October X-1 year, then he treated with pericardial drainage. He had no malignancy, but laboratory test showed hypocomplementemia, and antinuclear antibody was positive. In April X year, he was complicated autoimmune hemolytic anemia. We started high-dose prednisolone (PSL 50 mg/day), but did not respond well. Laboratory test demonstrated anti-ribosomal P antibody was positive, he was diagnosed SLE. Initial treatment was not effective, so we started cyclosporine, but it was discontinued because of renal disorder. Then we started methylprednisolone pulse therapy and cyclophosphamide pulse. After then, he had massive hemorrhage of colon, finally he died of multiple organ failure on the 107<sup>th</sup> day. The case of elderly-onset SLE of male is rare, so it is difficult to diagnose. We report the valuable case with review of the literature.

### P36-8

#### Two cases of late-onset systemic lupus erythematosus accompanied by autoimmune hepatitis

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Kawasaki Municipal Ida Hospital

Conflict of interest: None

[Case 1] A 70-year old woman presented with arthralgia, thrombocytopenia. Laboratory evaluations were as follows: AST 466 IU/L, ALT 555 IU/L, IgG 4547 mg/dl. Hypocomplementemia was also found. The titer of ANA was 1:640 (homogeneous and speckled pattern). Anti-dsDNA antibody was present. Liver biopsy demonstrated chronic hepatitis with severe activity. She was diagnosed as having late-onset systemic lupus erythematosus (SLE) and autoimmune hepatitis (AIH). Treatment with prednisolone (PSL) 40 mg/day and azathioprine (AZA) 25 mg/day was started. Symptoms improved and liver functions were normalized. [Case 2] A 79-year old woman presented with arthralgia. Laboratory evaluations were as follows: AST 856 IU/L, ALT 1043 IU/L, IgG 2650 mg/dl. Hypocomplementemia was also found. The titer of ANA was 1:160 (homogeneous and speckled pattern). Anti-DNA antibody was present. Liver biopsy demonstrated chronic hepatitis with severe activity. She was diagnosed as having late-onset SLE and AIH. Treatment with PSL 30 mg/day and AZA 25 mg/day was started. Symptoms improved and liver functions were normalized. [Conclusions] It is important to consider a diagnosis of AIH when SLE patients demonstrate severe liver dysfunction.

### P36-9

#### A case of SLE with acute pancreatitis as the initial symptoms

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Conflict of interest: None

[Case] 28 year old woman [Main complaint] fever and rash [Progress] Since July X, she was aware of a rash and muscle pain. A blood test showed pancytopenia and positive antinuclear antibody, so she was referred to our hospital. SLE was diagnosed from lupus rash, oral ulcer, urinary protein, pancytopenia, antinuclear antibody positive, anti dsDNA antibodies positive, anti Sm antibody positive, etc. On August 14, she complained of strong nausea and mild abdominal pain, and a blood test showed an increase in amylase. Assuming complications of lupus pancreatitis, prednisolone 90 mg was started on the same day. On the 15th, there was a prominent exacerbation of abdominal pain, increased amylase level, and contrast-enhanced CT showed grade IV pancreatitis. In addition to infusion and proteolytic enzyme inhibitor, intravenous cyclophosphamide was started in combination. After improvement of symptoms, in consideration of fertility, we switched to mycophenolate mofetil and tacrolimus and hydroxychloroquine and belimumab in combination to induce remission. [Discussion] The frequency of pancreatitis associated with SLE is 3 to 4%. Drug-induced agents such as steroids and immunosuppressants often trigger the pancreatitis onset. We report pancreatitis as an organ lesion of SLE.

### P36-10

#### Protein-losing gastroenteropathy as the initial manifestation of elderly onset systemic lupus erythematosus

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Conflict of interest: None

We report an unusual case of a Japanese 71-year-old systemic lupus erythematosus (SLE) presented with protein-losing gastroenteropathy (PLG) as an initial manifestation. This patient's illness began in May 2021 with a fever, fatigue and frequent diarrhea. On admission to our hospital,

the patient had pleural effusion and ascites with proteinuria and hypoalbuminemia (2.5 g/dL). Additionally, ANA with homo-speckled appearance, anti-Sm, RNP, dsDNA, ACLs and SS-A/Ro antibodies were positive and hypocomplementemia was detected. According to these findings, the patient was diagnosed as SLE and pleural effusion and ascites were considered due to nephrotic syndrome. However, renal function was normal and hypercholesterolemia was absent. With abdominal CT findings, protein loss in the gastrointestinal tract was considered and 99mTc-albumin scintigraphy was performed. The result revealed the presence of PLG. The patient was treated with high dose prednisolone and tacrolimus and showed a good response. In general, hypoalbuminemia in the setting of SLE is most frequently caused by protein loss due to renal dysfunction. Although its occurrence is rare, PLG is also a potential cause of hypoproteinemia and albumin scintigraphy is useful for the diagnosis of PLG.

### P36-11

#### A case of successfully treated type B insulin resistance syndrome related to systemic lupus erythematosus with multi target therapy

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Conflict of interest: None

[Case] A 46-year-old woman was hospitalized due to pancytopenia, proteinuria, renal dysfunction, and continuous hyperglycemia. She was diagnosed as having systemic lupus erythematosus (SLE) with positive antinuclear antibody (×2560, sp), hypocomplementemia, and lupus nephritis ISN/RPS III-G (A). She was treated with prednisolone (PSL) at 40 mg/day. Hyperglycemia was deteriorated even with 80 units/day of insulin. She was diagnosed with type B insulin resistance syndrome (TBIRS) by positive insulin receptor antibody. Mycophenolate mofetil and tacrolimus therapy was introduced. After continuous intravenous insulin therapy, hypoglycemia in the early morning was gradually appeared. Diazoxide, insulin secretion inhibitor, was initiated started. By this multiple target therapy ameliorated activity of lupus nephritis and severity of fluctuated glucose level by decreasing insulin receptor antibody. She was discharged on the 58th day. [Clinical significance] TBIRS is a rare disease characterized by hyperglycemia in daytime and hypoglycemia in early morning, which is associated with autoimmune diseases. There has been no established treatment method yet, thus this multi target therapy maybe the candidate for treatment of TBIRS related to SLE.

### P36-12

#### Belimumab therapy of glucocorticoid (GC)-ineffective SLE with lysinuric protein intolerance

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Conflict of interest: None

Lysinuric protein intolerance (LPI) is caused by defective transport of dibasic amino acids resulting in low protein synthesis and various clinical symptoms. Of about 40 Japanese LPI patients, 30% of them have autoimmune disease, severe viral infections and hemophagocytic syndrome (HPS). A 16-year-old woman was diagnosed as LPI at one year old and got HPS and pneumonia at 12 years old. She developed nephrotic syndrome with positive ANA and low complement but anti-dsDNA antibodies were not elevated. After the treatment of methylprednisolone as SLE, serum levels of LDH and ferritin were remarkably elevated and complement was decreased, which improved with immunoglobulin (IVIG). Renal pathology showed full-house pattern by fluorescence antibody assay resulting in lupus nephritis class IV. No proteinuria was observed after mizoribine therapy. After dose up of prednisolone for thrombosis of hand vein at 21 years old, serum LDH and ferritin levels were remarkably elevated and



coagulopathy was advanced. Low complement and high serum BAFF activity were continued after treatment of MMF, which improved by belimumab (BEL) therapy. While HPS findings progressed by GC, IVIG and BEL were effective. There is no report of BEL therapy in LPI with SLE, suggesting that BEL may be effective.

### P36-13

#### **A pediatric case of systemic lupus erythematosus with hypertriglyceridemia suspected to be caused by anti-GPIIIBP1 antibody**

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Conflict of interest: None

A 14-year-old girl was diagnosed with SLE based on fever, hematuria, proteinuria, hypocomplementemia, elevated ANA/anti-dsDNA antibody titers, and renal biopsy results (LN class IIIA/C). She had elevated serum triglyceride (TG) levels (1374 mg/dl), but total cholesterol and HDL levels were low (104 and 13 mg/dl). Her family history includes no hyperlipidemia. VLDL and chylomicron levels were elevated, and post-heparin plasma lipoprotein lipase was low (26 ng/ml). Considering the risk of pancreatitis, fat restriction and fibrates were started before intravenous mPSL (IVMP). Two days later, TG levels had decreased (537 mg/dl), and IVMP was started. Fibrates were discontinued, and lipid restriction was gradually relaxed due to further decrease in TG levels. PSL, MMF, and HCQ were administered. TG levels normalized at 19 days after starting IVMP. Auto-antibody against glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIIIBP1) was positive before IVMP by immunoblot analysis, and decreased after TG normalization. In this case, immunosuppressive therapy decreased anti-GPIIIBP1 antibody levels, and improved hypertriglyceridemia. We consider this case to be informative for understanding the pathophysiology of hyperlipidemia due to an autoimmune mechanism.

### P37-1

#### **Heterogeneity of Systemic Lupus International Collaborating Clinics/American college of Rheumatology Damage Index (SDI) item and reduction of damage accrual in patients with systemic lupus erythematosus (SLE)**

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Conflict of interest: None

[Objective] To clarify damage accrual in 83 patients with SLE. [Methods] Medical record review. SDI items were divided into glucocorticoid (GS) use and disease activity origin. Patients were classified in LLDAS  $\geq 50\%$  of observation or DORIS remission. [Results] Cumulative SDI items were 116. GS use items were avascular necrosis 15, bone fracture 12, cataract and/or retinopathy 22, diabetes 8, cerebrovascular 13, cardiovascular disorder 7 and venous thrombosis 5. Items attributed to disease activity were progressive renal damage 10, gastrointestinal 7 and skin ulceration and pulmonary hypertension 5. There were 12 malignancies including B cell lymphoma. Patients maintaining PSL 2.5 mg/day had significantly less renal disease and cerebrovascular accident than patients maintaining PSL  $\geq 5$  mg/day. Patients with immunosuppressants had more malignancy. The logistic analysis showed remission flares and renal involvement were risk factors, but PSL 2.5 mg/day maintenance was protective against damage accrual. Patients with DORIS remission and/or LLDAS  $\geq 50\%$  of observation had significantly lower SDI score and less renal and cerebrovascular damage. [Conclusions] Occurrence of SDI item was heterogeneous. Early induction to DORIS remission and/or LLDAS might be associated with reduced damage accrual.

### P37-2

#### **A cross-sectional study of the number of outpatient physician changes and disability index in SLE patients: The LUNA Registry**

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Conflict of interest: None

[Objective] SLE patients experience multiple outpatient physician changes. The purpose of this study was to evaluate the effect of the change of physician on the level of disability. [Methods] Patients with SLE enrolled in the 13-center multicenter registry (LUNA) were included. The primary outcome was the SDI, and logistic regression analysis was performed to examine the association between SDI and the number of annual physician changes per year (person/year), including age, gender, duration of illness, and the number of hospitalizations after SLE diagnosis in the model. Multiple regression analysis was performed using the Lupus PRO Satisfaction with Care as secondary outcomes. [Results] 295 subjects were enrolled. In multivariate analysis, the primary outcome, SDI, had an OR of 1.07 (95% CI: 0.53-2.16), which was not significantly different from the primary outcome. The secondary outcome, Lupus PRO, had a beta-coef of 3.00 (-7.21-13.21) and was also not significantly different. [Conclusion] There was no significant association between the number of outpatient physician changes after the onset of SLE and the disability index and QoL scale of physician satisfaction.

### P37-3

#### **The association between the trust in physician and the burden of treatment costs for daily life in SLE patients; The TRUMP2-SLE study**

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Conflict of interest: None

[Objective] Trust in physicians influences disease prognosis through adherence and other factors. In addition, the burden of treatment costs on daily life (financial toxicity) is an issue that physicians must take into consideration. In this study, we investigated whether trust in physicians is related to economic toxicity in SLE patients. [Methods] A cross-sectional study of patients with SLE attending five universities from June 2020 to August 2021. Exposure was the trust in physician, as measured by the 5-item Wake Forest Physician Trust Scale, individual version. The outcome was financial toxicity, measured by the 11-item COST. Multiple regression analysis was used to examine the association between trust in physicians and financial toxicity, with adjustment variables including age, gender, disease activity, cost of immunosuppressive drugs and socioeconomic status. [Results] The median age was 44 years, 89.1% were female, the Wake Forest Physician Trust Scale was 80, and the median COST was 23. Higher physician trust was associated with lower financial toxicity (0.70 points lower per 10 points of physician trust (95% CI 0.20-1.21)). [Conclusions] The establishment of a physician-patient trust relationship reduced the sense of economic burden.

### P37-4

#### The study of quality of life, bone mineral density, and sleep time in patients with systemic lupus erythematosus: from Juntendo SLE Prospective Registry Study (JUMP study)

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Conflict of interest: None

[Objective] It is known that patients with systemic lupus erythematosus (SLE) who spend the majority of their time in lupus low disease activity state (LLDAS) have a low rate of complications, relapses and a good quality of life (QOL). In this study, we investigated the relationship between LLDAS, QOL, bone mineral density (BMD), and sleeping time. [Methods] The subjects were 72 patients registered in the SLE prospective study (JUMP) conducted at our facility. The QOL, BMD, sleeping time, disease activity were investigated. The QOL was evaluated using the EQ-5D and SF36, and the BMD was measured by the dual-energy X-ray absorptiometry. [Results] The mean age was 45.4±13.9 years, with 8 males and 64 females. Of these, 40 were LLDAS and 32 were non-LLDAS. The QOL performed by EQ-5D and SF36 were significantly higher in the LLDAS. However, body pain (BP) in SF36 was low in both groups, and when the BMD was compared, the T score was low in both. The average sleeping time was 6.7±1.0 hours, but amount of sleep was not related to LLDAS, DEXA, QOL, and so on. [Conclusions] In the management of patients with SLE, prevention of osteoporosis and relieving pain are important factors in improving the QOL. In this study, no findings related to amount of sleep were found in SLE patients.

### P37-5

#### Bacteremia in systemic lupus erythematosus: risk factors, clinical and microbiological characteristics, and outcomes in the single-center retrospective cohort

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Conflict of interest: None

[Objectives] We evaluate the characteristics of patients with bacteremia and SLE, then we compare the group that survived to the group that died. [Methods] This study was a retrospective single-center observational study. We included patients who received blood culture tests in our hospital from April 2009 to April 2020, and we analyzed bacteremia in 65 patients with SLE. [Results] The median observation period was 39 (interquartile range: 6-74) months. The median age was 54 (43-64) years. Patients consisted of 6 males and 59 females. In 49 cases, the patient survived. In 16 cases, the patient died. The dead group was older, lower Glasgow Coma Scale scores, higher sequential organ failure assessment (SOFA) scores, and lower fibrinogen levels. [Conclusions] When physicians encounter patients with suspected bacteremia, they should pay attention to the consciousness assessment, SOFA score, and be aware of infections caused by common microorganisms and opportunistic infections.

### P37-6

#### Clinical characteristics of elderly onset (E-O) systemic lupus erythematosus (SLE); comparison with young-middle aged onset (YM-O) SLE

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University of Tsukuba Hospital

Conflict of interest: None

[Objective] To clarify clinical characteristics of E-O SLE. [Methods] We examined consecutive patients with newly onset SLE, who admitted to our department between Jan 2012 and Apr 2021. We regarded patients who developed SLE at ≥60 years old as E-O, while patients at <60 years old as YM-O. 1) Patients' background, 2) clinical symptoms and comorbidities, 3) laboratory data, 4) organ involvements, and 5) induction therapy were compared between E-O and YM-O groups, retrospectively. [Results] 1) 15 E-O (66.5±4.7 years old, 9 males/6 females) and 32 YM-O (36.0±10.3, 2/30) patients were identified. Male patients were significantly more dominant in E-O group than in YM-O group. 2) Malar rash (1/15 cases) and oral ulcer (1/15) were significantly less common, while Sjögren's syndrome (SS) was significantly more common in E-O group (8/15) than in YM-O group (17/32, 17/32, 6/32). 3) Blood cell counts, complement, and anti-DNA antibody titers were similar between groups. 4) Frequency of nephritis, serositis, and ILD, and SLEDAI at baseline were comparable among two groups. 5) Corticosteroid and immunosuppressants were similarly used for induction therapy in both groups. [Conclusions] Male dominance and uncommon malar rash and oral ulcer, associated with SS were characteristic features of E-O SLE.

### P37-7

#### Clinical features and treatment in 24 cases of Rhupus syndrome

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Conflict of interest: None

[Objective] The combination of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) is known as "Rhupus". We are often difficult to diagnose and treatment of Rhupus. [Methods] We investigated "Rhupus" is diagnosed by attending physician and is the fulfillment of the diagnostic criteria for both SLE and RA from 2015 to September 2021. [Results] 24 patients (23 female, 1 male) with rhupus were 6.4% of SLE patients. In 12 patients SLE was the initial illness and in 3 both diseases started simultaneously. All were anti-dsDNA antibodies positive, anti-SS-A antibodies positive 8 cases, anti-phospholipid antibody positive 4 cases, RF positive 12 cases, anti-CCP antibody positive 13 cases and 7 cases negative both of RF and anti-CCP antibody. More than half showed Skin rash and hematological damage, 5 nephritis and 2 CNS. Small joint arthritis was the most, but 1 cases had atlantoaxial dislocation and giant bursitis, and 10 cases were stain blocker classification III or IV. PSL usage all, MMF 3 cases, TAC 19 cases, HCQ 10 cases, MTX 18 cases and 11 cases of bs DMARDs and Janus Kinase inhibitors 2 cases. [Conclusions]

In this study, a few cases showed severe organ damages of SLE. We should be considered usage of bs DMARDs for showed erosion Joint deformity.

### P37-8

#### **A case of systemic lupus erythematosus (SLE) manifesting as infectious mononucleosis (IM)**

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Conflict of interest: None

[Case] Female in her 30s [Main complaint] Fever [Clinical course] The patient was diagnosed with rheumatoid arthritis (RA) 13 years prior to admission, based on polyarthritis, positive rheumatoid factor, and positive anti-CCP antibody. The patient was treated with methotrexate 10-14 mg/week for RA, and remission was maintained. The patient had persistent fever for 1 week prior to admission, and after admission, the first infection with EB virus (EBV) was found, and IM was diagnosed. During the course of the disease, pleurisy, thrombocytopenia, proteinuria, and low complement were observed, and SLE was diagnosed. Prednisolone (PSL) 25 mg/day (0.5 mg/kg/day) was started for pleurisy, but the patient was refractory to treatment and the dose was increased to PSL 50 mg/day. The patient responded to treatment, pleurisy, thrombocytopenia, urinary findings, and hypocomplementemia improved, so PSL was tapered and the patient was discharged on the 38th day. [Clinical significance] Although there have been many reports on the relationship between EBV and SLE, no clear causal relationship has been proven. The present case is suggestive of the relationship between EBV infection and SLE, and we report it with some discussion of the literature.

### P37-9

#### **A case of SLE suspected of being complicated by autoinflammatory disease (familial Mediterranean fever) in which colchicine was successful for periodic fever**

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Conflict of interest: None

[Case] A 39-year-old woman developed SLE with fever, multiple arthralgias, and lymphopenia, and became antinuclear antibody-positive and anti-Sm antibody-positive in X-10 year. Administration of prednisolone (PSL) at 30 mg/d improved symptoms and PSL was gradually reduced. Periodic fever appeared from around April in X year. The dose of PSL was increased to 30 mg/d, and mizoribine or tacrolimus (TAC) was used in combination. However, a fever of approximately 39.0°C appeared once every 2 to 3 weeks, and spontaneous remission was repeated in 1 to 3 days. There was general malaise at the time of fever, but no joint symptoms, serosal irritation symptoms, or meningitis-like symptoms were observed. CRP increased during fever but disappeared after its resolution. No mutations with clear pathogenic significance were found in autoinflammatory disease-related genetic tests. Administration of colchicine was started. Thereafter, the periodic fever disappeared, and PSL was gradually decreased to 5 mg/d for maintenance. [Discussion] This case may have been caused by gene mutation associated with autoinflammatory disease that has not yet been identified. If periodic fever with a poor treatment response is observed in cases of SLE, the possibility of autoinflammatory disease should be considered.

### P37-10

#### **A case of Systemic lupus erythematosus presenting with only alopecia at the time of diagnosis**

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Conflict of interest: None

(Case) A 22-year-old woman presented to a dermatology clinic complaining of patchy hair loss for two years. Antinuclear antibodies (ANA) were found, and she was referred to our department. She was asymptomatic, looked very well and reported no fever, arthritis, chest pain, abdominal pain, diarrhea, erythematous rash, photosensitivity or oral ulcer. On admission, patches of non-scarring hair loss were observed in temporal and parietal scalp. Dermoscopic examination showed no findings characteristic of alopecia areata (AA) such as black dot, exclamation-mark hair or broken hair. The remainder of the physical examination was normal and there was no hair loss other than the scalp. Laboratory findings revealed positive ANA, elevated anti-DNA 70 IU/mL and hypocomplementemia. There was no other more probable dermatological differential disease, and she met criteria proposed by Systemic Lupus International Collaborating Clinics group (SLICC). We diagnosed as patchy non-scarring alopecia caused by SLE, and started hydroxychloroquine. (Conclusions) Although alopecia isn't life-threatening, if SLE is left untreated, other organ disorders may appear. Therefore, you should consider SLE when you see a patient with patchy non-scarring alopecia.

### P37-11

#### **Two cases of systemic lupus erythematosus (SLE) that developed while using TNF alpha inhibitors**

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Conflict of interest: None

It has been reported that lupus-like symptoms may occur during the use of TNF alpha inhibitors. In most cases, the symptoms improved after stopping the drug. Here we report two cases that steroid treatments were required because severe organ involvements did not improve despite drug withdrawal. Case presentation: Case 1: A 70-year-old woman diagnosed as rheumatoid arthritis 5 years ago. Four years later, etanercept (ETN) was started. A few months later, she developed erythema multiforme and enteritis, and her arthritis worsened. Therefore, ETN was changed to tocilizumab. Two months later, she was transported by emergency due to impaired consciousness. Laboratory data demonstrated positive antinuclear antibody (ANA), positive anti-ssDNA antibody, hypocomplementemia, and elevation of cerebrospinal fluid IL-6. The steroid pulse treatment was performed under the diagnosis of central nervous system lupus. Case 2: A 69-year-old woman developed uveitis 6 years ago. Due to frequent exacerbation, adalimumab (ADA) was started 4 years ago. One month ago, pancytopenia was observed and we diagnosed SLE with positive ANA and positive anti-dsDNA antibody. Because severe thrombocytopenia did not improve despite stopping ADA, we started steroid treatment.

### P37-12

#### **Two cases of SLE that developed after SARS-CoV-2 vaccination**

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Conflict of interest: None

[Background] The concept of adjuvant-induced autoimmune syndrome (ASIA), which develops after vaccination due to additives, has been proposed. Although there are cases where it is difficult to prove a causal relationship, it is possible that the number will increase with the spread of the SARS-CoV-2 vaccine. We report cases of suspected SLE due to ASIA experienced in our department. [Case 1] A 26-year-old female. She was vaccinated with SARS-CoV-2 vaccine in early August. From late August, her bilateral lower leg edema appeared. She had nephrotic syndrome and was diagnosed with lupus nephritis by renal biopsy. [Case 2] A 62-year-old male. He had a history of cardiogenic cerebral infarction in X-7. After vaccination of SARS-CoV-2 vaccine, fever and weakness of limbs appeared, and cognitive decline was observed rapidly. He was diagnosed with SLE. [Discussion] Diagnosis of ASIA is difficult due to lack of recognition and diversity of confounding factors, and there are many un-



clear points such as the relationship between the type of adjuvant and the disease and the genetic predisposition such as HLA related to the onset. It is expected that data will be accumulated, and it should be kept in mind that vaccination can induce various autoimmune diseases.

### P37-13

#### **A SLE patient developing NPSLE like neurological symptoms and hemophagocytic syndrome after COVID-19 vaccination**

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Conflict of interest: None

**Case report:** 61-year-old woman was raced to our hospital because of consciousness disturbance. She was diagnosed with lupus myelitis in 47-year-old and has been treated. In July and August 20XX, She received COVID-19 vaccine. In the end of August, she noticed general joint pain and weakness in bilateral lower limbs. Next month, she was raced to our hospital because of decreasing consciousness. Her conscious level was JCS III-300, and body temperature was over 40°C. She had right concomitant deviation, clonic spasms and paralysis in left side. Cerebrospinal fluid (CSF) tests showed an increase IL-6 level, and both culture and viral PCR were negative. She was suspected to develop NPSLE, and was treated with steroid pulse therapy on day 1. Her symptoms were ameliorated, however she had high fever again on day 8. We added steroid pulse therapy. But she had thrombocytopenia and increased levels of serum LDH and ferritin, and bone-marrow examination and CSF tests showed hemophagocytosis. We diagnosed with hemophagocytic syndrome. She was treated with etoposide, dexamethasone and cyclosporin. **Clinical importance:** The safety of the COVID-19 vaccine in patients with autoimmune disease has not been fully established. So, it is important to accumulate rare adverse events of COVID-19 vaccine.

### P37-14

#### **A case of systemic lupus erythematosus (SLE) follownig COVID-19**

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Conflict of interest: None

[Case] A 86-year-old man was admitted to our hospital for persistent pleuritis in September. His medical history was prominent for having COVID-19, 9 months before. He was successfully treated with favipiravir without sequelae. 8 months before, he had right chest pain and fever. With diagnosis of right pleuritis, he was treated with an antibiotic. Elevated CRP was decreased from 15 to 1 mg/dL. 4 months before, he developed left chest pain and general malaise. On admission, left pleural effusion was noted and CRP was 9 mg/dL. Blood test showed antinuclear antibody x 80 (Speckled, Granular), dsDNA Ab 13 IU/mL, cardiolipin IgG Ab 13 U/mL, U1-RNP Ab 28 U/mL, SS-B Ab 35 U/mL, CCP Ab 234 U/mL and the Combs test was positive. Although left pleural effusion was improved by antibiotic, general malaise, arthralgia and elevated CRP (5-7 mg/dL) persisted. He was diagnosed with SLE according to 1997 ACR criteria ([1] pleurisy, [2] ANA, [3] dsDNA Ab, and [4] lymphopenia). Employment of 40 mg of prednisolone ameliorated all symptoms and CRP became negative. [Discussion] There are some reports, describing detection of various autoAbs and development of lupus after COVID19. Our current case suggests a relationship between COVID-19 and autoimmune diseases. [Reference] Curr Opin Rheumatol 2021;33:155-162.

### P38-1

#### **A case of elderly-onset systemic lupus erythematosus with a Castleman's disease-like clinical course that led to clinical remission with hydroxychloroquine**

Hirota Yamazawa, Toshihiko Shiga, Kaori Ishimura, Hiroki Akazawa, Chisato Ashida, Akinori Okada, Daisuke Tomita, Tetsu Itami, Kenji Sakai, Kazuya Kishimoto, Yuji Nozaki, Koji Kinoshita, Masanori Funauchi, Itaru Matsumura

Department of Hematology and Rheumatology, Kindai University Hospital

Conflict of interest: None

[Case] A 82-year-old man visited a local doctor for general malaise and was found to have hypergammaglobulinemia, so he was referred to the hematology department of our hospital. Bone marrow examination showed no obvious abnormality, but CT scan showed enlarged lymph nodes. Lymph node biopsy revealed pathological findings suggestive of Castleman's disease. Blood tests showed positive antinuclear antibodies, high levels of anti-dsDNA antibodies, low levels of complement, and high levels of IgG4, and he was referred to the Department of Rheumatology on suspicion of collagen disease. [Progress] Urinalysis revealed mild urinary protein findings, and a renal biopsy was performed for diagnostic purposes, resulting in the diagnosis of lupus nephritis (ISN/RPS type II). As the patient was a mild case, treatment was started with 200 mg of hydroxychloroquine (HCQ) and 25 mg of losartan. After 9 months, the serological findings improved, the urine became protein negative, and the lymph node enlargement decreased. [Discussion] Although there have been several reports of SLE with a Castleman's disease-like clinical course, the improvement of nephritis, lymph node enlargement, and serological abnormalities with single-agent HCQ is rare, and we report this case with literature discussion.

### P38-2

#### **Examination of the therapeutic effect and safety of subcutaneous belimumab and mycophenolate mofetil**

Masanori Sudo<sup>1,2</sup>, Satoshi Ito<sup>1</sup>, Sayuri Takamura<sup>1,2</sup>, Shunsuke Sakai<sup>1,2</sup>, Daisuke Kobayashi<sup>1,2</sup>, Kei Funamura<sup>1</sup>, Asami Abe<sup>1</sup>, Hiroshi Otani<sup>1</sup>, Kiyoshi Nakazono<sup>1</sup>, Akira Murasawa<sup>1</sup>, Ichiei Narita<sup>2</sup>, Hajime Ishikawa<sup>1</sup>

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Conflict of interest: None

[Objective] To investigate the clinical features of subcutaneous belimumab (BEL) or mycophenolate mofetil (MMF) in patients with systemic lupus erythematosus (SLE). [Methods] 15 patients who received BEL (BEL group, M1, F14) were recruited. The clinical features were examined at 0, 12, and 24 weeks after the administration. 9 patients who received MMF (MMF group, M1, F8) were also recruited, and each item was compared respectively. [Results] In the BEL group, there was no significant difference in WBC, Hb, PLT, CRP, and anti-DNA antibodies at 0, 12, and 24 weeks, but CH50 (38.9 vs 46.7 vs 43.2,  $p = 0.018$ ) was significantly improved, and the amount of PSL (12.0 vs 10.5 vs 9.5,  $p = 0.007$ ) was significantly reduced. In the MMF group, CH50 (33.3 vs 39.2 vs 35.4,  $p = 0.034$ ) and PSL amount (12.0 vs 9.3 vs 7.6,  $p = 0.001$ ) showed similar results. There were no significant differences in CH50 ( $p = 0.212$ ) and PSL amount ( $p = 0.525$ ) between the two groups, but the number of side effects was significantly different from 1 in the BEL group (pulmonary aspergillosis) and 6 in the MMF group (Eczema herpeticum, sepsis, etc.) ( $p = 0.004$ ). [Conclusion] BEL may be safe and useful for the treatment of SLE patients, and it is hoped to consider the proper use and indication of BEL and MMF in the future.

### P38-3

#### **Evaluation of the efficacy of belimumab for the treatment of systemic lupus erythematosus without significant organ damage**

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Seirei Hamamatsu General Hospital

Conflict of interest: None

[Objective] To efficacy of belimumab (BLM) for patients with systemic lupus erythematosus (SLE) without major organ involvement. In this study, we compared the efficacy of BLM in patients with SLE at our hospital. [Methods] 34 patients with SLE treated by BLM at our hospital between 2019 and 2021 were selected and listed about gender, arthritis, existence of erythema, alopecia, arthritis, hydroxychloroquine use, and examined retrospectively for SLEDAI, complement titer, and antibody titers.

ter 12 months after BLM introduction. [Result] The mean age was 41.8±9.3 years. 24 patients had HCQ, 4 had arthritis, 5 had erythema, and 6 had alopecia. 18 were positive for anti-dsDNA antibodies, and 19 presented with two or more systems of low complement blood. All showed a significant decrease in SLEDAI ( $p=0.000877$ ) and improvement in complement and antibody titers 12 months after BLM introduction. In addition, patients with alopecia showed a significant decrease in SLEDAI ( $p=0.0218$ ), and CH50 titer also tended to increase, although not significantly ( $p=0.0564$ ). [Conclusion] BLM is effective in treating general physical findings and serological abnormalities in SLE. In particular, patient with alopecia could expect more effectiveness of BLM, and may be a factor to consider about introduction.

### P38-4

#### Usage of belimumab in our department

Akihiro Tanaka<sup>1,2</sup>, Mariko Futamura<sup>1,2</sup>, Hidehiko Makino<sup>1,2</sup>, Minoru Shigesaka<sup>1,2</sup>, Saki Tsujimoto<sup>1,2</sup>, Keiko Shimamoto<sup>1,2</sup>, Yonsu Son<sup>1,2</sup>, Yoshio Ozaki<sup>1,2</sup>

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Conflict of interest: None

[Objective] It has been shown to be effective against lupus nephritis, and belimumab (BLM) is being actively used to induce remission of systemic lupus erythematosus (SLE). Based on these findings, we report on the status of BLM treatment for SLE in our department. [Methods] From December 2017 to September 2021, 25 SLE patients who used BLM in our department were included. We confirmed the history of BLM administration, continuation status, steroid dose reduction effect, etc. The age at the start of treatment is 19 to 63 years, and the illness period is 0.2 to 21.1 years. [Results] BLM administration was often added for the purpose of reducing the dose of steroids, and was used in 1 case for induction of remission. BLM continued in 21 of 24 cases, and 3 discontinued cases was 2 adverse events and 1 case of pregnancy. The average PSL dose at the start of BLM was 10 mg, and 5.2 mg at 52 weeks. The mean SLEDAI values were 7.3 before BLM, and 3.5 at 52 weeks after. [Conclusions] There were no serious adverse events and infection. A certain steroid weight loss effect and SLEDAI improvement effect were observed. In addition, we were able to confirm cases in which disease activity was significantly reduced when used for induction of remission.

### P38-5

#### The efficacy in dose reduction of corticosteroids and the analysis of backgrounds to affect it by combination use of hydroxychloroquine and belimumab in maintenance phase of systemic lupus erythematosus

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Faculty of Medicine, Tokai University

Conflict of interest: None

[Objective] To clarify the efficacy and predictors of prednisolone (PSL) sparing effect by combination use of hydroxychloroquine (HCQ) and belimumab (BLM) in systemic lupus erythematosus (SLE) patients during maintenance therapy. [Methods] We enrolled SLE patients who were taking HCQ and BLM over 24 weeks with PSL less than 15 mg as maintenance dose at the time of HCQ and BLM initiation. We excluded the patients who added immunosuppressant after HCQ and BLM initiation. We analyzed the changes of PSL dose and clinical parameters and patients' backgrounds before HCQ and BLM initiation. [Results] The mean age and disease duration of 116 SLE patients were 44.2±11.9 and 14.2±10.9 years, respectively. Mean PSL dose were significantly reduced from the baseline to 24 and 120 weeks after initiation of HCQ and BLM. We found the improvement of SLEDAI score, hypocomplementemia and/or anti-dsDNA antibody titer (SLEDAI score: 5.5 vs. 2.5, C3: 67.8 vs. 75.2 mg/dl, C4: 9.4 vs. 12.6 mg/dl, anti-dsDNA antibody titer: 49.0 vs. 26.0 U/ml at 120 weeks,  $P<0.01$ , respectively.) [Conclusions] Combination use of HCQ and BLM could reduce PSL dose during maintenance phase and we found the improvement of hypocomplementemia and anti-dsDNA anti-

body titer.

### P38-6

#### A Case of Eculizumab Remarkably Effective for Severe SLE

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Conflict of interest: None

[Case] 58-year-old male [Chief complaint] Skin rash, fever and disturbance of consciousness [Present medical history] In October X-1, he visited another hospital because of skin rash, fever and disturbance of consciousness. Pancytopenia, positive for ANA, anti-RNP antibody, anti-Sm antibody, decreased C3, and posterior reversible encephalopathy syndrome (PRES) on head MRI was observed. Those were all improved by methylprednisolone pulse and post-treatment prednisolone, assuming complications of SLE. In July X, he was admitted to our hospital because of same symptoms as before, when prednisolone was reduced to 6 mg/day. Thrombocytopenia, decreased C3, increased ferritin, LDH and fragmented erythrocytes in peripheral blood, and new PRES were observed. We diagnosed exacerbation of SLE. Steroid pulse therapy, plasma exchange, IVIg, and IVCY were administered, but his condition did not improve. We assumed excessive activation of the complement was involved. We administered eculizumab. His condition improved quickly. After using it twice, prednisolone was reduced with mycophenolate mofetil and hydroxychloroquine. He is currently in remission. [Conclusion] Eculizumab may be effective for severe SLE which is refractory to standard therapy and further accumulation of evidence is expected.

### P39-1

#### A case of secondary selective IgM deficiency associated with systemic lupus erythematosus, antiphospholipid antibody syndrome

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Conflict of interest: None

A 45-year-old woman. Two sisters are being treated with SLE. From X-20, butterfly erythema, fever, joint pain appeared. SLE were diagnosed, ANA, anti-dsDNA antibody, symptoms, and treatment with prednisolone (PSL) 5-10 mg was started. Urine protein appeared in July X-12, renal biopsy showed lupus nephritis III (A/C) type, immunofluorescence (IF) showed a full-house pattern. Improvement with increased PSL and tacrolimus 3 mg. At the first our medical examination, anti-DNA antibody 36 IU/mL, anti-phospholipid antibody positive, complement low, Cre 1.12 mg/dL, urinary protein 0.5 g/gCr, IgG 1657 mg/dL, IgA 461 mg/dL, IgM <2 mg/dL, IgE 53.2 IU/mL, selective IgM deficiency was observed. From September, increasing urinary protein of 1-2 g/gCr, and hospitalized for relapse of lupus nephritis. Renal biopsy on day 3 revealed lupus nephritis IV-G (A/C)+V type, and treatment was started with PSL 45 mg and intravenous cyclophosphamide pulse therapy. In this renal biopsy IF, IgG, IgA deposits were observed, but IgM were not. Since this case was measurable with IgM 55-60 mg/dL until July X-12, there is a possibility of secondary selective IgM deficiency associated with SLE and APS. We report on SLE, APS and selective IgM deficiency based on a review of the literature.

### P39-2

#### A case of systemic lupus erythematosus suggested as a complication of antiphospholipid antibody syndrome due to the presence of ischemic colitis on evaluation of constipation

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Department of Rheumatology, Yamanashi Prefectural Central Hospital

Conflict of interest: None

The patient was a 70-year-old woman with a history of leukopenia and

thrombocytopenia. In January of X-2, he came to our hospital with polyarthritis, positive antinuclear antibody and anti-SS-A antibody. In October of the same year, urine occult blood, proteinuria, and anti-ds-DNA antibody became positive, so a diagnosis of systemic lupus erythematosus was made, and treatment with HCQ, PSL, and MMF was started. In June of X, constipation appeared and did not improve, so she visited a gastroenterologist and was prescribed Linacotide, but without improvement, a colonoscopy was performed in August. The results showed suspicious for ischemia or vasculitis, and a biopsy revealed suggestive of ischemic changes rather than vasculitis. Since the disease course was not consistent with a generalized ischemic colitis, the patient was referred to our hospital. Additional blood tests showed no inflammatory findings and a weak positive lupus anticoagulant. Therefore, cilostazol was started, and the symptoms began to improve. In this case, an unexpected lesion was found among the common symptoms, and it had a significant impact on the patient's QOL. We would like to report this case as an important case in which even minor symptoms required further evaluation.

### P39-3

#### A case of catastrophic antiphospholipid syndrome mimicking lupus enteritis

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Conflict of interest: None

[Case] A 57 year-old male with a history of SLE/APS, who had been stable condition with prednisolone 15 mg every other day and warfarin, presented to the emergency department complaining of severe abdominal pain. An abdominal CT-scan revealed diffuse small bowel edema and ascites, which were compatible with a diagnosis of lupus enteritis. Laboratory tests showed anemia and thrombocytopenia. Although IV methylprednisolone 60 mg/day was started, his symptoms were refractory. He also developed rapidly progressive renal failure and was started hemodialysis Day 10. Upper-gastrointestinal endoscope revealed duodenal ulcer, and histological findings were significant for small vessel thrombosis in lamina propria. Repeated CT scan showed ischemic lesions in renal and spleen. Based on rapidly progressive multi-organ thrombotic lesions, diagnosis of catastrophic APS (CAPS) was made. He was treated with plasma exchange therapy, intravenous immunoglobulin and belimumab as well as heparin and aspirin. His abdominal findings gradually improved and he was discharged on Day 67. [Discussion] CAPS is a rare, multi-organ thrombotic disease which can involve small or large intestine. Therefore, it may be difficult to differentiate CAPS from lupus enteritis in patients with SLE/APS.

### P39-4

#### Pulmonary embolism due to the production of antiphospholipid antibodies in a patient with administration of adalimumab

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Conflict of interest: None

[Case] A 37-year-old woman was diagnosed with Crohn's disease 3 years ago. Adalimumab (ADA) and mesalazine were started and achieved a remission. She showed negative anti-nuclear antibody (ANA) and normal APTT at that time. High fever, left hip pain, myalgia and swelling of left lower limb, and shortness of breath appeared 3 years later. She had no history of other diseases, drug allergies, and miscarriages. She showed decreased total complement activity, prolonged APTT, elevated D-dimer, positive aCL- $\beta$ 2GPI, elevated ANA titer, and positive anti-DNA antibodies. CT scan revealed the right pulmonary artery thrombosis and the deep vein thrombosis of the left lower limb. Her symptoms could be diagnosed as lupus syndrome and suspected to be induced by ADA. After stopping ADA and starting anticoagulation, her symptoms disappeared and CT scan showed reduced thromboses. Mesalazine was continued and Crohn's disease was not recurred. Without an additional therapy, she showed increased total complement activity, negative aCL- $\beta$ 2GPI, and decreased anti-DNA antibody after 4 months. [Significance] Lupus syndrome in-

duced by TNF inhibitor has been reported, but thrombosis due to the production of antiphospholipid antibody should also be careful.

### P39-5

#### An anti-phospholipid syndrome patient developed Chronic thrombo-embolic pulmonary hypertension during high-intensity warfarin treatment

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Conflict of interest: None

[Patient] 61-year-old Male [Present illness] He developed deep vein thrombosis and was diagnosed as triple positive (anti-cardiolipin antibody, anti- $\beta$ 2GPI antibody and lupus anticoagulant) antiphospholipid syndrome (APS) at age 34. Despite of warfarin treatment, he had developed pulmonary embolism at age 46 and increased intensity of warfarin to PT-INR 2.5-3.0. He started to suffer dyspnea on exertion and was admitted to our hospital with the suspected diagnosis of chronic CTEPH with elevated estimated pulmonary artery pressure (61 mmHg) and multiple-perfusion defects, detected by the echocardiogram and perfusion lung scintigraphy, respectively. [Clinical course] He was classified as WHO functional Class II of pulmonary hypertension with reduced 6 minute walk distance. Right heart catheterization revealed mean pulmonary artery pressure 28 mmHg and pulmonary vascular resistance 5.4 WU. Based on these findings, we diagnosed as CTEPH with high-risk APS. Selexipag (SLX) treatment was initiated that resulted in the improvement of 6MWD in 2 months. [Clinical significance] APS with triple positive is a high-risk thrombotic condition that may develop CTEPH during high intensity warfarin therapy. SLX may have potential therapeutic effect on these high-risk patients, as well as CTEPH in general.

### P39-6

#### A case of cerebral venous sinus thrombosis associated with SLE and APS

Tomoaki Iwanaga, Erika Imai, Takafumi Tanaka, Masataka Nakamura, Motoko Ishida, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Tomoya Miyamura

National Hospital Organization Kyushu Medical Center

Conflict of interest: None

The patient is a 28-year-old female. She was diagnosed as Evans syndrome complicated with Sjogren's syndrome in childhood and treated with PSL and MZR. She was diagnosed as SLE by erythema on the cheek, non-erosive arthritis, positive anti-ds-DNA antibody, positive anti-Sm antibody, positive anticardiolipin antibody, positive anti-CL $\beta$ 2GPI antibody, and hypocomplementemia, and steroid treatment was started. The patient was diagnosed with cerebral venous sinus thrombosis and started anticoagulation and glyceol. The patient was diagnosed as having cerebral venous sinus thrombosis and was started on anticoagulation and glyceol. After the start of treatment, headache, nausea, and swelling of the right neck improved, but diplopia and internal strabismus in the right eye did not. In patients with SLE or APS, neurological symptoms, especially those not consistent with arterial vascular control, should be considered as a complication of cerebral venous sinus thrombosis.

### P40-1

#### Association analysis of XL9 region variant and HLA-DRB1\*15:01 with systemic lupus erythematosus in a Japanese population

Aya Kawasaki<sup>1</sup>, Yuya Kondo<sup>2</sup>, Takashi Fujimoto<sup>3</sup>, Isao Matsumoto<sup>2</sup>, Makio Kusai<sup>4</sup>, Hirofumi Amano<sup>4</sup>, Naoto Tamura<sup>4</sup>, Yasuyoshi Kusanagi<sup>5</sup>, Kenji Itoh<sup>5</sup>, Takayuki Sumida<sup>2</sup>, Naoyuki Tsuchiya<sup>1</sup>

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Conflict of interest: None

[Objective] *HLA-DRB1\*03:01* and *DRB1\*15* haplotypes are associated with systemic lupus erythematosus (SLE) in European populations. In the Japanese population, the frequency of *DRB1\*03:01* is very low, but association of *DRB1\*15:01* with SLE is detected. Recently, association of XL9 variant located between *DRB1* and *DQA1* with SLE was reported in European and African populations (Kamitaki et al, 2020). In this study, we investigated whether the XL9 variant is associated with SLE, along with its linkage disequilibrium with *DRB1\*15:01*. [Methods] Association of XL9 rs2105898 with SLE was tested in 442 patients with SLE and 780 healthy controls using logistic regression analysis. [Results] XL9 rs2105898T was significantly increased in SLE (odds ratio:1.34,  $P=0.0016$ ). Between rs2105898 and *DRB1\*15:01*, weak linkage disequilibrium was observed ( $r^2$ : 0.26). When the association of rs2105898 was conditioned by *DRB1\*15:01*, the association lost statistical significance ( $P=0.82$ ). On the other hand, the association of *DRB1\*15:01* remained after conditioning by rs2105898 ( $P_{\text{unconditioned}}$ :  $P=4.8E-08$ ,  $P_{\text{conditioned}}$ :  $P=7.6E-06$ ). [Conclusions] Although association of XL9 variant with SLE was detected in a Japanese population, the association of XL9 may be attributable to linkage disequilibrium with *DRB1\*15:01*.

## P40-2

### Comparison of inflammatory cytokine production in systemic lupus erythematosus and COVID-19

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Conflict of interest: None

[Objective] Inflammatory cytokines production is enhanced in COVID-19 patients. We have been studying and reporting on the production of inflammatory cytokines in SLE. In comparison cytokine-producing cells in COVID-19 and SLE, we tried to characterize the cytokine-producing mechanisms of COVID-19 and SLE. [Methods] Peripheral blood mononuclear cells from COVID-19 patients, SLE patients and HC were stimulated with 2'3'-cGAMP, an intracellular nucleic acid receptor STING ligand. Bone marrow-derived cells were evaluated by using intracellular cytokine staining and flow cytometry. [Results] LDN in COVID-19 were significantly increased compared with SLE and HC. IFN $\alpha$ -positive LDN was also significantly increased. Non-classical monocytes tended to be increased in patients with severe COVID-19. Although IFN $\alpha$ <sup>+</sup> monocytes were not significantly increased between with COVID-19 and SLE, IL-1 $\beta$  production in non classical monocytes was enhanced in COVID-19. [Conclusions] IFN $\alpha$  and IL-1 $\beta$  play important roles in the pathology of COVID-19. In addition, LDN and non-classical monocytes increase due to emergency myelopoiesis. In this study, it was shown that in COVID-19 compared with SLE, the enhancement of IFN $\alpha$  and IL-1 $\beta$  production by LDN and non-classical monocytes may be involved in the exacerbation.

## P40-3

### Associations between serum heme oxygenase-1 and disease activity in systemic lupus erythematosus

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Conflict of interest: None

[Objective] Decreased expression of heme oxygenase (HO-1) was observed in M2 macrophages of patients with lupus nephritis (LN), suggesting a decrease in the anti-inflammatory effect of HO-1. We analyzed

whether serum HO-1 is useful as an indicator of disease activity in systemic lupus erythematosus (SLE). [Methods] We divided SLE patients into a lupus low disease activity state (LLDAS) achieved group and an LLDAS non-achieved group. And 12 cases were randomly selected in each group, and serum HO-1 was measured by the ELISA method. Whether there was a statistical difference in serum HO-1 between each group and healthy subjects was evaluated by t-test. [Results] The serum HO-1 concentration was  $3.59 \pm 2.81$  ng / ml (mean  $\pm$  standard error) in the LLDAS non-achieved group and 0 ng / ml in the LLDAS achieved group, showing no statistical difference between the two groups ( $p = 0.22$ ). In the healthy group, the serum HO-1 concentration was 0.073 ng / ml, and no statistically significant difference was observed from each group of SLE. [Conclusions] In this study, there was no statistical difference in serum HO-1 between the LLDAS-achieved group and the LLDAS-non-achieved group in SLE patients. We couldn't concluded that serum HO-1 is useful as an index of SLE disease activity.

## P40-4

### The role of belimumab examined by its effects on changes in subpopulations of SLE-related cells and B cell receptor signaling

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Conflict of interest: None

[Objective] There are no appropriate criteria for belimumab administration according to clinical background, therefore more accurate evaluation of efficacy is needed. We examined relationship between change in disease-related cells and clinical symptoms before and after belimumab administration. [Methods] Blood samples were collected from 20 SLE patients before and after administration, and changes in subpopulations were analyzed by FACS. Statistical analyses were performed to detect correlation with clinical findings and changes in those subpopulations. The roles of BTLA, expressed on disease-related cells, were examined by western blotting. [Results] BTLA positive cells in memory B cells were increased after belimumab treatment. Correlation analysis showed positive correlations between serum levels of C4 and BTLA positive cells in memory B cells. Stimulating healthy B cells with anti-BTLA antibodies and subsequently with BAFF or control, phosphorylation of Syk, Btk, and PLC $\gamma$ 2 were more enhanced in BTLA-stimulated group than non-stimulated in condition of stimulation by BAFF. [Conclusions] Our results indicate belimumab affects expression of BTLA and its signal transduction, involved in suppression of B cell signal activation, and contributes to improvement of disease.

## P40-5

### Detailed analysis of T cell changes during BAFF inhibition by belimumab in SLE

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Conflict of interest: None

[Objective] Belimumab (BEL) corrects B cell abnormalities in Systemic lupus erythematosus (SLE), but it is unclear how it affects other immune cells such as T cells. [Methods] Peripheral T cells from 22 SLE patients who started BEL and were followed up longitudinally for 1 year were evaluated using mass cytometry. A total of 25 T cell-related surface markers (CD3, CD4, CD8, CD25, CXCR3, CD28, CTLA-4, PD-1, etc.) were analyzed at the single cell level. Peripheral blood samples were taken before the use of BEL (baseline), 3 months and 12 months after the start of treatment. 20 SLE patients (baseline, 12 months later) who did not receive BEL were used as controls. Mixed-effects model was used to select candidates with significant changes in the BEL group ( $p < 0.05$ ). [Results] Analysis of changes in the proportion of T cell subsets showed an increase in naive-Treg and CD4<sup>+</sup>CD8<sup>+</sup> DP T cells. Analysis of changes in co-stimulatory/inhibitory molecules expression in each T cell subsets showed an

increase in TIM-3 on Treg, TIM-3 on Th17.1, CD28 on Tfh, and OX40 on CM-CD8 T cells. On the other hand, PD-1 on effector CD4 T cells and CTLA-4 on CD4-CD8- DN T cells were decreased. [Conclusions] Our data reveal candidates for BEL treatment-related unpredictable changes in the T cells.

## P41-2

### Serum KL-6 is decreased by nintedanib in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD): an extended report

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Conflict of interest: None

[Objective] Nintedanib has been widely used in SSc-ILD, but it remains difficult to assess its therapeutic effect. Here, we examined serial changes of circulating biomarkers after nintedanib therapy to evaluate their prognostic value for treatment efficacy. [Methods] We enrolled SSc-ILD patients who were treated with nintedanib for >12 months. Baseline patient characteristics, and serial changes of LDH, CRP, KL-6, platelet count, and erythrocyte sedimentation rate were retrospectively collected. Changes in biomarker levels were examined for their correlation with changes in pulmonary function indices. [Results] Of 403 cases in our SSc cohort, 20 patients with SSc-ILD were eligible in this study. Baseline characteristics included disease duration of 58±44 months, 65% extensive ILD, FVC of 75.0±17.8%, and 45% on concomitant mycophenolate. The stable dose of nintedanib was 300, 200, and 100 mg in 6, 11, and 3 cases, respectively. KL-6 was significantly reduced after initiation of nintedanib ( $p = 0.004$  by repeated-measures ANOVA). Changes in KL-6 were not correlated with changes in lung function indices over time. [Conclusion] Nintedanib reduced serum KL-6 levels in patients with SSc-ILD, but we failed to demonstrate its prognostic value for subsequent pulmonary function changes.

## P41-3

### Systemic sclerosis with severe vascular damage positive for anticentriole antibody; 2 case reports

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Conflict of interest: None

[Background] Anticentriole antibody is rarely observed autoantibody and mostly in association with systemic sclerosis (SSc) and scleroderma spectrum disorders (SSD). [Case 1] A 54-year-old female developed Raynaud's phenomenon (RP) at age of 51. She had finger-limited skin sclerosis and nail fold bleeding (NFB), while morphea was observed in her arms and knees. SSc-specific autoantibodies were negative; however, the centriole pattern of staining was observed with high titers (1:320) using IIF. She was diagnosed with LcSSc complicated with Morphea. At age of 57, she suddenly developed gangrene of finger. Gradual increase in the TRVmax was observed and cardiac catheterization showed increased mPAP (20 mmHg). We are carefully following the appearance of pulmonary artery hypertension (PAH). [Case 2] A 72-year-old female, who had developed RP at age of 70, was suffered from exertional dyspnea. She was diagnosed with PAH. Puffy fingers and skin sclerosis were absent, but NFB was positive. Anticentriole antibody was positive at 1:320. We diagnosed her as SSD. [Clinical Significance] The presence of anticentriole antibody is associated with SSc or SSD in which skin sclerosis is often absent. They frequently develop PAH, digital ulcers, and gangrenes. We should be aware of vascular symptoms.

## P41-4

### A case of scleroderma renal crisis with thrombotic microangiopathy developed during perinatal period

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cal School, Kochi University

Conflict of interest: None

A 36-year-old woman with a two-year history of systemic scleroderma and interstitial pneumonia presented with new onset hypertension, massive proteinuria. Two months ago, she delivered. At our outpatient clinic, new onset hypertension and massive proteinuria were observed. Laboratory testings showed positive anti-RNA polymerase III antibody, the elevated serum creatinine level (1.7 mg/dL), crushed red blood cells, and thrombocytopenia. Renal biopsy revealed stenosis of the arterioles and the interlobular arteries and thrombosis in the glomerular capillaries. Based on the above findings, she was diagnosed as scleroderma renal crisis (SRC) with thrombotic microangiopathy (TMA). Treatment with an ACE inhibitor was initiated. Her blood pressure improved and proteinuria, anemia and thrombocytopenia resolved. At our outpatient clinic, her renal function was normalized. SRC is the renal complication associated with acute renal failure and new onset of severe hypertension in patients with scleroderma. In SRC, it is not uncommon to have TMA, which causes serious multi-organ damage. On the other hand, TMA can also develop in preeclampsia associated with pregnancy and childbirth. We report a rare case of SRC that became apparent during the perinatal period, when preeclampsia is common.

## P41-5

### Clinical and serological features of anti-centromere antibody positive limited cutaneous systemic scleroderma

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Conflict of interest: None

[Objective] Anti-centromere antibody positive limited cutaneous systemic scleroderma (lcSSc) tends to be neglected because of the mild range and degree of skin symptoms compared to diffuse cutaneous type. However, it progresses chronically and complicates severe organ dysfunction and merges many other autoimmune diseases. Clinical features of centromere antibody positive lcSSc are examined. [Methods] 120 patients who had hospitalized in our outpatient clinic from 2012 to 2021 were enrolled. All patients met the American College of Rheumatology classification criteria for lcSSc. We assess their clinical characteristics and data. [Results] Female were 106 (88%). Mean age was 67.2 years old. The duration between onset of Raynaud phenomenon and first visit was 8.5 year. Clinical characteristics; Incidence of Raynaud phenomenon and sclerodactylia were 76 and 88%. Organ damages; interstitial pneumonia, pulmonary hypertension, PBC, Sjogren syndrome, Hashimoto's disease were 29%, 26%, 48%, 58%, and 46%, respectively. [Conclusions] Anti-centromere antibody positive lcSSc is a disease which predominantly occurs in females, and complicates interstitial pneumonia, pulmonary hypertension, primary biliary cirrhosis, Sjogren's syndrome, and Hashimoto's disease at extremely high rates.

## P41-6

### Association study of IFIH1 gene polymorphisms in systemic sclerosis (SSc)

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Conflict of interest: None

[Objective] MDA5 is an intracellular virus sensor that recognizes virus-derived RNA and activates type I IFN induction and the NF- $\kappa$ B pathway. Several studies reported that polymorphisms in the *IFIH1* gene which encodes MDA5 are associated with autoimmune diseases such as systemic lupus erythematosus and type 1 diabetes. In this study, we examined whether *IFIH1* polymorphisms are associated with SSc. [Methods] We investigated 271 SSc patients. Single nucleotide polymorphism (SNP) rs35732034 was determined using the DNA sequence by the Sanger method. We analyzed the association of clinical data and autoantibodies with

*IFIH1* gene polymorphisms of SSc. [Results] The Minor allele frequency of the SNP in the SSc group was 0.039, which was not different from the previous report in the Japanese general population (Tohoku Medical Megabank Organization: 0.0417). Differences in the frequency of the SNP were anti U1-RNP antibody ( $P = 0.01$ ), anti SS-A antibody ( $P = 0.02$ ), and malignant tumor ( $P = 0.02$ ) among SSc patients, but there were no significant differences when corrected by multiple comparisons. On the other hand, a significant difference was observed in renal dysfunction with  $P = 0.0003$ . [Conclusions] Our results suggest *IFIH1* polymorphism may be involved in renal dysfunction associated with SSc.

### P41-7

#### A case of systemic sclerosis (SSc) relapsed after COVID-19 vaccination

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Conflict of interest: None

The effect of COVID-19 vaccine on SSc is unclear. We experienced a case of SSc worsening scleroderma after COVID-19 vaccination. [Case] A 46-year-old Japanese man noticed Raynaud's symptoms at his fingers and was referred to our hospital in 20XX-3. Significant skin sclerosis spread from his fingers to the whole body was observed. mTSS score is 36 points. He was diagnosed with SSc because he had a high titer of anti-Scl-70 antibody. After the treatment with PSL 30 mg and IVCY were started, scleroderma gradually improved. The dose of PSL was reduced and IVCY was changed to tacrolimus after 6 courses. After that treatment, mTSS score improved to 4 points. In August 20XX, after COVID-19 vaccination, difficulty in bending fingers, upper limbs, and facial skin became taut. Skin symptoms worsened after the second vaccination three weeks later. mTSS score had risen to 16 points, indicating a relapse of SSc. [Discussion] Although the pathophysiology of SSc is unknown, it is thought that various immune cells and cytokines are involved. On the other hand, the effect of COVID-19 vaccine on SSc is unknown. We experienced a case of exacerbation of scleroderma after vaccination. We report this case because it is an interesting case for considering the pathophysiology of SSc.

### P41-8

#### Two cases of seronegative Systemic Sclerosis

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Conflict of interest: None

[Case 1] A 48-year-old man. He was found to have diffuse skin sclerosis of the extremities and trunk, and abnormally high CK levels. Although his autoantibodies were negative, he was diagnosed as overlap of systemic sclerosis and polymyositis, with interstitial pneumonia. The patient was treated with glucocorticoid pulse therapy, oral prednisolone, and intravenous cyclophosphamide for progressive interstitial pneumonia. [Case 2] A 59-year-old man. He was aware of shortness of breath on exertion. His CK level was mildly elevated, but there was no muscle pain or weakness, and no obvious abnormalities in MRI. Overlap of systemic sclerosis and polymyositis was suspected, but all autoantibodies were negative. At her request, the patient was started on oral cyclophosphamide and nintedanib for slowly progressive interstitial pneumonia and skin sclerosis. The progression of his symptoms slowed down and his CK levels decreased. [Clinical significance] There is no large size report of Seronegative systemic sclerosis in Japan. Our cases and past reports agree that the disease is predominantly male and of the diffuse cutaneous sclerosis type. However, it has not been reported that muscular symptoms are common, and there may be ethnic differences. Further case series are needed.

### P41-9

#### A case of scleroderma and rheumatoid arthritis duplication syndrome for which triple therapy was considered to be effective for pulmonary hypertension with interstitial pneumonia

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Conflict of interest: None

[Case] 50-year-old woman [History] In January X-10, she was diagnosed with rheumatoid arthritis (RA). She had dry cough and elevated KL-6 since April X-9, and was referred to our hospital in August. She was diagnosed with scleroderma (SSc). She had interstitial pneumonia (IP), and has continued treatment. In March X-2, She had respiratory distress during exertion, and diagnosed pulmonary hypertension (PH) with an average pulmonary arterial pressure (mPAP) of 30 mmHg on cardiac catheterization, and took in sildenafil, and introduced home oxygen therapy because of hypoxemia. She took in beraprost sodium since June X-2, but since September X she had respiratory distress during exertion, and discontinued beraprost sodium. Post-hospital scrutiny revealed no exacerbation of IP, with TRPG of 114.5 mmHg on echocardiography and mPAP 49 mmHg on cardiac catheterization. On the pulmonary ventilation and blood flow scintigram, no evidence of pulmonary embolism. The cause of her respiratory distress was PH. PH was considered to be associated not only with IP but also with pulmonary arterial hypertension (PAH). Macitentan and selexipag were added and stabilize PH. [Clinical significance] PH with SSc and RA associated with IP may be accompanied by PAH. It is suggested that this treatment is effective.

### P41-10

#### Clinical and serological features of systemic sclerosis: a single center study

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Conflict of interest: None

[Objective] Systemic sclerosis (SSc) is characterized by clinical symptoms due to specific autoantibodies. Most of patients with SSc in Kochi prefecture have been introduced to our hospital. Herein we examined the clinical features of SSc in our prefecture. [Methods] We retrospectively examined 451 patients with positive SSc-specific autoantibodies who visited our hospital from July 2012 to June 2020. [Results] There were 48 cases of Scl70 antibody positive, 30 cases of RNAPIII antibody positive, 174 cases of centromere antibody positive, and 199 cases of RNP antibody positive. In organ damages, interstitial pneumonia was predominantly observed in Scl70 antibody-positive cases, primary biliary cirrhosis in centromere antibody-positive cases, and scleroderma renal crisis in RNAPIII antibody-positive cases. Interstitial pneumonia was most frequent in Scl70 antibody-positive 28 cases (58.3%), following RNAPIII antibody-positive 16 cases (53.3%), RNP antibody-positive 61 cases (30.6%), and centromere antibody-positive 40 cases (22.9%). [Conclusions] The positive frequency of SSc-related specific antibody in Kochi Prefecture is mostly positive for centromere antibody or RNP antibody with lcSSc, and clinical symptoms tend to be severe in Scl70 antibody or RNAPIII antibody positive cases.

### P41-11

#### A case of systemic sclerosis who developed intestinal pseudo-obstruction and pneumatosis cystoides intestinalis

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Kawasaki Municipal Ida Hospital

Conflict of interest: None

[Case] A 72-year-old male with systemic sclerosis (SSc) presented to our hospital with nausea, vomiting and abdominal distention. A year and a



half ago, he realized whole skin hardening and Raynaud's phenomenon. Anti-centromere antibody-positive diffuse cutaneous SSc was diagnosed, therefore prednisolone and mycophenolate mofetil were initiated. There were no notable abnormalities in vital signs and laboratory data on admission. Physical examination revealed mild abdominal tenderness and no signs of peritoneal irritation, however, abdominal X-ray and CT showed pneumoperitoneum and intestinal emphysema. We diagnosed him as intestinal pseudo-obstruction and pneumatosis cystoides intestinalis due to SSc. Conservative treatments such as fasting, prokinetic agents and an antibiotic remarkably improved his symptoms and pneumoperitoneum. The elemental diet was started on the 12th hospital day, and he was discharged on the 38th day. [Discussion] Pneumatosis cystoides intestinalis might be accompanied by pneumoperitoneum, and intestinal pseudo-obstruction sometimes requires home parenteral nutrition. Severe gastrointestinal lesions associated with SSc are not frequent but serious complications that greatly affect the prognosis. Here we report based on a review of the literature.

## P42-1

### Angiopoietin-1 concentration in fingertip blood represents the severity of capillary damage of systemic sclerosis

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Conflict of interest: Yes

[Objective] As results of UMIN35332 and 35333 studies to investigate the heating effect on neck, elbows, or wrists using disposable warmer for Raynaud's phenomenon (RP) in systemic sclerosis (SSc), we found neck or elbows heating relieves RP and upregulates capillary extension factor angiopoietin-1 (Angpt-1) at fingertips (Modern Rheum, roab014). We also reported RP was highly improved at elbows heating in the cases of advanced capillaroscopy image, and the reverse tendency was observed at the neck heating. Here, we investigated the relationship between the severity of RP and Angpt-1 or an angiogenesis inhibitor endostatin (ES). [Methods] The correlation between the VAS for RP and the Angpt-1 or ES levels in fingertip blood before and after heating each part in the above tests were examined. [Results] The pre-heating Angpt-1 showed a negative correlation with VAS changes ( $\Delta$ VAS) of neck heating and a positive correlation of elbows heating. The ES before and after heating each part did not correlate with the  $\Delta$ VAS. [Conclusions] The relationship between the  $\Delta$ VAS during neck or elbows heating and pre-heating Angpt-1 is similar to the relationship between the  $\Delta$ VAS and pre-heating capillaroscopy severity. The Angpt-1 level in fingertip might represent the severity of capillary damage of SSc.

## P42-2

### Comparison of right heart catheter findings and post-diagnostic treatment between scleroderma and non-scleroderma groups in 27 cases of pulmonary hypertension associated with connective tissue disease

Kenji Sakai, Hirotaka Yamazawa, Kaori Ishimura, Daisuke Tomita, Tetsu Itami, Toshihiko Shiga, Kazuya Kishimoto, Yuji Nozaki, Koji Kinoshita, Masanori Funauchi, Itaru Matsumura

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Conflict of interest: None

[Objective] Inflammation is considered to be involved in the pathology of pulmonary hypertension (PH) accompanying connective tissue disease (CTD), and use of immunosuppressive therapy is recommended. However, the effectiveness at PH associated with systemic sclerosis (SSc) is low. We analyzed the trend in SSc-PH on right heart catheterization (RHC) and the treatment after diagnosis. [Methods] We analyzed 27 patients with CTD who underwent RHC and were diagnosed as PH. Patients were divided into 2 groups by SSc group, non-SSc group. The average pulmonary artery pressure, pulmonary artery wedge pressure, systolic right ventricular pressure, cardiac output, cardiac index, pulmonary vascu-

lar resistance, diastolic pressure gradient were compared. [Result] 15 cases were SSc group and 12 cases were non-SSc group. Diastolic pressure gradient was significantly lower in the SSc group. One patient in SSc group with overlapping dermatomyositis responded well to treated with oral prednisolone and intermittent intravenous cyclophosphamide. [Conclusions] The significant difference in diastolic pressure gradient may suggest postcapillary damage such as myocardial damage. Although immunosuppressive therapy is considered to be refractory in SSc-PH, it may be considered in overlapping cases.

## P42-3

### A case of pulmonary hypertension due to scleroderma suggesting that immunosuppressive treatment may be effective

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Conflict of interest: None

[Case] 50 yo. female. She was diagnosed scleroderma due to skin sclerosis, Raynaud symptoms, and anti-Scl-70 antibody in December X. She began to take Bozentan for finger apex ulcer in April X+1. In September X+1, Her examination revealed mild interstitial pneumonia and mild pulmonary hypertension. She began to take MMF2.5 g/day, and no progression observed (TR-PG=30 mg). In March X+3, She developed general shingles and withdrawal of MMF. In April, herpes zoster was improved, She re-started to take MMF from 1 g/day. In May, She was awareness of exorvation of shortness of breath, and labo date revealed increase in NT-proBNP and echo examination showed TR-PG=40 mmHg. This showed an exacerbation of pulmonary hypertension. We indicated the increase quantity of MMF, and re-check 3 month later. In August X+3, there was an improvement in shortness of breath, and NT-proBNP was also normalized. Echo study showed a decreased to 26 mmHg in TR-PG. This date suggested that the increase the quantity of MMF improved pulmonary hypertension. [Clinical Significance] Pulmonary hypertension due to scleroderma has reported little effect of immunosuppressive treatment. This time, we experienced a case of pulmonary hypertension of scleroderma in which immunosuppressive treatment (MMF) may be effective.

## P42-4

### A case of systemic sclerosis with progressive lung involvement and nephrotic syndrome after the diagnosis of silicosis

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Conflict of interest: None

The patient is a 43-year-old male with a history of wrecker and metal polisher. In year X-5, small nodules were identified in lungs. Autoantibodies were negative, and silicosis was indicated by his lung biopsy. He missed follow-up, but he found it difficult to clench his fists on Feb X. He was diagnosed as systemic sclerosis (SSc) based on physical examination and the positivity of anti Scl-70 antibody. Only subtle ground glass opacity (GGO) was noted and he started prednisolone (PSL, 15 mg/day). However, he got a cough on Nov and CT showed the aggravation of GGO. PSL was increased to 40 mg/day and cyclophosphamide was monthly administered from Dec for 4 month. On Mar X+1, examination revealed the onset of nephrotic syndrome. Though 60 mg/day dose of PSL was begun, he coughed up a bloody sputum with respiratory failure on Apr X+1. Alveolar hemorrhage was suspected, and steroid pulse and plasma exchange were performed. He recovered from respiratory failure, and nephrotic syndrome was also ameliorated. The pathology of SSc is still unclear. Several reports indicate the relation between silicosis and SSc. Our patient developed anti Scl-70 antibody-positive SSc with multiple organ involvement after the diagnosis of seronegative silicosis and we discuss the pathology of this case.

## P42-5

### Effect of temperature variation on serum KL-6 levels in patients with systemic sclerosis

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Conflict of interest: None

[Objective] Serum KL-6 levels have been used as a biomarker for ILD. We sometimes experience fluctuations in the KL-6 levels regardless of ILD status, however, the factors affecting this phenomenon are unclear. We hypothesized that serum KL-6 levels may be affected by temperature, and tested this using our database from patients with SSc. [Methods] The period above the average temperature was defined as the warm season (WS), and below it was defined as the cold season (CS). ILD was classified based on chest CT. SSc patients who had been seen in our department since January 1, 2017, and whose KL-6 was measured at least 4 times since 2014 and at least once in the WS once in the CS, were extracted. The association between temperature variation and KL-6 levels was statistically analyzed. [Results] A total of 76 patients with SSc were enrolled, 40 (52.6%) with dcSSc, and 25 (32.9%) with ILD. The levels of KL-6 were significantly higher in the CS than in the WS (489 IU/L vs 445 IU/L,  $p = 0.03$ ). In the SSc-ILD group, the levels of KL-6 were also significantly higher in the CS (552 IU/L vs 506 IU/L,  $p = 0.03$ ), but not in the non-ILD group (227 IU/L vs 217 IU/L,  $p = 0.15$ ). [Conclusions] Cold stimulation may affect KL-6 levels in patients with SSc.

## P42-6

### A retrospective study on the prognosis of pulmonary hypertension (PH) associated with systemic sclerosis (SSc)

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Conflict of interest: None

[Objective] Pulmonary hypertension (PH) is a fatal complication of systemic sclerosis (SSc). The aim of this retrospective study is to identify prognostic factors in SSc-PH. [Methods] We enrolled 12 (4 males, 8 females) patients with SSc-PH at our department from 2008 to 2020. Clinical features, laboratory and imaging data were analyzed. [Results] The age at the diagnosis of SSc and PH was  $69.0 \pm 9.9$  y/o and  $70.3 \pm 8.9$  y/o, respectively. 7 of 12 patients died at  $70.6 \pm 8.3$  y/o, and duration of SSc and PH was  $6.3 \pm 4.3$  years and  $4.1 \pm 3.5$  years respectively. SSc-related autoantibodies were negative in all patients of death group (DG) and positive in all patients of survival group (SG) ( $P < 0.001$ ). The odds ratios of all-cause mortality in patients with cardiac conduction system abnormalities was 3.75 (95% C.I.: 0.33-42.47). Mean pulmonary artery pressure (mPAP): DG  $39.8 \pm 11.1$  mmHg, SG  $29.8 \pm 5.9$  mmHg and pulmonary vascular resistance (PVR: DG  $10.3 \pm 6.6$  WU, SG  $6.4 \pm 4.7$  WU) by right heart catheterization of DG were significantly higher compared to the SG ( $P < 0.01$ ). [Conclusions] Our study suggests that seronegative SSc, arrhythmia, high mPAP and PVR were poor prognostic factors in SSc-PH. Early and accurate diagnosis, adequate follow-up for PH and complications were important in SSc-PH.

## P42-7

### A case of systemic scleroderma associated with interstitial pneumonia in which nail epithelial capillary abnormalities were improved by combined treatment with immunosuppressive therapy and antifibrotic agents

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Conflict of interest: None

A 78-year-old woman presented with Raynaud's symptoms in September X. Her blood tests showed positive anti-nuclear antibody, anti-RNP antibody, and anti-SS-A antibody and interstitial lung disease (ILD) was diagnosed on chest X-ray. Dyspnea on exertion was worsened and elevation of KL-6 were observed from July X+3, so she was admitted to our hospital in March X+4 for exacerbated dyspnea. Video capillary microscopy (NVC) of the nail contour showed giant capillaries and capillary hemorrhage, indicating a scleroderma active pattern. She was diagnosed as systemic sclerosis (SSc) according to the ACR/EULAR classification criteria based on abnormal nailfold capillaries, ILD, telangiectasia, and Raynaud's phenomenon. Treatment for slowly progressive SSc-ILD was started with prednisolone 25 mg/day (0.5 mg/kg/day), tacrolimus 1.0 mg/day, and nintedanib 200 mg/day. After the start of treatment, dyspnea improved, and the ILD image on CT showed improvement. The number of microhemorrhages had markedly decreased, and giant capillaries had disappeared. The capillary findings in SSc are generally progressive and the progression is resistant to treatments. This case showed the combination of immunosuppressive therapy and antifibrotic therapy may improve microvascular disorders.

## P42-8

### Experience in treating progressive interstitial pneumonia with anti-RNA polymerase III antibody positive systemic sclerosis in our department

Takao Kiboshi, Shogo Matsuda, Takayasu Suzuka, Yumiko Wada, Hideyuki Shiba, Reiko Wakura, Kenichiro Hata, Takeshi Shoda, Takuya Kotani, Tohru Takeuchi

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Conflict of interest: None

[Objective] To report the treatment experience of progressive interstitial pneumonia (PIP) with anti-RNA polymerase III antibody (RNAPIIIAb) positive systemic sclerosis (SSc) in our department. [Methods] 10 patients who were treated for RNAPIIIAb positive SSc-PIP in our department. [Results] Of the 31 RNAPIIIAb positive SSc patients, 19 had IP complications. Of these, 10 were treated for SSc-PIP. The following is the median (interquartile range). Age 69 (53.5-76.3) years, 8 females. There were 5 cases of diffuse type and 7 cases of acute or subacute IP. The mMRC scale is 2.5 (1.3-3.8), the mRSS is 6 (1.5-27), and disease duration is 32 (7.8-74.5) months. It was KL-6 1109 (694.3-2001.3) U/ml, Cre 0.8 (0.6-1.0) mg/dl, %FVC 70.4 (60.5-82.7)%, %DLco 32.7 (28.2-40.1)%. Of the 10 cases, gastrointestinal complications in 7, and malignant tumor in 3 cases. At the start of SSc-PIP treatment, prednisolone was used in 25 (20-58.8) mg/day in 6, steroid pulse therapy in 2, and intravenous cyclophosphamide (IVCY) in 6 patients. Two of the 10 patients died of IP. [Conclusions] RNAPIIIAb positive SSc-PIP was acute or subacute in many cases. Many immunosuppressive agents were used, including IVCY, but 20% of cases died. In addition, gastrointestinal complications and malignant tumor complications were also observed in many cases.

## P42-9

### A case of pulmonary arterial hypertension only with positive autoantibody: Predicting response to immunosuppressive therapy by Nailfold Video Capillaroscopy (NVC)

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Conflict of interest: None

A 72-year-old woman became aware of dyspnea on exertion in November X-1. She was diagnosed with interstitial pneumonia (IP) and suspected to have pulmonary hypertension by echocardiography in February X, and referred to our hospital in March X. She had Raynaud's phenomenon (RP), positive anti-nuclear antibody and anti-RNP antibody at presentation. Nailfold video capillaroscopy (NVC) showed no microangiopathy. Pulmonary arterial hypertension (PAH) (mean PAP: 28 mmHg) was diagnosed on right heart catheterization. We assumed Mixed connective tissue

disease (MCTD)-PAH and started prednisolone 1 mg/kg and intravenous cyclophosphamide (IVCY), which resulted in mean PAP improvement: 22 mmHg after 2 weeks. IVCY was administered every month until August X, and mean PAP decreased to 20 mmHg. In PAH, immunosuppressive therapy (IST) is effective in MCTD but not in SSc. Although appropriate diagnosis is required, it is difficult to differentiate MCTD from SSc in PAH only with positive autoantibodies. Generally, scleroderma late pattern is shown in SSc-PAH, but this case showed no microangiopathy. This finding helps us to think that PAH is derived from MCTD, leading to treatment with IST. Our finding suggests that NVC may be helpful for the differentiation between MCTD-PAH and SSc-PAH.

## P42-10

### A case of thrombotic microangiopathy due to systemic scleroderma that could not save lives

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Conflict of interest: None

[Case] Female in her 50s [Chief complaint] Joint pain [Current medical history] She became aware of edema of her fingers when she woke up. she began to wake up with hypoesthesia from her elbows to her fingertips. She was admitted to our department because she had fever and malaise. She admitted an increase of LDH and she was hospitalized. [Progress] Skin findings, anti-Scl-70 antibody positive, etc. were observed, and scleroderma was diagnosed. She showed an increase in LDH, CK, and D-dimer on admission, and no hypertension, resulting in thrombotic microangiopathy (TMA) due to normotensive scleroderma renal crisis. She thought she was. She started infusion of methylprednisolone 500 mg immediately after admission. She then became bradycardic and suffered cardiopulmonary arrest and underwent cardiopulmonary resuscitation. She confirmed a resumption of heartbeat, but she could not identify a clear cause of cardiopulmonary arrest. She received cerebral warming therapy and vasopressor, but she was confirmed dead. Her ADAMS13 activity was normal and her ADAMTS13 inhibitor was also negative, resulting in a secondary TMA. [Clinical Significance] This case is a valuable case in which TMA was caused by systemic scleroderma and a rapid course was observed even after the start of treatment.

## P42-11

### A case of eosinophilic gastroenteritis in a patient with systemic sclerosis who is positive for anti-RNA polymerase III antibody

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Conflict of interest: None

[Clinical Significance] Eosinophilic gastroenteritis (EGE) is associated with systemic sclerosis (SSc) and should be considered as a differential diagnosis of gastrointestinal symptoms in a patient with SSc. Glucocorticoids (GC) and dietary therapy are the mainstay of treatment for EGE. However, positivity of anti-RNA polymerase III antibodies (ARA) and GC use in patients with SSc are risk factors for the development of renal crisis. In our case, six-food elimination diet and ketotifen were effective without GC use. [Case] 52-year-old female [HPI] She developed epigastric pain one week prior. Esophagogastroduodenoscopy (EGD) and CT scans of the abdomen showed no abnormalities, and she was referred to our hospital. [PMH] SSc (45 years old, ARA positive, limited cutaneous), no history of allergic diseases. [Test results] [Blood test] Eosinophils 2,000/ $\mu$ L, CRP 0.12 mg/dL [EGD] No abnormality. [Histopathology] Duodenum: Lymphocyte and eosinophil infiltration. Eosinophil count 149/hpf. Gastric mucosa: Eosinophil count 97/hpf. Esophageal mucosa: No eosinophils. [Clinical course] After she was diagnosed as EGE, ketotifen and six-food elimination diet were started. Blood eosinophil count normalized and the abdominal symptoms resolved in two weeks.

## P43-1

### A Case of Amyopathic Dermatomyositis Accompanied by a Rapidly Progressive Interstitial Lung Diseases, Which Was Not Saved by Plasmapheresis and Four-Drug Combination Therapy Including Tofacitinib

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Conflict of interest: None

Patient: A 67-years-old woman Medical history: From X-26 days developed a fever, symptoms of coughing and dyspnea. On X-2 days, mild muscle weakness and cutaneous symptoms such as Gottron's sign were observed. She was transferred to our hospital on X day. At the time of admission, SPO2 was 98% (O2 1L), and chest CT showed rapid enlargement of the slit glass shadow. Blood tests showed ferritin 2071 ng/ml, and anti-MDA-5 antibody 3720 index. We diagnosed that as Clinically amyopathic dermatomyositis. We administered Steroid pulse, Tacrolimus, plasma exchange and IVCY. The patient's respiratory condition gradually worsened, and she was intubated and placed on a ventilator on the 11th day. Tofacitinib was started on the 12th day to strengthen the treatment. However, TOF was terminated on the 33rd day due to the development of ventilator-associated pneumonia. Thereafter, elevated ferritin, LD levels and respiratory status were dropping suggested that the primary disease got worsen. She passed away on the 42th day. Clinical Significance: We experienced a case of Clinically amyopathic dermatomyositis in which plasma exchange and tofacitinib were administered from early onset, but failed to suppress the rapidly progressing interstitial pneumonia.

## P43-2

### A case of rapidly progressive interstitial lung disease (ILD) in anti-aminoacyl-tRNA synthetase (ARS) antibody-positive dermatomyositis rescued through long-term veno-venous extracorporeal membrane oxygenation (VV-ECMO)

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Conflict of interest: None

[Case] A 39-year-old man with a history of mycoplasma pneumonia. Two months prior to admission, he had a cough, myalgia and respiratory distress. He was treated with antibiotics as pneumonia but worsened, and he was intubated and placed on a ventilator on the second day. Despite steroid pulse therapy, the patient deteriorated further and was transferred to our hospital. A chest CT scan showed extensive ground-glass opacity (GGO) in the bilateral lower lobes. We suspected myositis-related ILD based on his skin rash and CK elevation, and triple therapy with methylprednisolone, tacrolimus, and cyclophosphamide was started. In addition, VV-ECMO was started for severe respiratory failure. After that, positive anti-ARS antibody was proved. The inflammatory reaction, skin rash, and GGO tended to improve, but the fibrosis progressed, and the tidal volume was decreased. Although he was thought to be difficult to withdraw from ECMO, he improved slowly over a long period of time and was weaned from VV-ECMO on day 59. He was discharged home on foot after 5 months of hospitalization without any serious complications. [Discussion] Inflammatory myopathies are frequently complicated by ILD. We report the usefulness of VV-ECMO in severe ILD associated with anti-ARS antibody syndrome.

## P43-3

### The clinical features of dermatomyositis / polymyositis who were well controlled by low-dose steroid treatment: a cross-sectional observational study

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Conflict of interest: None

**Objectives:** The aim of this study was to clarify the clinical characteristics of dermatomyositis (DM)/ polymyositis (PM) who were well controlled by low-dose (LD) prednisolone (PSL) treatment. **Methods:** Thirty-seven patients who were diagnosed as having DM/PM from April 2012 to August 2020, and continued treatment until August 2021 in our hospital were enrolled. These participants were divided into two groups according to the maintenance dose of PSL less than 6 mg/day, or more. The effective range of tacrolimus (TAC) blood concentration was defined as 5 ng / mL or more. **Results:** The median age in the LD group (n=14) and non-LD group (n=23) was 60.5 years and 65 years, and the median dose of PSL was 5 mg/day and 10 mg/day. The prevalence of interstitial lung disease was almost same between groups. There were two and one participants who were positive for anti-SRP antibody (ab) and anti-PM-Scl100 ab only in non-LD group. Although there was no difference in the ratio of TAC user between groups (50% vs 65.2%), the effective blood concentration of TAC was higher in LD group than in non-LD group (71.4% and 26.7%). **Conclusion:** In the treatment of DM/PM, maintenance of effective blood concentration of TAC may be important for the reducing of PSL dose without disease flare.

### P43-4

#### Recurrences in two long-term survivors of anti-MDA5 antibody-positive dermatomyositis with interstitial lung disease

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Conflict of interest: None

[Case 1] A 54-year-old woman was diagnosed as anti-MDA5 antibody (Ab)-positive dermatomyositis (DM) with interstitial lung disease (ILD). She was treated with prednisolone (PSL), tacrolimus (TAC) and intermittent intravenous cyclophosphamide (IVCY) every 4 weeks. Three months later, she experienced the first recurrence of ILD. Additionally, the second recurrence with mediastinal emphysema occurred seven months after the initiation of PSL, because of delayed IVCY treatment due to fungal infection. Her ILD improved by adding plasma exchange therapy. [Case 2] A 59-year-old woman with anti-MDA5 Ab positive DM-ILD was promptly treated with PSL, TAC, and IVCY therapy. Three months later, her IVCY treatment was rescheduled as she developed pneumatois cystoides intestinalis. The first recurrence occurred five months after the diagnosis of DM-ILD, and the second one with anti-MDA5 Ab titer elevation occurred 16 months after, while maintenance therapy with PSL and Azathioprine. Nearly-half of anti-MDA5-Ab positive DM-ILD patients would die by six months, in spite of intensive care. In contrast, the other half are considered to be long-term survivors who have good prognosis without ILD recurrence. Recurrence could be rarely occurred in the long-term survivors due to inadequate treatment.

### P43-5

#### Examination of the association of the myositis specific antibodies and myositis associated antibodies by EUROLINE and clinical course in our hospital

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Conflict of interest: None

[Objective] Various studies have been conducted on the relationship between autoantibodies and clinical features in inflammatory myopathies (IIM). However, autoantibodies listed in insurances in Japan are part of them. In this study, we will examine the patients who have checked the myositis specific antibodies (MSA) and myositis-associated antibodies (MAA) by EUROLINE in our hospital. [Methods] We retrospectively examined the patients in which MSA and MAA were measured by EUROLINE from 2015 to 2021. We extracted the background, clinical data, and

the reasons why we had checked these antibodies. Moreover, we also followed up on MSA and MAA. [Results] 49 patients were enrolled in this study. The reasons for examination of MSA and MAA were CK elevation ( $n = 17$ ), muscle symptoms such as myalgia and weakness ( $n = 11$ ), IIM ( $n = 10$ ), positive in anti-ARS antibodies ( $n = 8$ ), and others. 24 patients were positive for some MSA or MAA. We followed up on the MSA and MAA in 39 patients. Some cases had atypical clinical courses compared to the previous reports. [Conclusions] It could be useful for predicting the diagnosis, prognosis, or complications among the patients who suspected IIM by checking the MSA and MAA. It is necessary to accumulate the cases in the future and conduct further studies.

### P43-6

#### A case of polymyositis with sarcoid myositis diagnosed by muscle biopsy

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Conflict of interest: None

[Case] A 59-year-old woman was admitted to our hospital because of muscle weakness. Four years ago, she was diagnosed with breast cancer and sarcoidosis by axillary lymph node biopsy. On admission, the MMT score was 4/4 of proximal upper limb muscles and 2/2 of proximal lower limb muscles. Antinuclear antibody was 160-fold (speckled), and anti-RNP antibody was 32.7 U/mL. Autoantibodies for myositis were negative. A muscle biopsy showed inflammatory cell infiltration around blood vessels and myofibers, indicating inflammatory myopathy. In addition, there were scattered noncaseating epithelioid cell granulomas due to sarcoidosis. Based on muscle weakness, elevated CK 208 U/L, myogenic patterns of electromyography, elevated CRP 3.57 mg/dL, and muscle biopsy findings, she was diagnosed as having polymyositis with sarcoid myositis. She started treatment with prednisolone 40 mg/day (1 mg/kg). CK and CRP rapidly improved. [Conclusions] Although the combination of polymyositis and sarcoid myositis is rare, most patients have been reported to have good outcomes with steroid monotherapy. Our patient also showed a good response to the steroid treatment. Muscle biopsy is useful to differentiate between polymyositis and sarcoid myositis and to consider the treatment plan.

### P43-7

#### Factors associated with the development of progressive fibrosing interstitial lung disease (PF-ILD) in idiopathic inflammatory myopathies

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Conflict of interest: None

[Objective] To investigate factors associated with the development of progressive fibrosing interstitial lung disease (PF-ILD) in idiopathic inflammatory myopathies (IIM). [Methods] This study was enrolled 39 patients who were diagnosed with IIM-ILD between 2008 and 2019. PF-ILD was defined using the criteria of the INBUILD trial. We retrospectively compared baseline characteristics and sequential changes of KL-6 between PF-ILD group and non PF-ILD group. The Elevation of KL-6 (E-KL-6) was defined as at least a 25% increase in KL-6 levels twice in a row, and the Persistence of high KL-6 levels (P-KL-6) was also defined as over 1000 U/mL on 3 consecutive measurements. [Results] PF-ILD group ( $n=11$ ) had more anti-ARS antibody positivity (34.8 vs 72.7%,  $p=0.07$ ), but there was no clear difference in baseline characteristics including KL-6

at diagnosis ( $p=0.75$ ). The proportion of patients with E-KL-6 tended to be higher in PF-ILD group (13 vs 45.5%,  $p=0.08$ ), but no difference in that with P-KL-6 ( $p=1$ ). A competing risk analysis revealed that anti-ARS antibody positivity ( $p=0.01$ ) and the proportion of patients with E-KL-6 ( $p=0.05$ ) were significantly higher in PF-ILD group. [Conclusions] Anti-ARS antibody positivity and KL-6 elevation may be predictors of the development of PF-ILD in IIM.

### P43-8

#### **Efficacy of tofacitinib (TOF) for anti-MDA5 antibody-positive clinically amyopathic dermatomyositis (CADM) refractory or resistant to standard treatment**

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Conflict of interest: None

A 53-year-old man presented to our hospital with skin rash from one month. Physical examination revealed the inverse Gottron's papules, Gottron's papules, mechanic hands, and shawl sign. Muscle weakness was not observed. Blood test showed anti-MDA5 antibody was positive. Chest CT revealed random ground-glass attenuations (GGA). We diagnosed him with anti-MDA5 antibody-positive CADM and treated with pulse methylprednisolone, followed by prednisolone (PSL) 70 mg/day, intravenous cyclophosphamide (IVCY), and tacrolimus (Tac). The treatment led him to the improvement. He discharged our hospital, and PSL was tapered to 20 mg/day. However, one month later, he was readmitted due to a fever and the exacerbation of GGA. Considering his disease was refractory to IVCY, we considered to add TOF 10 mg/day. The ethical approval for the use of TOF was obtained by the ethics committee of our institution. We added TOF with pulse methylprednisolone, followed by PSL 70 mg/day. PSL was tapered to 10 mg/day, and his disease status has been stable. There is a consensus to treat this disease with high dose PSL, Tac and IVCY. In the case of refractory to this treatment, there are some reports showed the effectiveness of TOF. It might be considered that TOF could be useful in relapsed cases.

### P43-9

#### **Characteristics of malignancy in dermatomyositis and polymyositis and cancer-associated myositis specific antibody. A retrospective cohort study in a Japanese municipal hospital**

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Conflict of interest: None

[Objective] To investigate the characteristics of cancer-associated myositis (CAM) in a retrospective cohort of dermatomyositis/polymyositis (DM/PM) and clinically amyopathic dermatomyositis (CADM), and to investigate clinical significance of cancer-associated myositis specific antibody (caMSA), anti-Tif1 $\gamma$  and anti-NXP2 antibodies, in CAM. [Methods] Thirty-eight patients with newly diagnosed DM/PM/CADM visiting between April 2014 and November 2021 were included. CAM was defined as cases with malignancy or recurrence within 5 years. Predictive factors for CAM were investigated with logistic regression analysis. [Results] Our cohort included 38 cases and 12 cases of them had CAM. DM and dysphagia were more common in CAM than non-CAM. The frequency of anti-Tif1 $\gamma$  antibodies or caMSA was significantly higher in CAM. CAM tended to have higher CK levels. In univariate analysis, DM, dysphagia and caMSA significantly predicted CAM. In multivariate analysis, two models (caMSA and DM; and caMSA and dysphagia) were tested, and caMSA was only an independent factor in both models. Among CAM cases, significantly more patients with caMSA had Stage $\geq$ II and N or M factors. [Conclusions] In a DM/PM/CADM cohort study, caMSA was an independent predictor of CAM and was associated with advanced cancer.

### P43-10

#### **The challenging treatment of anti-MDA-5 antibody positive Amyopathic Dermatomyositis with rapidly progressive interstitial pneumonia in the infection of MRSA sepsis**

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Conflict of interest: None

[Case] A 42-year-old woman from Cote d'Ivoire. She was transferred to our hospital due to refractory fever, neck pain from other hospital. Chest x-ray showed infiltration shadows on bilateral lung and she was started the antibiotics while examining COVID-19 PCR, MDA-5 antibody and so on. COVID-19 PCR was negative. MRSA from blood culture was detected and VCM was started. CT scan and MRI showed that retropharyngeal abscess was suspected. Though we tried puncture drainage from that abscess, samples could not be collected. MDA-5 antibody positive was reported. She had skin rash of Gottron's sign, the V-sign, and we diagnosed amyopathic dermatomyositis (ADM) with interstitial pneumonia (IP). IP was worse rapidly, we decide to start the treatment with steroid pulse therapy, followed by oral high dose prednisone (PSL), intravenous cyclophosphamide, and tacrolimus therapy. Fortunately, sepsis of MRSA was not worse and IP was improved. PSL dose could be reduced to 10 mg/day and her body condition was stable without recurrence. [Discussion] This case was challenging treatment, because COVID-19 infection and MDA-5 ADM IP were sometimes similar on CT images and she was in the severe infection of MRSA sepsis. Further, we consider that this MRSA infection might have triggered the MDA-5 ADM.

### P43-11

#### **Do skin ulcers developed during the maintenance phase of anti-MDA5 antibody-positive dermatomyositis predict acute exacerbation of interstitial pneumonia?**

Akimasa Asai, Hironobu Nobata, Nao Asai, Mayumi Ito, Hirokazu Sugiyama, Makoto Yamaguchi, Shiho Iwagaitsu, Takuji Ishimoto, Shogo Banno, Yasuhiko Ito

Department of Rheumatology and Nephrology, Aichi Medical University

Conflict of interest: None

[Objective] The risk of developing rapidly progressive interstitial pneumonia (RP-ILD) in dermatomyositis (DM) is considered to be anti-MDA5 antibody positivity and skin ulceration. Although new skin ulcers are often experienced even after the completion of initial treatment, whether this predicts the development of RP-ILD has not been reported and was examined. [Methods] We retrospectively followed patients with anti-MDA antibody-positive DM diagnosed at our hospital between 2013 and 2021 to determine whether those with new or persistent skin ulcers after completion of initial treatment (within 6 months of diagnosis) subsequently developed RP-ILD. [Results] There were 14 patients with anti-MDA5 antibody-positive DM. Thirteen patients were in remission within 6 months of initial treatment, and one patient continued to have skin ulcer; RP-ILD improved in all patients, and there were 3 subsequent relapses. Among the 13 patients in remission, there were 3 cases of new skin ulcers after the initial treatment, and in these 3 cases, RP-ILD did not recur after the skin ulcer. [Conclusions] Our results suggest that RP-ILD may not necessarily occur in new skin ulcers with high anti-MDA5 antibody levels after the completion of initial treatment of anti-MDA5 antibody-positive DM.

### P43-12

#### **A case of anti-MDA-5 antibody-positive rapidly progressive interstitial pneumonia saved by combination therapy including JAK inhibitor and plasma exchange**

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Rheumatology & Collagen Diseases, Tazuke Kofukai, Medical Research Institute, Kitano Hospital, Osaka, Japan

Conflict of interest: None

A 63-year-old woman had fever, cough, and skin rash from mid-Jul. of X. On early Aug., she was admitted to the hospital because of Gottron's sign, mild muscle weakness, elevated myofibrillar enzymes and CRP, and GGO in both lungs. Needle electromyography showed myogenic changes in biceps brachii and iliopsoas muscles. The patient was diagnosed as anti-MDA-5 antibody-positive rapid progressive interstitial pneumonia (RPIP) and started combination therapy with prednisolone (PSL), tacrolimus (Tac), and intravenous cyclophosphamide (IVCY) biweekly on day 2nd in the hospital. However, her respiratory condition gradually worsened, requiring 5 L O<sub>2</sub> at rest, and plasma exchange (PE) was started three times a week on day 25. In addition, JAKi was administered from day 29 to day 48, and IL-6 inhibitor on day 49 and 63. PE was completed on day 85, and IVCY was performed six times. She was transferred to a rehabilitation center in Feb. of X+1 year and discharged her home in Sep. Now she is living daily life as before with 1 L O<sub>2</sub>. Recently, the efficacy of PE and JAKi in addition to the combination therapy has been reported for the treatment of anti-MDA-5 antibody-positive RPIP. In this report, we discuss the pathophysiology and treatment of the disease with our own experiences.

### P43-13

#### Three cases of pneumatosis cystoides intestinalis with idiopathic inflammatory muscle disease experienced in our hospital

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Conflict of interest: None

[Case 1] An 83-year-old man with immune-mediated necrotizing myositis was treated with prednisolone (PSL) and intravenous immunoglobulin (IVIG). Five months after the treatment, he experienced abdominal pain. CT scan revealed pneumatosis cystoides intestinalis (PCI). PCI was resolved spontaneously by treatment. [Case 2] An 85-year-old man with dermatomyositis (DM) was treated with PSL. Ten days after treatment, CT scan revealed PCI. On 13th day, abdominal pain and free air was observed. He was treated conservatively, but died on the 61th day. [Case 3] An 87-year-old man with DM was treated with PSL and IVIG. Seven days after treatment, he experienced bloody stool. On 8th day, CT scan revealed free air and PCI. He died on the 19th day. [Discussion] Idiopathic inflammatory muscle disease (IIM) is rarely associated with PCI, and the prognosis said to be good. Although the etiology is unclear, immunosuppressive agents, vasculitis, and intestinal obstruction have been suggested to be involved. We have experienced three cases of PCI associated with IIM, including two patients with unfortunate outcomes. This report shows that we should consider PCI as a differential disease when abdominal pain occurs in patients with IIM.

### P43-14

#### A case of treatment-resistant anti-Mi-2 antibody positive dermatomyositis

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Tokai University Hospital

Conflict of interest: None

A 39-year-old male noticed myalgia in both shoulders and thighs in July 20xx. Severe proximal muscle weakness rapidly progressed and it became difficult to walk. He had facial erythema, Gottron's papules, nail fold bleeding, and severe proximal muscle weakness. Laboratory examinations revealed serum creatine kinase (CK) was 15609 IU/l, C-reactive protein (CRP) was 1.41 mg/dl, and anti-Mi-2 antibody was also positive. He was diagnosed as anti-Mi-2 antibody-positive dermatomyositis (DM) and was transferred to our hospital for treatment. After 3 times of mPSL pulse with tacrolimus (more than 10 ng/mL of Trough level) therapy, his symptoms gradually improved as well as the decrease of serum CK concentration. Anti-Mi-2 antibody-positive dermatomyositis presents with typical rash and severe myopathy but is said to be rarely associated with interstitial pneumonia and malignant tumors. Generally, DM patients with

anti-Mi-2 antibody are reported as classic DM with good response to treatment and good prognosis. It is classically positioned as dermatomyositis with a good prognosis. It may show treatment resistance as in this case. We herein report this treatment-resistant case of anti-Mi-2 antibody-positive DM compared with our previously experienced cases and the literature review.

### P43-15

#### A case of juvenile dermatomyositis with rapid-progressive interstitial lung disease resulting in pneumomediastinum

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Conflict of interest: None

Patients with pneumomediastinum (PNM) in the course of dermatomyositis with interstitial lung disease (DM-ILD) have a poor prognosis. We will discuss the mechanism of PNM in this disease through the case of JDM with rapid-progressive ILD (RP-ILD) who developed PNM but improved well. An 8-year-old girl was transferred to our hospital with 3 months history of erythema, muscle weakness in the lower limbs and weight loss. Physical examination showed fine crackles on her back. She had Gottron's papules, erythema around fingernails, ulcer scars on finger tips, and muscle weakness of proximal muscles of lower limbs. Thigh MRI showed diffuse intramuscular hyperintensity. Chest CT showed bilateral consolidations and ground-glass opacity below the pleura. Laboratory findings showed ferritin 654 ng/ml, KL-6 2040 U/ml, and anti-MDA5 level 1820. She was diagnosed as JDM with RP-ILD and started combination therapy with steroids, cyclosporine and cyclophosphamide. On the 21st day of admission, she had chest pain, and CT showed PNM without exacerbation of ILD. Immunosuppressive therapy was continued and the PNM getting disappeared. In the etiology of PNM with DM, the vasculitic and idiopathic factors were predominant in this case, and continuation of therapy led to a favorable outcome.

### P43-16

#### A case of anti-NXP2-positive dermatomyositis with atypical viral infection-like symptoms at the onset and refractory, dysphagia, progressed rapidly, and resulted in respiratory failure

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Conflict of interest: None

A 35 y/o woman was admitted to our department because of fever, stomatitis, and myalgia for 2 weeks. Erythema and vesicles on the neck and trunk, myalgia, and myasthenia were observed. PCR tests for herpesvirus were negative. As significant eyelid edema, blistering with hemorrhage, worsening of skin rash on the buttocks with erosions, and difficulty in physical movement, she was started on methylprednisolone pulse therapy and treated with PSL 50 mg/day for severe viral infection. One week later, heliotrope rash and Gottron's sign appeared, therefore the clinical diagnosis of dermatomyositis was made. CT scan showed no interstitial lung disease, nor tumor. ANA, anti-ARS, anti-Mi-2, anti-TIF1-γ and anti-MDA-5 antibodies were negative. Later anti-NXP2 antibody showed positive. As myasthenia and dysphagia rapidly worsened, she was placed on ventilatory management. She was treated with glucocorticoid, tacrolimus, plasma exchange, and high-dose immunoglobulin, but the recovery of dysphagia was delayed. Clinical Implications. We report a case of anti-NXP2-positive dermatomyositis with atypical symptoms resembling viral infection, which was difficult to diagnose.

### P43-17

#### A case of distal myopathy difficult to distinguish from inflammatory disease

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Conflict of interest: None

A woman in her thirties was admitted to our hospital with a 2-year history of gait disturbance and a serum creatine kinase (CK) level of 417 IU/L. The patient walked with a foot drop. Her grip strength was reduced to 7 kg in each hand. Muscle weakness was observed in the cervical, deltoid, biceps triceps brachii, opponens pollicis, iliopsoas, quadriceps, thigh flexor, and tibialis anterior muscles. The patient presented with symmetrical proximal muscle weakness, muscle pain, elevated skeletal muscle-associated enzyme levels in the serum, and the muscle-related changes on electromyography, which further confirmed our initial diagnosis with polymyositis. Even though, neither her muscle weakness nor her serum CK levels improved by 30 mg/day prednisolone combined with various immunosuppressants including, cyclosporine, tacrolimus, azathioprine, methotrexate, rituximab or intravenous immunoglobulin. A homozygous c.358G>A mutation (p. Gly120Ser) was found during analysis of the *GNE* gene in her peripheral blood, and she was diagnosed with distal myopathy. Distal myopathy should be differentiated when weakness occurs in both the bilateral proximal and the distal muscles, e. g., the tibialis anterior muscle and when the therapeutic response to immunosuppressive treatment is inadequate.

### P43-18

#### **A case of anti-TIF-1 gamma antibody-positive dermatomyositis relieved by endoscopic submucosal dissection (ESD) for early gastric cancer**

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Conflict of interest: None

The case is a 71-year-old man. In April X, he was hospitalized due to proximal muscle weakness and dyspnea on exertion, and was diagnosed with anti-TIF-1γ antibody-positive dermatomyositis. Since swallowing muscle weakness was observed, treatment was started with high-dose steroids. Screening for malignant tumors, upper gastrointestinal endoscopy was performed, a 20 mm ulcerative lesion was found on the anterior wall, and biopsy revealed adenocarcinoma. Since thrombotic microangiopathy developed, plasma exchange therapy and tacrolimus (TAC) were used in combination to reduce the dose of steroids. Due to exacerbation of skin symptoms accompanied by increased CK, we decided to perform ESD immediately in consideration of the possibility of paraneoplastic syndrome. Although he used prednisolone 13 mg + TAC 3 mg, ESD was completed in June X without complications. October X, remission of dermatomyositis was obtained. Curative treatment of malignant tumors is expected to improve the myositis and may reduce the side effects of steroids. There are many reports that the disease of dermatomyositis is proportional to the disease of malignant tumors and that dermatomyositis is improved only by malignant tumor treatment, and it is important to intervene early even for minute lesions.

### P43-19

#### **A case of anti-NXP2 antibody positive dermatomyositis following recurrence of cervical cancer 6 years later**

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Conflict of interest: None

A 79-year-old woman was admitted for weakness and dysphagia. Eight years previously, she received radiotherapy for cervical cancer (Stage IIb). Two years later, she was found to have mediastinal and right hilar lymph node metastasis and was treated with chemotherapy. Since then, she has maintained stable disease for six years. She had suffered muscle pain and weakness of her shoulders and neck for five days. She

further developed dysphagia. Physical examination showed Gottron sign and muscle weakness with proximal muscle predominance. A CT scan revealed an enlarged left supraclavicular lymph node, leading to a diagnosis of recurrence of cervical cancer. Based on an elevation of creatine kinase and myogenic patterns on the electromyogram, the patient was diagnosed with dermatomyositis. Anti-nuclear matrix protein 2 antibody was found in her sera. Her conditions improved after therapy with high-dose prednisolone, azathioprine and intravenous immunoglobulin G, followed by radiotherapy to the left supraclavicular lymph node. Our experience indicates that anti-NXP2 positive dermatomyositis could develop after an interval of 8 years of malignancy.

### P43-20

#### **Investigation on the appropriate screening method for malignancy in dermatomyositis**

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Conflict of interest: None

[Objective] It is reported that the incidence rate of malignancy in dermatomyositis (DM) remains high for 5 years after the diagnosis of DM. However, no previous studies have warranted repeated screening for malignancy. In this study, we investigate the optimal screening method. [Methods] We analyzed all the 36 DM patients who met the Bohan and Peter classification criteria and visited our hospital from January 2015 to August 2021. We assessed the number and timings of malignancy diagnosis, and the screening methods. [Results] The average age at DM diagnosis was 58.4 years, and average follow-up period was 48 months. The initial screening with plain chest and abdominal CT (100%), upper (91%) and lower (89%) gastrointestinal endoscopy were performed within 12 months after DM diagnosis. At the end of follow-up, plain CT was re-examined in all cases. Seven patients were diagnosed with malignancy; 6 cases within 12 months of DM diagnosis by the initial screening and 1 case in the 14th month. SIR of malignancy was 16.81 during the first year and 0.97 for the rest of the follow-up period. [Conclusions] In our study, the initial screening for malignancy was beneficial. However, the prevalence of malignancy thereafter was not high, thus repeated screening was not warranted.

### P43-21

#### **Successful treatment anti-MDA5 antibody-positive interstitial lung disease with plasma exchange therapy in refractory or very severe cases**

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Department of Internal Medicine and Rheumatology, Juntendo University

Conflict of interest: None

[Objective] This study was extended report from our previous study that "Successful treatment of anti-MDA5 antibody-positive refractory interstitial lung disease with plasma exchange therapy" (Rheumatology (Oxford) 59(4):767-71, 2020). We aimed to reveal the effect of PE on survival in patients with refractory RP-ILD with anti-MDA5 antibodies. [Methods] We added 6 RP-ILD patients who were positive of anti-MDA5 antibodies with PE. Refractory RP-ILD was defined as radiological progression or oxygenation exacerbation within 4 weeks after intensive immunosuppressive therapy. [Results] The PE group included 6 new patients such as 1 with newly refractory cases, 3 with relapsed refractory cases, and 2 with newly severe hypoxia cases that P/F ratio was less than 200. The survival rate of the PE group was significantly higher than that of the non-PE group (83.3% and 25%, respectively,  $P = 0.03$ ). One patient who showed severe hypoxia at the start of treatment was improved from respiratory failure, but he died of candidemia. [Conclusions] We revealed the higher 1-year survival rate of PE for refractory or severe hypoxia RP-ILD in patients positive for anti-MDA5 antibodies. Physicians may consider that adding PE in refractory or severe hypoxia RP-ILD patients positive for anti-MDA5 antibodies.

### P43-22

#### **A case of breast cancer associated with anti-MDA5 antibody-positive clinically amyopathic dermatomyositis**

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Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

Conflict of interest: None

The patient was 58-year-old woman, who began to notice a tumor in her right breast. In the next month, erythema with scales on the upper eyelid, fingers, back of hands, and under the breast were observed. Three months later, malaise, fever, anorexia, and weight loss also appeared. She consulted a rheumatologist, and Gottron sign and shawl sign were observed. And chest CT showed ground glass opacity mainly in the lower lung field. The patient was admitted to the hospital and diagnosed with anti-MDA5 antibody positive dermatomyositis. She was treated with prednisone 60 mg and tacrolimus 3 mg, followed by steroid pulse therapy and intravenous cyclophosphamide therapy for the rapid progressive interstitial pneumonia. However, IP was not improved, plasma exchange was performed. The patient was transferred to our hospital for discuss with the other treatment options. When she admitted our hospital, right breast cancer was observed. The extended radical mastectomy was considered, but she received a partial mastectomy because of lung complication and immunosuppressive statement. Her clinical course was good, and discharged from the hospital on the 131th day. We report a cancer patient associated with anti-MDA5 antibody positive dermatomyositis.

### P44-1

#### **The clinical characteristics of five anti-OJ positive cases**

Satoshi Yamaguchi, Hiroyuki Hounoki, Aoi Kobiyama, Takafumi Onose, Miho Yamazaki, Ryoko Asano, Toshiki Kido, Atsushi Matsui, Reina Tsuda, Koichiro Shinoda, Kazuyuki Tobe

Department of First Internal Medicine, Toyama University Hospital

Conflict of interest: None

[Objective] Anti-OJ antibody is one of anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies and associated with autoimmune inflammatory myopathy (AIM) or interstitial pneumonia (IP). Detection of anti-OJ antibody is difficult. The aim of this study is to clarify the clinical features of anti-OJ antibody positive cases. [Methods] This was retrospective analysis of five adult patients with anti-OJ antibody detected by immunoprecipitation assays. These patients had visited our Hospital from 2018 to 2021. [Results] The mean age of the patients was  $71.8 \pm 12.8$  years. Three of the five were women. Two of the five had dermatomyositis and IP, two had IP. One case was preceded by IP and developed polymyositis. Two were treated with glucocorticoids, two with glucocorticoids and tacrolimus, and one with glucocorticoids, tacrolimus, cyclophosphamide and plasmapheresis. One died of right heart failure. Anti-ARS test and line blot assay did not detect anti-ARS antibodies in any case. In all cases, the antinuclear antibody (ANA) test was positive for anti-cytoplasmic antibody (CytAb). [Conclusions] It is known that the anti-OJ antibody is positive for CytAb in the ANA test. In anti-CytAb positive AIM or IP cases, immunoprecipitation assay should be performed to detect anti-OJ antibody.

### P44-2

#### **A case of anti-MDA5 antibody positive dermatomyositis with interstitial lung disease successfully treated with tofacitinib**

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Department of Collagen Diseases, Aso Corporation Iizuka Hospital

Conflict of interest: None

[Case] The patient was a 46-year-old woman. She was admitted to our department since she had symptoms of skin rash, fever and cough. Physical examination showed Gottron's sign and inverse Gottron's sign and interstitial pneumonia was seen on chest CT. She was found to have strongly positive anti-MDA5 antibody (4650 index), thus diagnosed as anti-MDA5 antibody positive dermatomyositis with interstitial lung disease. She was

initially treated with prednisolone (PSL) 1 mg/kg/day, tacrolimus (TAC) 3 mg/day and intravenous cyclophosphamide therapy (IVCY: 500 mg/bi-weekly). After a total of 12 courses of IVCY, tofacitinib (TOF) 10 mg/day was started with the presence of PSL and TAC. The dose of PSL was 7 mg/day and the titer of anti-MDA5 antibody was still 650 index when she started TOF, but the dose of PSL could be tapered to 4 mg/day and the level of anti-MDA5 antibody decreased to 72 index for 16 months after starting TOF. Moreover, skin eruption disappeared and interstitial pneumonia improved. [Clinical significance] TOF has been reported to improve the survival rate and lung lesions in patients with early-stage anti-MDA5 antibody positive dermatomyositis with interstitial lung disease. Consistent with previous results, we report a case suggesting the effectiveness of TOF for this disease.

### P44-3

#### **A case of anti-MDA5 antibody positive dermatomyositis presenting with atypical skin rash**

Takafumi Onose, Toshiki Kido, Ikuma Okada, Miho Yamazaki, Hiroyuki Hounoki, Koichiro Shinoda, Kazuyuki Tobe

University of Toyama

Conflict of interest: None

A 53-year-old man was referred to the dermatologist for itching sensation on his left upper arm in February. In April, a biopsy was performed and prednisolone was started with the diagnosis of profound lupus erythematosus. Although necrosis appeared in same area, he was referred to the Department of Dermatology at our hospital in August. In October, another skin biopsy was performed. Fever, cough, white sputum, dyspnea and skin rash on the front forehead, posterior left auricle and neck, and left elbow appeared. He was admitted to the Department of Respiratory Medicine in mid-November with a diagnosis of interstitial pneumonia and was started on 1000 mg steroid pulse. He was treated with multiple immunosuppressive drugs, plasma exchange, and ECMO, but the patient died on the 28th day. Recently, high expression of myxovirus resistance protein A (MxA) has been observed in skin lesions of MDA5-ADM patients, and the importance of the IFN1 pathway has been reported. Since MDA5-ADM may first appear in atypical skin lesions as in this case, a comprehensive evaluation including immunostaining should be considered.

### P44-4

#### **A case of refractory polymyositis with positive anti-nuclear matrix protein (NXP)-2 antibody**

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Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

Conflict of interest: None

A 36-year-old woman, who had been healthy, was referred in February X. Pain in both thighs appeared in December X-1, and in both upper arms and edema of the extremities were observed in January X. MRI showed myositis but muscle biopsy pathology showed atypical for myositis. MxA positive myofibers were found later, which was consistent with myositis. Symptoms progressed rapidly and dysphagia was observed. We started treatment with PSL 60 mg/day (PSL of 1 mg/kg/day), but the edema didn't improve and we performed steroid pulse therapy (methylprednisolone for 3 days). After that, we started colchicine and tacrolimus, but blood levels of tacrolimus was insufficient, changed to cyclosporine. However, she didn't respond well, high-dose immunoglobulin therapy (IVIg), second steroid pulse therapy and intravenous cyclophosphamide were administered. Dysphagia and muscle strength improved, so she was discharged. She was later found to be positive for NXP-2 antibody. Muscle biopsy showed MxA-positive muscle fibers, and we experienced a case of refractory polymyositis with positive NXP-2 antibody. We report this case with some literature discussion, including our own experience with polymyositis.

#### P44-5

##### **Clinical characteristics of patients with dermatomyositis/polymyositis showing hypocomplementemia**

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Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine

Conflict of interest: None

[Objective] We investigated the clinical features of patients presenting with hypocomplementemia in dermatomyositis (DM) and polymyositis (PM). [Methods] The clinical records of 89 patients with DM/PM who had admitted to our hospital were investigated. Patients with normal serum levels of C3, C4, and CH50 were defined as normal (N) group, whereas those with low levels of serum complement were defined as low complement (LC) group. Clinical findings including interstitial lung disease (ILD), laboratory results, pulmonary evaluations, and outcomes were compared between two groups. [Results] Of the 89 patients, 26 patients were classified into the LC group. There were no significant differences in clinical findings and laboratory results between two groups. The ratio of PaO<sub>2</sub>/FiO<sub>2</sub> was lower in the LC group than in the N group. Of the 7 patients who required a mechanical ventilator, 6 were classified in the LC group. In patients with ILD, frequency of deterioration within one year since initiating treatment was significantly higher in the LC group than that in the N group. [Conclusions] This study suggested that hypocomplementemia may be implicated in the disease severity and predict the prognosis in patients with ILD related to DM/PM.

#### P44-6

##### **11 case series report of anti-MDA5 antibody-positive dermatomyositis**

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Conflict of interest: None

Anti-Melanoma Differentiation-Associated gene 5 (MDA5) antibody-positive dermatomyositis (Ab+ DM) is known as high mortality disease because it often complicates rapidly progressive interstitial lung disease (RP-ILD). Combination immunosuppressive therapy (triple therapy) with high-dose glucocorticoid, calcineurin inhibitor, and cyclophosphamide, has been generally used to treat anti-MDA5 Ab+ DM. Recently, some reports indicated the effectiveness of additional therapy with tofacitinib (TOF), and a few reports described successful treatment of plasma exchange (PE). We report 11 patients with anti-MDA5 Ab+ DM treated in our department between 2011-2021. All patients received the triple therapy, and in most of them we started the treatment before oxygenation was needed. 2 patients received the additional therapy with TOF, and 2 patients received the additional therapy with TOF and PE. Despite many of our cases have poor prognosis factors, such as high titer of anti-MDA5 antibody titer or high serum ferritin level, 10 patients survived and only 1 patient died. This indicates that the triple therapy and the additional therapy with TOF at the early stage improve the prognosis of this disease.

#### P44-7

##### **A case of severe Anti-NXP2 antibody positive dermatomyositis**

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Inflammation and Immunology Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Conflict of interest: Yes

A 45-year-old male with fever, weakness of proximal muscles of extremities, heliotrope rash, Gottron's sign, V neck sign, shawl sign, and scratch dermatitis appeared in the middle of May 202X. She was admitted to A Hospital on June 2. High serum CK level MRI images revealed high signal on T2-weighted images of bilateral thighs. Anti-myositis antibodies such as anti-ARS, anti-MDA5, anti-TIF1- $\gamma$ , and anti-Mi2 antibodies were all negative, but muscle biopsy revealed findings consistent with dermatomyositis, leading to the diagnosis of dermatomyositis. There was no evidence of interstitial pneumonia on CT imaging. Methylprednisolone and

prednisolone were administered, but the disease tended to worsen, including serum CK and CRP levels. He transferred to our hospital on 6/25 and underwent multiple rounds of plasma exchange (PE), the dosage of PSL was increased (60 mg/day), and intermittent intravenous cyclophosphamide (IVCY) was administered. After PE (4 times in total) and IVCY (2 times in total) were performed, inflammatory response and serum CK levels improved. PSL decreased gradually and the patient was transferred to another hospital for rehabilitation on August 10.

#### P44-8

##### **A case of rapid progressive interstitial pneumonia (RP-ILD) caused by anti-MDA5 antibody-positive dermatomyositis amyotrophica (CADM) requiring multidisciplinary treatment**

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Department of Rheumatology and Allergy, Narita Red Cross Hospital

Conflict of interest: None

[Background] Anti-MDA-5 antibody-positive CADM has a poor prognosis due to RP-ILD. Currently, a three-drug combination treatment protocol of steroids, calcineurin inhibitors, and intermittent intravenous cyclophosphamide (IVCY) is widely used, but RP-ILD may not be controlled, and further treatment methods are being investigated. [Case] 48-year-old male. Fever, arthralgia, CK elevation, skin rash, anti-MDA5 antibody positive, ILD led to the diagnosis of anti-MDA5 antibody positive CADM complicated with RP-ILD. He was treated with steroid pulsed therapy, IVCY, and tacrolimus. Prednisolone 70 mg was administered as post-treatment, but oxygenation worsened, so the second course of pulsed steroid therapy was performed, and tofacitinib (TOF) was started. He was responsive to the therapy and administered the third course of steroid pulse therapy. The patient's oxygenation deteriorated further. The fourth course of steroid pulse therapy and mycophenolate mofetil was started, but the patient worsened despite the steroid pulse therapy, and death was confirmed on the 30th day. [Conclusion] In this case, we experienced a case of death due to exacerbation of the primary disease regardless of the infectious disease. We report on this case based on a review of the literature.

#### P44-9

##### **A case of dermatomyositis after the use of an immune checkpoint inhibitor**

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Conflict of interest: None

A 67-year-old woman was diagnosed with small cell lung cancer (stage 4a T2aN2M1) in March X. She was started treatment with carboplatin and etoposide and atezolizumab. In June after the 4 cycles, swelling and pain in both upper arms appeared, and myositis, and skin rash. We suspected myositis related immune checkpoint inhibitors. We did tests of various autoantibody and skin biopsy and muscle biopsy. An anti TIF1- $\gamma$  antibody was positive and muscle biopsy showed pathological findings consistent with dermatomyositis. We diagnosed anti TIF1- $\gamma$  antibody positive dermatomyositis that developed after the use of an immune checkpoint inhibitor. Because she has dysphagia, we did steroid pulse therapy (mPSL 1000 mg/day $\times$  3 days)+ IVIG (2500 mg/day $\times$  5 days), and PSL 60 mg/day as post treatment. Myositis and skin rash were gradually improved. This is a rare case of anti TIF1- $\gamma$  antibody positive dermatomyositis.

#### P44-10

##### **Malignant tumor-related dermatomyositis with anti-MDA5 antibody: a case report**

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Conflict of interest: None



[Case] 49-year-old female. [main complaint] fever, rash. [past medical history] colon cancer. [Current medical history] She was diagnosed as dermatomyositis (DM) at a local general hospital because of fever, mechanic's hands, Gottron's papules, Myalgia/weakness of the proximal limbs and polyarthralgia in July 20XX. In addition to positivity with anti-MDA5 antibody, CT scan revealed the interstitial shadow on the right lobe, suggesting that interstitial pneumonia might progress rapidly. Also, ovarian cancer was detected by the check-up. Thus, the operation of ovarian cancer was performed in August at first, and the patient was referred to our hospital for further treatment. At the admission, rash and myalgia was dramatically improved and anti-MDA5 antibody titer, KL-6 and ferritin levels were also decreased even without immunosuppressive treatment. Based on these findings, we started prednisolone alone. Even after the postoperative chemotherapy, no exacerbation of DM was observed. She was discharged on October 12th. [Conclusion] We experienced the anti-MDA5 antibody-positive DM patient who was complicated with a cancer. Surgical resection and mild immunosuppression gave a favorable outcome. In this case, development of malignancy might strongly associate with the clinical course of DM.

#### P44-11

##### **A case of focal myositis with intramuscular nodules that appeared and disappeared every few days or weeks in both lower limbs**

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Conflict of interest: None

A 70-year-old man was referred to our department because of an 8-month history of low fever, myalgia in both lower limbs and weight loss of -7 kg in 9 months. C-reactive protein (CRP) was 16 mg/dL and Creatin Kinase was normal. Examination revealed multiple painful nodules on both lower extremities that appear and disappear in a few days to a few weeks. PET-CT showed nodular accumulation in the same area, and contrast-enhanced MRI showed T1-weighted short tau inversion recovery (STIR) high signal and contrast effect. CT-guided needle biopsy was performed, which revealed myositis with fibrosis and T-cell-dominant lymphocytic infiltration. The diagnosis of localized myositis was made based on the presence of intramuscular nodules confined to the lower limbs, negative myositis-specific antibodies, no muscle weakness or elevated myogenic enzymes, and no specific rash of dermatomyositis. The patient was treated with 55 mg/day (1 mg/kg) of prednisolone, which promptly resulted in negative CRP and no new intramuscular nodules. Since then, the dose of PSL was reduced to 20 mg on an outpatient basis without relapse. Since localized myositis is a rare disease with no established disease concept and is often difficult to diagnose, we report this case including a discussion of the literature.

#### P44-12

##### **A case of polymyositis with atezolizumab-induced immune-related adverse event**

Yoshiki Ishizaki, Keiichi Sakurai, Machiko Mizushima, Nobuyuki Endo, Yutaka Goto, Tatsuya Kawasaki, Shoshi Shinagawa, Shotaro Suzuki, Tomofumi Kiyokawa, Yukiko Takakuwa, Kumiko Tonooka, Kazuko Yamazaki, Mitsuru Imamura, Takahiko Sugihara, Hiroko Nagafuchi, Seido Ooka, Masaaki Mori, Kimito Kawahata

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine

Conflict of interest: Yes

82-year-old male. He was diagnosed as adenocarcinoma of the lung and the left upper wedge resection was performed in 20XX-2. In 20XX-1, multiple brain and liver metastases were found, and he was diagnosed with recurrence of primary lung adenocarcinoma. He was enrolled in a phase II trial of carboplatin-pemetrexed-atezolizumab (CBDCA-PEM-ATZ) combination followed by PEM-ATZ maintenance therapy for elderly patients with non-squamous non-small cell carcinoma. The first course of CBDCA-PEM-ATZ was started from 20XX. CPK increased and muscle weakness was observed after the start. The thigh simple MRI recognized the high signal in STIR in bilateral thigh muscle. Physical examination re-

vealed muscle weakness. Laboratory findings were negative for myositis-specific antibodies. Electromyography showed myogenic changes, and muscle biopsy showed myogenic changes. We diagnosed polymyositis (PM), immune-related adverse event (irAE) caused by ATZ. ATZ was discontinued. However, dysphagia developed and prednisolone was started. On the 14th day of treatment, muscle strength improved. Discussion: We report a case of PM associated with irAE due to ATZ. The PM of irAE is often fatal, but in this case, the patient was able to survive. We report this case, including a discussion of the literature.

#### P44-13

##### **The implication of microchimerism (MC) for the onset of transcriptional intermediary factor 1 (TIF1) positive dermatomyositis (DM) through pregnancy**

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Conflict of interest: None

Recently, several myositis specific antibodies had been come into use and the clinical courses had become predictable according to each antibody types. In adult DM patients, TIF1- $\gamma$  is characterized by malignant complication especially in elderly patients. On the other hand, it is not applicable to younger patients. It is speculated that MC might be involved in the onset of DM through pregnancy. MC means the existence of genetically another person's cells in a body, which corresponds to the fetomaternal cell transfer during pregnancy. The relationship between MC and autoimmune disorders has been suggested, and it is supposed that embryonic antigens transfer to maternal body to cause autoimmune reaction. We present this type DM case who lost her second child through miscarriage in 8 weeks. The patient was 35 years old and had her first child 18 months before. She had mild femoral pain and dysphagia. The result of screening for malignancy was negative, and characteristic skin lesions of DM were shown without interstitial pneumonia. Though there is no certain evidence of relationship between MC and the onset of DM, there is a child bearing population in TIF1- $\gamma$  positive DM without malignancy. We should consider the young group with TIF1- $\gamma$  positive DM during pregnancy and after birth.

#### P44-14

##### **The efficacy of relatively low-dose corticosteroids combined with calcineurin inhibitors and intravenous immunoglobulin for polymyositis and dermatomyositis**

Tatsuki Abe, Yuka Date, Yuki Matsuno, Masafumi Kobayashi, Sayaka Kubota, Hideki Shimizu

Department of Rheumatology, Funabashi Municipal Medical Center

Conflict of interest: None

[Objective] Polymyositis (PM) and dermatomyositis (DM) are treated empirically by high-dose corticosteroids with or without immunosuppressive agents and intravenous immunoglobulin (IVIG). However, the initial dose of corticosteroids is not well-determined. The objective of this study is to evaluate the efficacy of relatively low-dose corticosteroids combined with calcineurin inhibitors (CNI) and IVIG. [Method] We conducted a single-center, retrospective, observational study. Of 23 PM/DM patients who came to our department since 1 October 2018, we included patients who started treatment with oral steroids in our hospital and excluded clinically amyopathic DM and cancer-associated myositis. Clinical and laboratory data were collected. [Results] 5 patients (2 male (40%), mean age 68 $\pm$ 10 years) were included. 4 patients (80%) had interstitial pneumonia. The mean CK was 2389 $\pm$ 732.4 U/L before treatment. All patients were treated by oral prednisolone (41 $\pm$ 2.0 mg/day) with methylprednisolone pulse therapy. CNI was introduced to all patients. IVIG was administered for 3 patients. CK was returned to normal by 45 $\pm$ 9.2 days. 1 patient recurred and were successfully treated with IVIG. [Conclusions] In conclusion, relatively low-dose prednisolone combined with CNI and IVIG was effective for PM/DM.

#### P44-15

##### **A case of 6 anti-ARS antibody positive myositis**

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Graduate School of Medical and Dental Sciences

Conflict of interest: None

[Background] Patients with anti-aminoacyl-tRNA synthetase (ARS) antibody shows myositis, interstitial pneumonia (IP), arthritis, Raynaud symptom, fever, and mechanic's hand. They are thought to form a homogeneous disease group. We report a case of dermatomyositis with IP who had new 6 anti-ARS antibodies. [Case] A 54 years old man showed 5 months loss of upper limb muscle strength, arthralgia, palpitation, erythema of dorsum of the hands, fever. Laboratory data: CK 750 IU/L The myositis specific antibodies including anti-ARS antibody covered by insurance were all negative. CT: IP, echocardiograph: cardiac hypofunction, needle electromyography: positive sharp wave, muscle biopsy: inflammatory myopathy. He was diagnosed as dermatomyositis with IP and successfully treated with mPSL pulse, PSL35 mg and tacrolimus. We confirmed the existence of anti-arginine, aspartate, glutamine, glutamyl-prolyl, leucine, lysine-tRNA synthetase by the immunoprecipitation with his serum and cell line lysate. [Discussion] There are no reports of the existence of above-mentioned antibodies as antibodies associated with anti-ARS antibody syndrome. These new anti-ARS antibodies will be new markers of seronegative myositis or anti-ARS syndrome and a clue of mechanism elucidation.

#### P44-16

##### **Anti-SRP-positive immune-mediated necrotizing myopathy successfully treated with early combined therapy with high-dose glucocorticoid, tacrolimus, and intravenous immunoglobulins**

Tatsuya Shimada, Misako Higashida-Konishi, Mitsuhiko Akiyama, Satoshi Hama, Keisuke Izumi, Hisaji Oshima, Yutaka Okano  
National Hospital Organization Tokyo Medical Center

Conflict of interest: None

[Case presentation] A 54-year-old woman experienced weakness of her proximal extremities. Serum levels of creatine kinase was elevated, and anti-SRP antibody was positive. Electromyography showed the myopathic change, and magnetic resonance imaging demonstrated the gadolinium enhancement of proximal extremities. The biopsy specimen of her triceps revealed the necrotic fibres, in which phagocytic cells and the deposits of membrane attack complex were observed. We diagnosed her with anti-SRP antibody-positive immune-mediated necrotizing myopathy. Her muscle weakness rapidly deteriorated within 6 days, resulting in the bedridden state. We immediately initiated combined therapy with high-dose prednisolone, tacrolimus, and intravenous immunoglobulins. Her muscle weakness improved to independent walking within 3 months. [Conclusion] No standard treatment strategy has been established in anti-SRP-positive immune-mediated necrotizing myopathy. Our case was successfully treated with early combined immunosuppressive therapy. Considering that complement activation and phagocytosis were supposed to be the central pathophysiology of this disease, intravenous immunoglobulins and tacrolimus can be effective.

#### P44-17

##### **A case of anti-MDA5 antibody-positive clinically amyopathic dermatomyositis controlled with steroid alone by chemotherapy for ovarian cancer**

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Conflict of interest: None

[Case] A 50-year-old woman presented with rash on her hands and auricle for 1 month. Topical corticosteroid does not effective. Physical examination revealed inverse Gottron's sign. A serological analysis identified anti-MDA5 antibodies. CT scan revealed patchy ground-glass opacities in both lungs and ovarian tumor. We diagnosed clinically amyopathic dermatomyositis (CADM) and started prednisolone (PSL), intravenous

cyclophosphamide (IVCY), and tacrolimus (TAC). After the initiation of combination therapy, ground-glass opacities gradually improved. Ovariectomy revealed high-grade serous carcinoma, and disseminated lesions were also confirmed on the serosal surface of the uterus and the omentum. We discontinued IVCY and TAC and administered paclitaxel and carboplatin for 6 courses. After the chemotherapy, CT confirmed disseminated lesions. We switched treatment with topotecan and bevacizumab. After the switching of chemotherapy, the disseminated lesions disappeared. We treated CADM with PSL alone but did not show any progression of lung lesion. The relationship between anti-MDA5 antibody-positive CADM and malignant tumors remains unknown. From this case, it is considered that treatment for malignant tumors is important even in cases of anti-MDA5 antibody positive CADM.

#### P44-18

##### **A case of dermatomyositis with dysphagia who was successfully treated with IVIG repetition and balloon dilatation**

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Conflict of interest: None

[Case] A 69-year-old woman. From January 202X, muscle pain of the upper limbs, dysphagia were observed. Gottron sign were noted on the back of the hand, and a blood test revealed high CK levels and positive antinuclear antibody. Myositis-related antibody was negative, but MRI showed fat suppression T2 hyperintensity by the left supraspinatus. From skin biopsy and muscle biopsy, it was diagnosed as dermatomyositis. The examination of the malignant tumor revealed cervical cancer, and the policy was to administer radiation therapy at the gynecological department, but the dysphagia progressed. Therefore, PSL 40 mg was orally administered and IVIG was performed for 5 days before radiation treatment was started. In addition, dysphagia of the cricopharyngeal muscle was found by swallowing contrast examination, so swallowing rehabilitation using balloon dilatation was performed daily. The tumor shrank with radiation therapy and the dysphagia improved. However, on the 94th day, worsening of dysphagia was observed. When IVIG was performed again, dysphagia improved. She was discharged on day 135 with PSL10 mg. [Clinical significance] We report a case of dermatomyositis with dysphagia who was successfully treated with IVIG repetition and balloon dilatation, with a review of the literature.

#### P44-19

##### **A case of relapse of anti-SRP antibody-positive myositis successfully treated with intravenous immunoglobulin (IVIg)**

Takuya Tomokawa<sup>1</sup>, Kazusato Hara<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Atsushi Kawakami<sup>2</sup>

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Conflict of interest: None

[Case] A 87-year-old male was found to have elevated levels of muscle devitalizing enzymes in November, X-2, and was referred to our department as suspicious for myositis. He was diagnosed with anti-SRP antibody-positive myositis based on mild muscle weakness and gripping pain in the proximal muscles of the extremities, MRI and EMG findings suggestive of myositis, and anti-SRP antibody positivity. He had no dysphagia. He was started on two courses of steroid pulses and 40 mg (0.8 mg/kg) of oral prednisolone (PSL), but muscle symptoms remained. Intravenous immunoglobulin (IVIg) was added, and his symptoms was gradually improved. After tacrolimus (TAC) was added, PSL was gradually reduced. He had acute pancreatitis in April, X-1. The possibility of a drug-induced reaction to TAC was suspected, so it was discontinued. Subsequent treatment for myositis was continued with PSL alone. He had a flare-up of myositis in January, X. As a result of two courses of steroid pulses, the increase to 40 mg of PSL, and two courses of IVIg, the myositis went into remission again. Since then, he has been on maintenance therapy with PSL alone without relapse. [Clinical Significance] This is a

valuable case of the possible efficacy of IVIG for the relapse of anti-SRP antibody-positive myositis.

## P44-20

### A case of anti-MDA5 positive dermatomyositis with recurrent mediastinal emphysema

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Conflict of interest: None

A 32-year-old female noticed edema in eyelid and extremities in February. In April, she also noticed dyspnea on exertion and muscle weakness. She visited our clinic in May. Physical examinations revealed that she had Gottron's sign and palmar erythema and proximal muscle weakness. Laboratory findings indicated the elevation of serum CK, ferritin level and anti-MDA5 antibody positivity. Chest CT revealed that she had interstitial lung disease (ILD). Finally, she was diagnosed as dermatomyositis (DM) with rapidly progressive ILD and was admitted to our hospital for treatment. Treatment with methyl-prednisolone (mPSL) pulse therapy followed by 60 mg PSL, tacrolimus (changed to cyclosporin A later) daily and plasma exchange therapy (PE) was initiated. Although clinical symptoms seemed to improve at the beginning, complication of mediastinal emphysema (ME) occurred in addition to worsening of ILD. Therefore, intermittent cyclophosphamide pulse (IVCY) and mPSL pulse therapy were performed. As the worsening of ME is persistent, IVCY and PE therapy was performed repeatedly. ILD was gradually improved although ME still remained. We herein report the treatment-resistant case of anti-MDA5 positive DM with recurrent ME and discuss pathogenesis of ME in relation to previous literature review.

## P44-21

### A case of anti-MDA5 antibody-positive dermatomyositis in a black French woman treated with hydroxychloroquine for refractory skin lesions

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Department of Rheumatology, Yodogawa Christian Hospital

Conflict of interest: None

[Case] A 43-year-old black woman of French [clinical history] She had continued polyarthralgia for a month, visited other hospital. Then Laboratory data revealed the elevation of CRP values and anti-CCP antibody (Ab.) positive, She was diagnosed with rheumatoid arthritis. Salazosulfapyridine was started but did not improve the symptoms, she visited our hospital. The patient had a painful skin rash with ulcers on upper arms, face and scalp, periungual erythema, inverse Gottron's sign, mechanic's hand, and stomatitis. Myogenic enzymes were elevated, and CT scan of the chest showed pale frosted shadows in the bilateral lower lung lobes. The patient was diagnosed with anti-MDA5 antibody-positive dermatomyositis-complicated with interstitial pneumonia. We started high-dose prednisolone, tacrolimus and cyclophosphamide. But the rash were not improved, we added hydroxychloroquine. [Clinical significance] Japanese patients of anti-MDA5 Ab. positive DM is frequently complicated with rapidly progressive interstitial pneumonia leading to poor prognosis. On the other hand, racial differences changes clinical characteristics and prognosis, therefore, effective treatment differ according to race. We reported the case with the review of literatures

## P45-1

### Potential of tocilizumab therapy for acellular arteritis to corticosteroid withdrawal

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Conflict of interest: Yes

[Objective] This study was to evaluate the effects of steroid reduction and withdrawal in patients with giant cell arteritis (GCA) treated with tocilizumab (TCZ) at our department. [Methods] As of September 2021, we examined 7 patients in the TCZ+PSL group (T+P group) and 12 patients in the PSL group (P group) among GCA patients who could be followed at our hospital and other hospitals. The evaluation items were CRP, hemopoietic sedimentation rate, white blood cell count, platelet count, TCZ administration interval, PSL dose, and the presence or absence of relapse or adverse events, and the results were compared until 36 months after the start of treatment. [Results] In the T group, PSL was withdrawn in all patients by 13 months after the start of TCZ, and the TCZ dosing interval could be extended to 2 weeks or more. Relapse was observed in 5 of 12 patients in the P group, whereas no relapse was observed in the T+P group during the observation period. Adverse events were observed in 8 patients in the P group and 4 patients in the T group, but there were no cases of discontinuation due to adverse events. [Conclusions] In GCA, TCZ may be effective in reducing PSL dose, withdrawal, and relapse prevention.

## P45-2

### A case of aortitis after administration of pegfilgrastim during chemotherapy for breast cancer

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Conflict of interest: None

A 55-year-old woman received mastectomy for right breast cancer 65 days before admission. Chemotherapy with docetaxel and cyclophosphamide followed by administration of pegfilgrastim for prophylaxis of neutropenia was started 15 and 12 days before admission, respectively. She reported persistent high fever 9 days before admission. She visited our hospital and admitted for further evaluation and care because blood test showed marked elevation of acute phase reactants. Contrast-enhanced CT showed thickening of the walls of her ascending and descending aorta and bilateral carotid arteries. Since blood culture, treponemal tests, and IGRA using TB specific antigen were all negative, secondary aortitis to infections was considered negative. Also, there were no findings suggestive of autoimmune diseases such as IgG4-related disease or Behçet's disease. She was diagnosed with drug-induced aortitis and treated with prednisolone 30 mg 8 days after admission. Her fever and laboratory data improved promptly. Follow-up contrast-enhanced CT showed improvement in arterial wall thickening. She was discharged 15 days after admission. Rheumatologists should be aware that pegfilgrastim can cause aortitis. We will report this case with some literature reviews.

## P45-3

### A Case of Giant Cell Arteritis after SARS-CoV-2 Vaccination (BNT 162b2 mRNA)

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The Department of Rheumatology, Tokyo Kyosai Hospital

Conflict of interest: None

[Case] An 87-year-old woman presented with new bilateral temporal pain on the same night after receiving the first dose of SARS-CoV-2 vaccine (BNT162b2 mRNA). The pain worsened, and mandibular pain also appeared, accompanied by low-grade fever, and the second vaccination was discontinued. Five weeks after vaccination, the patient began to have high fever and was referred to our department. Induration and tenderness of the bilateral temporal arteries were observed, and CRP levels were high. Ultrasonography showed thickening of the walls of bilateral shallow temporal arteries (halo sign). Histological examination of the temporal arteries was compatible with giant cell arteritis (GCA). She was started on prednisolone 35 mg/day (1 mg/kg/day), and her symptoms and arterial wall thickening rapidly improved. [Discussion] Most of the reported cases occurred immediately after vaccination, with a median of 2.5 days. The frequency of headache up to 7 days after the vaccination has been reported to be 0% for the first dose and 25% for the second dose in elderly subjects. The frequency of headache after 10 days was also reported to be 0.23%. In the



elderly, GCA should be considered in the presence of new temporal pain, even immediately after SARS-CoV-2 vaccination.

#### P45-4

##### **A case of giant cell arteritis with intracranial vascular stenosis improved after two balloon dilation procedures**

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Internal Medicine for Collagen Disease, Japanese Red Cross Fukuoka Hospital

Conflict of interest: None

We report a 68-year-old woman with giant cell arteritis (GCA) with intracranial vascular stenosis refractory to immunosuppressive therapy. In March of year X, increased inflammatory response of unknown origin was found. Autoantibody tests were all negative. In April, visual field disturbance appeared. She was diagnosed with GCA by the wall thickening of the temporal artery and the aorta. In spite of steroid pulse therapy, hemiparesis and motor aphasia developed. MRI showed acute cerebral infarction and stenosis at the end of the left internal carotid artery. Her symptoms temporarily improved after prednisolone (PSL), methotrexate and antiplatelet therapy, however, the neurological findings began to worsen, and MRI revealed decreased blood flow in the left middle cerebral artery region. Balloon dilatation was performed, and subsequently, her symptoms got better and the dose of PSL was gradually tapered. On postoperative day 21, imaging showed recurrence. Little improvement was found following the second steroid pulse therapy. Additional balloon dilatation was successfully performed, resulting in increased blood flow without any recurrence afterwards. Endovascular treatment of intracranial vessels in GCA is rarely reported, and this presentation suggests its efficacy.

#### P45-5

##### **A case of Takayasu's arteritis and ulcerative colitis treated with tocilizumab in a patient who wished to become pregnant**

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Conflict of interest: None

[Background] Takayasu's arteritis (TKA), rarely complicated with ulcerative colitis (UC), is common in young women. [Case] A 25-year-old woman previously diagnosed with UC. Tapering of prednisolone (PSL) from 20 mg to 10 mg increased the levels of C-reactive protein (CRP) without UC relapse. Computed tomography (CT) showed thickening of the ascending aorta and right cervical artery. TKA was diagnosed based on positron emission tomography/CT findings and positivity for human leukocyte antigen B52. Treatment with PSL 30 mg was initiated. Tapering of the PSL dose to 20 mg led to an increase in CRP. Despite treatment with adalimumab (ADA), new uptake was observed in the left internal carotid artery. ADA was switched to tocilizumab (TCZ), decreasing CRP levels. Further tapering of the PSL dose (10 mg) led to UC relapse, which was controlled by 5-aminosalicylic acid and steroid enema. At PSL 5 mg, she reported mild chest pain, and vasculitis was slightly increased. The PSL dose was increased to 10 mg, and the patient achieved remission. Three years later, she became pregnant. [Clinical significance] TCZ was effective against TKA, but not UC. The disease was controlled without increasing the dose of PSL. TCZ may be useful for TKA patients complicated with UC who wish to become pregnant.

#### P45-6

##### **PET-CT uncovered sitosterolemia in a case of suspected Takayasu's Arthritis**

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Conflict of interest: None

[Case] A 52-year-old male presented hypertension on his medical check-up. As he presented canonical bruit, subsequent head MRI was performed, revealed bilateral internal carotid artery stenosis. Takayasu's arteritis (TA) suspected, he was admitted to our hospital. [Clinical course] After admission, contrast-enhanced CT showed wall thickening and luminal stenosis in multiple blood vessels such as the abdominal aorta and common iliac arteries, which was compatible for TA. There was no fever or pain and less inflammation (CRP 0.57 mg/dL) during the course. FDG-PET was performed which showed least FDG accumulation on the arteries, while markedly accumulated on the tendons, especially the Achilles tendon. Review of family history revealed consanguineous marriage of their grandmother besides myocardial infarction and sudden death in his family. Despite no hyperlipidemia in general laboratory test, skin and tendon xanthoma were observed and serum level of sitosterol was significantly high (14 mg/dL > 1 mg/dL). We plan to check ABCG5/8 mutation for definite diagnosis. [Discussion] Sitosterolemia is an extremely rare autosomal recessive hereditary dyslipidemia. Primary dyslipidemia should be considered when large vessel angiitis is suspected. PET-CT was useful for the differential diagnosis.

#### P45-7

##### **A case of Cogan's syndrome diagnosed from scleritis, hearing loss, and large vessel vasculitis and successfully treated with tocilizumab**

Hiroki Tabata<sup>1</sup>, Tatsuhiro Ohshige<sup>1,2</sup>, Satoshi Hama<sup>1</sup>, Misako Konishi<sup>1</sup>, Mitsuhiro Akiyama<sup>1,2</sup>, Keisuke Izumi<sup>1,2</sup>, Hisaji Oshima<sup>1</sup>, Yutaka Okano<sup>1</sup>

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Conflict of interest: None

[Case] 61 y/o male [Complaint] conjunctival hyperemia, hearing loss, tinnitus [Clinical Course] He had left hearing loss, tinnitus and bilateral conjunctival hyperemia. Steroid eye drops were started, but the condition did not improve. Then, foggy vision appeared in his right eye and he was referred to our department. He had bilateral scleritis, iritis, left hearing loss and high inflammation (ESR 118 mm/1h, CRP 15.5 mg/dL). FDG-PET showed hyperaccumulation in the ascending aorta and abdominal aorta. He was diagnosed with Cogan's syndrome, and prednisolone (PSL) 50 mg/day was started. Two weeks later, dose of PSL was reduced to 40 mg/day and tocilizumab (TCZ) subcutaneous injection was introduced. Although the hearing loss remained, the tinnitus, pain in the lower leg, iritis, scleritis and inflammation improved. [Discussion] Cogan's syndrome is classified as variable vessel vasculitis by the CHCC 2012 and causes inflammation of vessels of all sizes. There are no specific markers, and it is characterized by two main symptoms: anterior segment inflammation and inner ear damage. DMARDs are often used in addition to high-dose PSL, but there have been some recent reports of success with TCZ. TCZ may also be considered for Cogan's syndrome, which is similar to large vessel vasculitis.

#### P45-8

##### **A case of giant cell arteritis diagnosed after multiple cerebellar infarctions without inflammatory response**

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Conflict of interest: None

The patient was a 79-year-old man. He was diagnosed with ischemic optic neuropathy in April. He became aware of rotatory dizziness on July

3, and a simple MRI revealed multiple bilateral cerebellar infarctions on July 5. Physical examination revealed partial loss of right visual field and cerebellar ataxia symptoms without fever or headache symptoms. Although there was no obvious inflammatory reaction, contrast-enhanced MRI scan showed global wall thickening in bilateral vertebral arteries, and vasculitis was suspected. Ultrasonography showed global wall thickening of the temporal and vertebral arteries, and PET-CT showed abnormal FDG accumulation in these arteries. A temporal artery biopsy showed multinucleated giant cells and lymphocytes infiltrating, leading to the diagnosis of giant cell arteritis (GCA). PSL 1 mg/kg was started, and he progressed well without any new symptoms. GCA is known as a large vasculitis with inflammatory response. Severe complications include ischemic optic neuropathy and cerebral infarction, which may require urgent decision making. In this case, the patient developed cerebral infarction but did not have any systemic symptoms or inflammatory reaction. Various imaging and histological examinations may be useful in the diagnosis of an atypical GCA.

## P45-9

### Peripheral Ulcerative Keratitis Associated With Large Vessel Vasculitis

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Conflict of interest: None

<Background>Peripheral ulcerative keratitis (PUK) is a non-infectious ulcer at the peripheral corneal stroma. Autoimmune diseases can cause PUK, but PUK caused by large vessel vasculitis (LVV) has rarely been reported. <Case>A 71-year-old woman was hospitalised for low-grade fever for 2 weeks, malaise, back pain for 1 week, and pain and hyperaemia in her left eye for 1 day. There were no other symptoms such as headache, neck pain or joint pain. Her medical history included hypertension. Ophthalmologic examination revealed ulcer at the peripheral corneal stroma with episcleritis in her left eye, which suggested PUK. Erythrocyte sedimentation rate, 117 mm/h and C-reactive protein, 16.47 mg/dL were elevated. Tests for anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, as well as rheumatoid factor and anti-CCP antibody were negative. 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) was performed and showed accumulations in the carotid arteries and pulmonary arteries bilaterally. Based on the FDG-PET findings, she was diagnosed with LVV. She was treated with topical betamethasone eye drops for PUK and oral prednisolone for LVV. Her symptoms and PUK findings completely disappeared. <Clinical significance>This case suggests that LVV can cause episcleritis and PUK.

## P45-10

### A case of Takayasu arteritis in a young man diagnosed by unstable angina with diffuse stenotic lesions of coronary arteries

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Conflict of interest: None

A 36-year-old man had had shortness of breath during exercise for approximately 2 years, and also had chest pain during exercise for approximately 5 months. He referred to cardiologist in our hospital with a complaint of a chest pain and, ECG was demonstrated ST-segment depression. He was diagnosed with stable angina pectoris and, had diffuse stenotic lesions in the coronary arteries on coronary angiography. The patient was scheduled for coronary artery bypass surgery. However, the preoperative examination revealed an unexplained elevated CRP. Contrast-enhanced CT showed increased contrast enhancement of the adventitia in bilateral subclavian arteries and thoracoabdominal aorta, and PET-CT showed FDG accumulation in bilateral common carotid arteries, brachiocephalic artery, and left subclavian artery. He was diagnosed with the diagnosis of Takayasu arteritis, and started on prednisolone and methotrexate. Then, his subjective symptoms disappeared. In this case, there were no symptoms other than angina pectoris, but the CRP level had persistently exceeded 1 mg/dL. Although Takayasu arteritis with angina pectoris as the initial symptoms is extremely rare, it should be suspected in young angina pectoris patients with persistently elevated CRP levels.

## P45-11

### A case of pegfilgrastim-induced large vessel vasculitis

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Conflict of interest: None

[Case Presentation] A 45-year-old woman was diagnosed with left-breast cancer and underwent partial left mastectomy 2 months ago. Subsequently, TC therapy (docetaxel + cyclophosphamide) was performed after the operation at day 1. At day 3, pegfilgrastim was administered to prevent leukopenia. At day 10, she developed fever over 38 degrees and bilateral neck pain. And she was referred to our department at day 14. Cervical echographic examinations showed obscuration of the adventitia from the periphery of the common carotid artery to the internal carotid artery. Cervical MRI scan revealed findings suggestive of inflammation. PET-CT showed accumulation of SUV max 4.5 around the bifurcation of both carotid arteries, the aortic arch, and the descending aorta. We suspected pegfilgrastim-induced aortitis and so discontinued pegfilgrastim, followed by observing the progress without steroid therapy. Fever disappeared at day 20, and tenderness of bilateral necks and the laboratory findings of inflammation gradually improved. [Conclusion] When patients during chemotherapy presented fever and neck pain after the administration of granulocyte colony-stimulating factor, physicians should be aware of the drug-induced large vessel vasculitis.

## P45-12

### A case of Takayasu arteritis with multiple pulmonary artery occlusions in lung ventilation/perfusion scan that contrast-enhanced computed tomography could not point out

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Conflict of interest: None

[Case] A 43-year-old Japanese man was admitted to our hospital complaining of dyspnea. Five years prior to this admission, he began feeling general fatigue. Contrast-enhanced CT showed arterial wall thickening of the ascending aorta, the aortic arch, and the left common carotid artery. Chest CT showed the subpleural consolidation in the left lower lobe and ground-glass opacities in the right upper and lower lobes. Lung ventilation/perfusion (VQ) scan showed a mismatch of perfusion and air in the extensive areas of both lungs. We started prednisolone 30 mg/day and anticoagulant therapy by edoxaban. Contrast-enhanced CT 6 months after induction treatment showed no worsening of the arterial wall thickening and reduction of the consolidation in the left lower lobe. [Discussion] Pulmonary arteries were reported to be involved in 6.9 to 80% of Takayasu arteritis (TA) patients. Among 33 patients treated for TA in our hospital, 11 patients had pulmonary artery involvement (PAI) and 8 patients had pulmonary infarction. TA Patients with PAI were reported to have a longer course of disease than patients without PAI. Lung VQ scan is useful in patients with a longer disease course who present with pulmonary parenchymal lesions in Chest CT or have symptoms suggestive of pulmonary infarction.

## P45-13

### Successful treatment with adalimumab monotherapy for Takayasu arteritis and Crohn's disease which developed at the same time: a case report

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Conflict of interest: None

A 38-year-old female was referred to our hospital because of chest pain during inspiration for a week. A few months before, she had presented with fever, stomatitis, diarrhea, and polyarthralgia. She underwent surgery for hemorrhoidal fistula. On admission, vital signs were normal except for temperature. She had stomatitis, tenderness in the abdomen and erosion

around the anus. The remainder of the physical examination is normal. Her C-reactive protein was 13.2 mg/dL. There were no abnormalities in immunological tests. Computed tomography (CT) revealed bilateral pleural effusion and wall thickening of aortic arch. Positron emission tomography/CT (PET-CT) showed uptake of <sup>18</sup>F-fluorodeoxyglucose (FDG) in the walls of the ascending aorta, aortic arch, pulmonary artery trunk and right brachial arteries. These findings were consistent with Takayasu arteritis (TAK). On the other hand, colonoscopy revealed some longitudinal ulcers and pathological findings were consistent with Crohn's disease (CD). She was diagnosed with TAK and CD and treated with adalimumab (ADA). Follow-up after three months, FDG uptakes in these vessels on PET-CT disappeared. It is important to consider the possibility that TAK and CD might be present at the same time. ADA monotherapy might be effective for TAK.

#### P45-14

##### **A case of Takayasu aortitis with spontaneous remission and progressive vascular stenosis**

Misato Kawakami, Norihiro Matsumura, Nobuyuki Endo, Yoshiki Ishizaki, Yusei Motonaga, Takayasu Ando, Marina Uchida, Tatsuya Kawasaki, Shotaro Suzuki, Yuko Hayashi, Keiichi Sakurai, Tomofumi Kiyokawa, Machiko Mizushima, Yukiko Takakuwa, Kumiko Tonooka, Mitsuru Imamura, Takahiko Sugihara, Seido Ooka, Hiroko Nagafuchi, Kimito Kawahata  
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Conflict of interest: None

The patient is a 32-year-old woman who wishes to have a baby. She had a slight fever and blood test shows CRP 10 mg/dl for a few months, but the fever resolved spontaneously. But one year after, her blood pressure become 190/100 mmHg and she admitted our hospital. Blood test: WBC 6600/μl, CRP 0.09 mg/dL, IgG4 61.7 mg/dL, ANA negative and MPOANCA negative. Ultrasound, MRI, and CT revealed bilateral common carotid arteries, left external carotid artery left internal carotid artery with severe stenosis/occlusion, dilatation of the ascending aorta, and mild wall thickening with circumferential ring-like thickening of the arch, the three branches of the arch, and the aorta from the descending to the sub-renal arteries on contrast-enhanced CT. FDG-PET showed no obvious inflammation. Fibromuscular dysplasia was excluded because of vascular lesion sites and the absence of bead-like changes. The patient was diagnosed as Takayasu aortitis with progressive vascular stenosis and residual vascular inflammation despite a decrease in activity with no treatment. She doesn't want to receive immunosuppressive agents for three months, and the CRP level remained around 0.2 mg/dL during The patient consented to treatment with steroids and tocilizumab, and we report her progress.

#### P45-15

##### **A case of Takayasu arteritis with pulmonary artery involvement diagnosed by multiple pulmonary nodules**

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Conflict of interest: None

Case: A 39-year-old woman. She developed back pain and shortness of breath, and a CT revealed multiple pulmonary nodules. Symptoms worsened, and a CT showed new lesions and narrowing of pulmonary vessels. A contrast-enhanced CT revealed aortic arch wall thickening and stenosis of the right pulmonary artery. She was suspected to have Takayasu's arteritis (TA). After hospitalization, pulmonary blood flow scintigraphy also showed decreased blood flow in the upper and middle lobes of the right lung, consistent with the distribution of nodular and infiltrative shadows, supporting pulmonary artery infarction. She was diagnosed as Type IIa-P+ with TA. After starting PSL 40 mg and aspirin 100 mg, both CRP and symptoms improved. However, one month later, wall thickening improved in contrast-enhanced CT, but pulmonary artery stenosis remained unchanged. After discharge, tocilizumab was introduced due to the fever and back pain, and PSL has now been reduced to 10 mg with no relapse.

Clinical implications: In TA, some patients present only pulmonary artery lesions, which may lead to pulmonary infarction and pulmonary hypertension. Therefore, TA should be considered when multiple pulmonary nodules are observed in addition to respiratory symptoms and increased inflammatory response.

#### P46-1

##### **A case of Eosinophilic granulomatosis with polyangiitis (EGPA) with atopic dermatitis treated with combined biologics**

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Conflict of interest: None

Case: A 61-year-old male patient with hypereosinophilia, and atopic dermatitis (AD) had been treated with prednisolone (PSL) 30 mg/d and cyclosporine A (CyA) 50 mg/d. Due to eosinophilia and skin symptoms PSL was difficult to taper from 20 mg/d. The patient was diagnosed with definite EGPA with a history of asthma and mononeuritis multiplex in our department. Following mepolizumab (MEP) initiation, eosinophilia improved and PSL was tapered. However, skin erythema and pruritus gradually worsened with elevating IgE. Peripheral eosinophils count was strongly suppressed and eosinophil infiltration nor vasculitis was observed by skin biopsy. We diagnosed his condition as exacerbation of pre-existing AD and started concomitant dupilumab (DUP). His skin symptoms and the serum IgE rapidly improved. Combination therapy has been continued without complications of infection or adverse events. Conclusion: Although there are case reports of EGPA associated with AD, EGPA is known to be associated with asthma with a low predisposition to atopy, and there is no strong relationship between AD and EGPA. The pathogenesis of EGPA is also known to be centered on IL-5, while that of AD is centered on IL-4. Anti-cytokine therapy for each disease was effective in patients with these combined diseases.

#### P46-2

##### **A case of eosinophilic granulomatosis with polyangiitis presenting with syphilitic erythema of the palms**

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Conflict of interest: None

A 26-year-old man developed cough and respiratory discomfort 6 months ago, and was diagnosed with bronchial asthma in a local clinic and prescribed an inhaled steroid. However, he had asthma attacks approximately once a week, indicating that his asthma was poorly controlled. Two weeks before presenting to our hospital, he had a fever of 39°C and palmar erythema. Three days before presenting to our hospital, he developed sensory disturbance in his left leg. A dark red, irregular, and oval erythema with mild itching was observed in both of his palms. The lesions were circular in shape and partly covered with scales, just like the skin lesions in syphilis. A biopsy from the area of palmar erythema showed liquefaction degeneration of the epidermis and dermo-epidermal junction and infiltration of eosinophils, neutrophils, lymphocytes, and macrophages in the area surrounding the superficial to mid-dermal layers. Nuclear dust and granulomas were also observed. Although there was no fibrinoid necrosis of the vessels, other pathological findings were consistent with those of EGPA. This was a rare case of EGPA presenting with syphilitic erythema of the palms.



### P46-3

#### **A case of crescentic glomerulonephritis with positive PR3-ANCA and anti-GBM antibodies after BNT162b2 SARS-Cov2 vaccination**

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Conflict of interest: None

The patient is a 57-year-old male. He was treated for Takayasu's arteritis with PSL 2 mg/day and infliximab 500 mg/body/8 weeks. He received his second dose of BNT162b2 SARS-Cov2 vaccination, and fever appeared on the same day. Later, swelling and tenderness of both hands and ankle joints, brown urine, purpura of extremities, and right-sided abdominal pain appeared, and the patient was examined. sCr 1.65 mg/dl, urine protein 3.7 g/gCre, and urine red blood cells >100/HPF were found. The day before admission, the patient was re-examined and found to have elevated sCr 2.94 mg/dl, PR3-ANCA 14.9 IU/ml, and anti-GBM antibody 3.3 IU/ml. A renal biopsy was performed, and light microscopy showed that 20 of 35 glomeruli showed crescentic glomerulonephritis. Immunostaining showed that IgG, IgA, IgM, C1q, and C3 were all negative. The diagnosis of microscopic polyangiitis was made. Methylprednisolone 1,000 mg/day was administered for 3 days from the first day of the disease, and PSL 60 mg/day was started from the fourth day of the disease. In addition, rituximab 700 mg/body/week was administered 4 times in total from the 5th day. However, in spite of the above treatment, the patient did not respond well to treatment and developed end stage renal failure.

### P46-4

#### **A Case of Suspected Elderly-Onset granulomatosis with polyangiitis with Corneal Ulcer and Posterior Uveitis**

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Conflict of interest: None

The patient was an 81-year-old woman. She had bilateral conjunctival hyperemia and eyelid swelling for 4 days prior to her visit. She was referred to our hospital because she had difficulty in opening her eyes and decreased vision. Bilateral upper eyelid swelling and hyperemia of the eyelids were observed, and scleritis and panuveitis were pointed out in the ophthalmological examination. Blood tests showed PPR3-ANCA 67.9 U/mL, MRI showed lacrimal gland mass, and screening for infections showed no significant findings. Granulomatosis with polyangiitis (GPA) was suspected. She was treated with eye drops; betamethasone, tropicamide, and dorzolamide. The elevated intraocular pressure was controlled. However, ocular pain and corneal ulceration appeared one week after admission, and treatment with PSL 1 mg/kg/day was started. Two weeks after admission to the hospital, RTX 375 mg/m<sup>2</sup> was added, and eyelid swelling, ocular conjunctival hyperemia tended to improve, epidermal coverage of the ulcer area was obtained after the start of treatment. We experienced a case of elderly-onset GPA with corneal ulcer and posterior uveitis. In the case of bilateral conjunctival hyperemia and eyelid swelling, autoimmune diseases such as ANCA-related vasculitis should be considered in the differential.

### P46-5

#### **Successful treatment of mepolizumab in a patient with cardiac lesions of Eosinophilic granulomatosis with polyangiitis (EGPA) without peripheral blood eosinophilia: a case report**

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Conflict of interest: None

A 58-year-old man with asthma and sinusitis developed purpura,

mononeuritis multiplex. He was diagnosed ANCA negative EGPA. After induction of remission with steroid pulse therapy and high dose prednisolone (PSL), the dose was reduced. But femoral head necrosis occurred and THA was performed. After sinusitis worsened, reduction of PSL 12.5 mg or less was difficult for 2 years and he was referred to our department. There was no increase in peripheral blood eosinophil count, CRP, ESR. Only IgE level slightly increased. Though he had only nasal symptom, BNP level gradually increased. On the echocardiogram, left ventricular wall motion was diffusely decreased and the ejection fraction was decreased to 56%. The BNP deteriorated, and it was considered to have residual eosinophilic inflammation in the tissue. Mepolizumab 300 mgq4w was started, and methotrexate was administered thereafter. After 2 years, the PSL dosage is reduced to 5 mg/day without relapse, and the BNP decreases to normal. Particularly in ANCA negative EGPA, it is considered to be eosinophilic infiltration in tissues, and even if there is no increase of peripheral blood eosinophil count, strengthening treatment with mepolizumab could be effective to improve the condition and reduce the steroid dosage.

### P46-6

#### **A case of granulomatosis with polyangiitis complicated by acute promyelocytic leukemia**

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Conflict of interest: None

A 77-year old female suffered from nasal obstruction and hearing loss from April 2015. She received on antibacterial drugs, but her symptoms persisted. These symptoms improved with 10 mg/day of oral prednisolone (PSL), however, her symptoms flared up when reduced to 5 mg. Chest CT showed consolidation in both lungs and hearing loss was noted. She was referred to the department of Otorhinolaryngology at our hospital. Based on a series of symptoms, granulomatosis with polyangiitis (GPA) was suspected, and she was referred to our department. Chest CT showed cavitary lesions, and head MRI showed granulomatous changes in the paranasal sinuses. Oral PSL 50 mg was started upon diagnosis of GPA, and she was discharged our hospital after tapering of steroids. Azathioprine (AZP) 50 mg was started in March 2016. In May 2018, sudden pancytopenia was observed. AZP and ST combination were discontinued with no improvement, then blasts appeared in the hemogram (11%). She was diagnosed as acute promyelocytic leukemia (APL) by bone marrow examination. She was discharged after FISH turned negative with ATRA and ATO therapy. We experienced a case of GPA complicated by APL as a first report. Attention is required to hematological malignancies when sudden pancytopenia was observed in GPA.

### P46-7

#### **A case of ANCA associated vasculitis with myositis localized to the iliopsoas and gluteal muscles**

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Conflict of interest: None

A 73-year-old woman diagnosed systemic scleroderma and Sjögren's syndrome (SjS) and followed without therapy presented fever, loss of appetite and weight and weakness of lower limb muscles occurred. In the manual muscle test, muscular strength of only iliopsoas and gluteus medius muscles decreased to scale 3. MRI scan revealed myositis in the bilateral iliopsoas and gluteus muscles, but CK and aldolase within reference values lowered the possibility of polymyositis and secondary myositis with SjS. The systemic examinations found no malignancy in the whole body. The systemic symptoms such as loss of appetite and weight with high level of CRP suggested vasculitis or sarcoidosis. Muscle biopsy of the right gluteus medius muscles is performed, and pathological examination found neutrophilic infiltration and fibrinoid necrosis in the small to medium-sized blood vessels and a lack of lymphocytic infiltration into the

muscle. In addition to increase of MPO-ANCA, the examination showed ANCA-associated vasculitis (AAV) with localized myositis in the iliopsoas and gluteus muscles, not polymyositis and secondary myositis with SjS. After diagnosis, high dose prednisolone successfully controlled AAV. Here we reported a rare case of AAV with myositis localized to the iliopsoas and gluteal muscles.

## P46-8

### Eosinophilic granulomatosis with polyangiitis with asymptomatic cholecystitis: 2 case reports

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Conflict of interest: None

<Introduction> EGPA is one of the small and medium-sized vasculitis that can cause multi-organ damages, but is rarely associated with cholecystitis. We report two cases of EGPA with asymptomatic cholecystitis. <Case 1> A 50-year-old woman. She had bronchial asthma, eosinophilia, mononeuritis, and purpura. The pathology of the purpura showed EGPA vasculitis. Asymptomatic cholecystitis was noted on admission and was surgically removed. The gallbladder pathology also showed findings of EGPA. <Case 2> 37-year-old man. EGPA was suspected based on the presence of sinusitis since 5 years ago, pneumonitis, purpura, arthritis, cardiomyopathy, and eosinophilia. Asymptomatic cholecystitis was present on admission. ANCA was negative. The pathological findings of purpura were not suggestive of EGPA, but the surgically removed cholecystitis showed EGPA vasculitis. [Consideration] In our study, most EGPA cholecystitis cases were ANCA-negative. The pathological findings in the two cases were different from the general impression of cholecystitis in that the microscopic findings showed vasculitis, while the macroscopic findings were mainly edema with no obvious abnormalities. This was thought to be one of the reasons why the patients were asymptomatic.

## P46-9

### Repeated gastrointestinal perforation in eosinophilic granulomatosis with polyangiitis: a case report

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Conflict of interest: None

[Background] There are very few cases of gastrointestinal perforation in EGPA, and even fewer cases of repeated perforations. [Case] A 54-year-old woman. At the age of 52, she was diagnosed with asthma and eosinophilia. On X-25, she had a burning sensation in the right ankle and became unable to dorsiflex. On X-7, he lost sensation in his left hand and became unable to dorsiflex his left ankle. On X-1, she visited the Department of Neurology at our hospital due to multiple peripheral neuropathies. On X day, she was admitted to our department for suspicion of EGPA. The eosinophils decreased rapidly after steroid pulse therapy. On the 15th day of admission, she has strong abdominal pain, and emergency surgery for gastrointestinal perforation. After surgery, she was treated with intravenous cyclophosphamide for inadequate therapeutic effect. On the 40th day, she developed peritoneal irritation, and she was reoperated for gastrointestinal perforation. Although the small intestine was extensively resected, the postoperative course was good, and she was discharged on the 138th day. [Conclusion] The cause of gastrointestinal perforation in EGPA is ischemia due to vasculitis. It has been reported that vascular damage caused by vasculitis is irreversible and should be treated early.

## P46-10

### A case of refractory adult-onset IgA vasculitis whose abdominal symptoms were benefited from plasma exchange

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Conflict of interest: None

[Case] A 65-year-old woman was admitted to the hospital for abdominal pain with rebound tenderness and palpable purpura on her legs. Endoscopy found ulcers in the duodenum and the terminal ileum. Duodenal biopsy revealed inflammatory cell infiltration in the submucosa and fibrin deposition in the walls of small vessels, suggesting vasculitis. Renal biopsy showed evidence of cellular crescentic glomerulonephritis with IgA deposition. We diagnosed with IgA vasculitis and started PSL 0.8 mg/kg, but abdominal pain persisted. She was additionally treated with factor XIII replacement, steroid pulse, PSL 1 mg/kg, and cyclophosphamide pulse (IVCY) therapies, but abdominal pain and purpura were exacerbated, and plasma exchange (PE) was started. Immediately, abdominal pain and purpura disappeared. [Discussion] According to an analysis of 260 patients in a French multicenter study, abdominal symptoms were observed in 53% of patients, and corticosteroids were effective for abdominal symptoms with acute abdomen, and IVCY was used in 22% of patients, but there were no descriptions about PE. Several case reports showed usefulness of PE for the treatment of acute glomerulonephritis, but not for abdominal symptoms as far as we have searched. So, our case seems valuable for reporting.

## P46-11

### A case of microscopic polyangiitis with a large vascular lesion

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Hyogo College of Medicine College Hospital

Conflict of interest: None

[Case] 70-year-old male The patient had a cough and visited the hospital. He was admitted to our hospital on suspicion of Takayasu arteritis (TAK) because of thickening of the wall of aorta in CT. The patient had fever and periaortitis on contrast-enhanced CT, so TAK was suspected at first. However, P-ANCA was positive, so ANCA-related vasculitis was differentiated. Urine protein and occult blood were found, and a renal biopsy was performed, resulting in the diagnosis of microscopic polyangiitis (MPA). After steroid pulse, the general condition improved and CT showed improvement in aortic wall thickening. The patient was started on methotrexate 6 mg/week along with a reduction in prednisolone dose and was discharged. [Discussion] There are rare cases of large vascular lesions in granulomatosis with polyangiitis and MPA. Among these, there have been cases of aortic dissection and aortic regurgitation that progressed to a fatal condition. In this case, the large vessel lesion improved with appropriate diagnosis and treatment. However, in cases of large vessel lesions, delay in diagnosis may affect the prognosis of life, and it is necessary to keep in mind the evaluation of large vessels as well as small vessels.

## P46-12

### A case of MPO-ANCA-positive renal disorder with eosinophilia showing eosinophilic infiltration in the interstitium

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Conflict of interest: None

[Case] A 69-year-old man. He revealed fever and arthralgia without past history of asthma and sinusitis. Eosinophil count was 1320 / $\mu$ L, CRP 16.6 mg /dL, and MPO-ANCA 400 U/mL. Proteinuria and hematuria were recognized and interstitial pneumonia on chest CT scan. Necrotizing arteritis and granulomas with eosinophilic infiltration were found in the cortical interlobular arteries. A diagnosis of ANCA-related vasculitis was made, and high-dose steroid and intravenous cyclophosphamide treatment resulted in a decreased MPO-ANCA titer and clinical remission. [Discussion] Eosinophilic granuloma with polyangiitis (EGPA) was strongly suspected in this case, but the present case did not meet ACR criteria (1990), Lanham criteria (1984), or Ministry of Health, Labor and Welfare criteria (1988). While necrotic pauci-immune glomerulonephritis is frequently observed in EGPA, eosinophil infiltration in the interstitium is characteristic

(Durel CA, et al. Rheumatology, 2021). Because the latter finding was observed, this case was considered to be EGPA nephritis without allergic disorder such as asthma.

### P46-13

#### **A case of rapidly progressive glomerulonephritis due to ANCA-related vasculitis complicated with Sjögren's syndrome**

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General Internal Medicine and Rheumatology, Gifu Municipal Hospital

Conflict of interest: None

[Case] A 58-year-old female was diagnosed as Sjögren's syndrome before 3 years, and right lung nodule was pointed out by chest CT scanning before 2 years. Urine occult blood appeared before 1 year and then dry eyes and mouths, general fatigue, limb numbness worsened in Jan 2021. Moreover, progressive decline in renal function were observed in May 2021, and introduced to our hospital in June 2021. Laboratory findings showed urine occult blood (3+), urine protein (3+), 37.4 mg/dl BUN, 2.42 mg/dl Cr. Anti-Ro/SS-A antibodies and anti-La/SS-B antibodies were markedly elevated at 16400 U/mL and 12500 U/mL respectively, and MPO-ANCA was elevated at 7.1 U/mL. Chest CT scanning showed multiple nodules which were thought to be due to Sjögren's syndrome and ANCA-related vasculitis (AVS). The patient was started on steroid pulse therapy followed by oral prednisone (45 mg/day) and then intravenous cyclophosphamide therapy (500 mg/day) was enforced. Subsequently, subjective symptoms and CT imaging improved. Renal biopsy and lip biopsy indicated interstitial nephritis and extensive crescent formation, and lymphocytic infiltration, respectively. [Discussion] We experienced a case of rapidly progressive glomerulonephritis due to AVS complicated with Sjögren's syndrome.

### P46-14

#### **A case of microscopic polyangiitis with predominantly interstitial infiltration in renal pathology**

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Conflict of interest: None

[Case] 80-year-old woman had noticed stiffness and abnormal sensation on her toes 3 months before admission. The next month, she underwent brain CT scan for headache, but there were no abnormalities. Two weeks later, she had fever and difficulty in moving, and was brought to the hospital. A full-body CT scan not revealing the source of fever, she was treated with piperacillin as Pyelonephritis. The fever persisted after treatment. Elevation of MPO-ANCA (5.6 IU/ml) being detected, she was referred and was admitted to our hospital. Since there was renal dysfunction (sCr 1.03 mg/L) in addition to neurological symptoms and MPO-ANCA positivity, microscopic polyangiitis (MPA) was suspected. Nerve conduction study showed axonal damage in her peroneal nerve. Although the main histopathological finding of the biopsied kidney was interstitial infiltration, an unusual finding in MPA, existence of pauci-immune type and fibrin deposit in a single glomerulus led to diagnosis of MPA. She was treated with prednisolone 40 mg/day and rituximab 500 mg/body and showed good progress in both symptoms and renal function. [Discussion] This case implicates that peritubular capillaritis, one of the reported mechanisms of renal interstitial inflammation in MPA may occur independently of glomerular lesions.

### P46-15

#### **A Rare Concurrence of Eosinophilic Granulomatosis with Polyangiitis and Pancreatic Cancer**

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Conflict of interest: None

We presented the case of a 70-years woman, diagnosed as eosinophilic granulomatosis with polyangiitis (EGPA) from post-operative pathological findings of laparoscopic pancreatectomy. She was referred to our hospital because of eosinophilia and pancreatic cancer. The cause of eosinophilia was initially diagnosed as pancreatic cancer, but after the surgery eosinophils remained high. Pathological findings of resected specimen showed adenocarcinoma, accompanied by leukoclastic vasculitis with eosinophilic infiltration. Treatment of high-dose corticosteroid promptly decreased eosinophils and improved the abdominal pain. Due to concerns of infectious risk and immunological influence under cancer, we rapidly tapered corticosteroid without any steroid-spring agents. Clinical Significance: Coexistence of EGPA and pancreatic cancer is rarely reported, and the treatment of AAV accompanied with malignancy is still controversial. We conducted literature review on cancer-associated AAV to seek a better approach.

### P46-16

#### **A Case of Eosinophilic Granulomatosis with Polyangiitis (EGPA) with acute onset of finger apex ulceration and polyneuritis**

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Conflict of interest: None

[Case] An 85-year-old woman. [Clinical history] Suddenly, She had bilateral drooping feet. She was treated for a Lacunar Infarction for 2 weeks. When the patient was transferred to our hospital on June 16 (the 1st day), She had bilateral numbness in hands and feet, bilateral finger apex ulceration, decreased tibialis anterior MMT, and increased eosinophils (892 / $\mu$ L) in peripheral blood. A nerve conduction velocity test showed polyneuritis. The nerve biopsy showed axonal degenerative neuropathy and perivascular eosinophilic infiltration, and we diagnosed her with EGPA. We started high-dose intravenous immunoglobulin (IVIG) therapy and prednisolone (PSL) 50 mg/day. The finger ulceration and the tibialis anterior MMT improved. On the 21st day, we started mepolizumab 300 mg/day. [Consideration] Because of the acute onset of symptoms, it was difficult to distinguish from other diseases. A nerve biopsy led to a definitive diagnosis. [Conclusion] We succeed to treatment to use of IVIG, PSL and Mepolizumab. Early diagnosis and treatment are important for neurological prognosis.

### P46-17

#### **A case of microscopic polyangiitis following pleuroparenchymal fibroelastosis**

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Conflict of interest: None

A 59-year-old woman complained of lower leg pain and dyspnea on exertion was referred to our hospital. She had an abnormal shadow predominantly located in the upper lobes on chest radiography for 15 years and was diagnosed as pleuroparenchymal fibroelastosis (PPFE) four years ago. She presented edema in the lower limbs one month before admission. A few days before admission, she felt difficulty of walking and became febrile. Laboratory findings showed abnormal urinalysis, elevated CRP and positive myeloperoxidase antineutrophil cytoplasmic antibodies. In addition to these findings, she had purpura in her lower legs, renal dysfunction, mononeuritis multiplex on admission. She was diagnosed as microscopic polyangiitis (MPA) and initially treated with methylprednisolone pulse in combination with rituximab. Her MPA was refractory, thus additional methyl-prednisolone pulse was needed. PPFE was not improved by immunosuppressive therapy, and she was complicated with pneumonia due to infection on treatment. PPFE is a rare subtype of idiopathic interstitial pneumonias. For the best of our knowledge, there has been never reported that PPFE precedes the occurrence of MPA. This case suggested



that MPA with PPFE have high risk for respiratory infection.

## P46-18

### **A case of refractory EGPA that was difficult to treat both bronchial asthma and vasculitis**

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Conflict of interest: None

A 60-year-old man presented with bronchial asthma, eosinophilia, renal dysfunction and diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) fifteen years ago. A remission was achieved using prednisolone and he initiated on azathioprine and mepolizumab as a maintenance agent. However, asthma attacks have been repeated with tapering prednisolone, and Mepolizumab was changed to Dupilumab. The symptoms of fever, headache, and right ear pain appeared a week before administration. A blood analysis showed elevated CRP and chest CT showed multiple nodular shadows so the patient was admitted to the hospital. EGPA was considered to be relapsed based on the findings of pulmonary nodule shadow and right granulomatous otitis media. The patient was administered intravenous methylprednisolone (pulse therapy), followed by PSL 60 mg/day. These therapy resulted in prompt alleviation of the symptoms and multiple nodular shadows gradually disappeared by CT scan. When the PSL was reduced to PSL 50 mg/day, the asthma attack recurred at night. Dupilumab was considered to be refractory, and mepolizumab was resumed instead of dupilumab. After that, the patient remains in good condition. We discuss those biological effects on EGPA along with a literature review.

## P46-19

### **Long term remission of microscopic polyangiitis (MPA) successfully treated with single dose of rituximab (RTX)**

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Suita Municipal Hospital

Conflict of interest: None

[Case] A 83-year-old man was referred to our department because of fever, hypoxemia, high CRP levels, purpura of both lower limbs and renal failure (day 0). He was diagnosed with MPA because of rapidly progressive glomerulonephritis, interstitial pneumonia and MPO-ANCA positivity. 55 mg of PSL was started on day 6 with single administration of 600 mg of RTX on day 8, resulting in prompt resolution of his symptoms and normalization of CRP. Because of intraperitoneal bleeding on day 11, revealing a beaded aneurysm in the right gastropiploic artery, embolization procedure was performed. Because MPA was under control, B cells being sufficiently low (CD19 0.4%), and because avoiding hematoma infection and opportunistic CMV infection flare, further administration of RTX was not done. Nevertheless, PSL was successfully reduced to 5 mg, while maintaining remission. Until now (day 500), the effect of RTX is persistent (CD19 0.4%), and the remission is maintained. [Clinical significance] This is a valuable case, which shows a single dose of RTX can maintain remission of MPA, avoiding the risk of infection and financial problems.

## P46-20

### **A case of Posterior reversible encephalopathy syndrome and cerebral hemorrhage after initiation of treatment for ANCA-related vasculitis**

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Conflict of interest: None

An 81-year-old woman was diagnosed with Microscopic polyangiitis (MPA) due to interstitial lung disease, purpura in both lower extremities, mononeuritis multiplex, and high MPO-ANCA levels. Treatment initiated with prednisolone from the 7th day. From the 12nd day, she suddenly developed headaches, general pain, cold sweat and hypertension. She had

consciousness disturbance and tonic-clonic seizures on the 14th day. Brain MRI T2 FLAIR showed hyperintensity area in deep white matter of bilateral occipital lobes, a diagnosis of Posterior reversible encephalopathy syndrome (PRES) was made. Antihypertensive therapy, methylprednisolone pulse therapy and intravenous pulse cyclophosphamide therapy were initiated, and her level of consciousness and imaging findings improved dramatically. However, her level of consciousness worsened from the 22nd day, and brain MRI showed bleeding in the right frontal lobe, and she died on the 24th day. Most of the onset of PRES in AAV (Anca-related vasculitis) is under immunosuppressive treatment including steroids, so we should pay attention to hypertension during the treatment. In addition, antihypertensive therapy and treatment for AAV were considered effective for the treatment of PRES in AAV.

## P46-21

### **Study of two cases of microscopic polyangiitis with rapidly progressive glomerulonephritis, having relevant with SARS-CoV-2 mRNA vaccine**

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Conflict of interest: None

[Clinical significance] We experienced two cases of microscopic polyangiitis (MPA) with rapidly progressive glomerulonephritis (RPGN), and successful remission induction, using different treatment (intravenous cyclophosphamide (IVCY), rituximab (RTX), plasma exchange (PE)). Two cases were developed after taking SARS-CoV-2 mRNA vaccine, suggested that the vaccination was associated with the development of MPA. [Cases] Case 1 was 65 years old man. He took vaccine on 16 th July and 6 th August, X. He was diagnosed with MPA due to RPGN (the level of creatinine was 7.0 mg/dl on admission, and the crescentic glomerulonephritis with pauci-immune type was detected in kidney biopsy), and high titers of MPO-ANCA (183 IU/ml). We treated with methylprednisolone pulse therapy, followed by 60 mg/day of prednisolone (PSL). However, the level of creatinine got worse (9.0 mg/dl), so we added PE and RTX. Case 2 was 68 years old man. He took vaccine on 23 rd June and 14 th July, X. He was diagnosed with MPA due to RPGN (the level of creatinine was 2.0 mg/dl on admission), interstitial pneumonia, multiple mononeuropathy, episcleritis and high titers of MPO-ANCA (90.9 U/ml). We treated with methylprednisolone pulse therapy, followed by 60 mg/day of PSL and IVCY.

## P46-22

### **Jaw claudication as the presenting symptom of eosinophilic granulomatosis with polyangiitis**

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Conflict of interest: None

Introduction: Jaw claudication (JC) is common symptom of the patients with temporal arthritis, which caused by ischemia of the masticatory muscles. Casa: 76 year-old Japanese woman with adult-onset asthma presented with JC, facial swelling and bilateral leg edema 2 months before. She also developed fever and paraneesthesia in her hands and right leg for 10 days. Physical examination revealed a slight fever, edema with sensory dullness of her right lower limb, and muscle weakness in right lower extremity. Laboratory data showed markedly eosinophilia (34,320/ $\mu$ L) with negative anti-neutrophil cytoplasmic antibodies. Electrophysiology was compatible with multiple mononeuropathies. Temporal artery biopsy revealed eosinophilic small vessel vasculitis surrounding an uninfamed temporal artery. We diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) and treatment with prednisone improved fever, JC and muscle weakness. Conclusion: Although JC is atypical symptom of EGPA, we should keep in mind that small vessel vasculitis also causes JC.

## P46-23

### A case of temporal arteritis complicated with eosinophilic granulomatosis with polyangiitis (EGPA)

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Conflict of interest: None

A 66-year-old man had a childhood history of asthma. He had cough and wheeze when the seasons change from several years ago. In 2014, he was diagnosed with bronchial asthma at nearby clinics. He was treated with inhalant and prednisolone at 10 mg/day. But he was referred to respiratory medicine in our hospital, because of his symptom was not improved. The laboratory findings showed that the eosinophil (2195/ $\mu$ L) were increased. He was suspected EGPA by clinical presentation, but anti-neutrophil cytoplasmic antibody (ANCA) was negative. In 2016, he was diagnosed with chronic sinusitis because of nasal obstruction and olfactory disturbance. In December 2020, he was referred to our rheumatology in chief complaint of head swelling from bilateral front to temporal. Eosinophilia (8000/ $\mu$ L) were worsened, but ANCA was negative. The vascular ultrasound imaging revealed wall thickening and halo sign of temporal artery. We considered temporal arteritis and performed the biopsy. The histopathological findings revealed eosinophilic infiltration in the blood vessel wall. Further he had interstitial pneumonia and mononeuritis multiplex and we diagnosed with EGPA. Temporal arteritis with eosinophilic infiltration associated with EGPA is rare. We herein describe a case with reference to the literature.

## P46-24

### A case of microscopic polyangiitis presenting with various organ involvement due to rapidly progressing vasculitis

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Conflict of interest: None

[Case] A 78-year-old man had fever and jaw pain since one month of hospitalization. The MPO-ANCA level was elevated to 55.4 IU/mL, but since there was no obvious organ damage, he was followed up, and the pain gradually spread to the whole body. The patient was admitted to our hospital as an emergency at night due to pain, and was considered to have a mild case of microscopic polyangiitis. Prednisolone 35 mg was started on the second day. On the same day at night, he suddenly had a seizure, and his level of consciousness did not improve even after seizure stopped. The level of creatinine kinase was further elevated, and the patient was started on steroid pulse therapy. On the third day, he presented with acute kidney injury, hyperkalemia, and lactic acidosis, and continuous hemodialysis (CHDF) was started. Contrast-enhanced computed tomography showed decreased contrast efficacy in the intestinal wall, suggesting non-occlusive intestinal ischemia (NOMI). His general condition was judged to be inadequate for surgery. CHDF was continued, but he died on the fourth day. The pathological autopsy revealed fibrinoid necrotizing vasculitis in various organs including the small vessels in the intestine and the muscle, which was thought to be the cause of myalgia and NOMI.

## P46-25

### An autopsy case of ANCA-negative vasculitis with elevated anti-SSA/Ro antibody showing diffuse alveolar damage

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Conflict of interest: None

[Case] A 67-year-old Japanese man was admitted to previous hospital for fever, dyspnea and wheezing. Computed tomography showed cardiomegaly, bilateral pleural effusion and lung fibrosis. He was hospitalized

for the treatment of severe intestinal pneumonia. He was suspected of Sjogren's syndrome (SjS) because anti-SSA/Ro antibody was positive. In contrast, MPO-ANCA and PR3-ANCA were negative. He was initially treated with high dose prednisolone, but intestinal pneumonia exacerbated. He transferred to our hospital. On day 15, he was suspected of hemophagocytic syndrome or thrombotic thrombocytopenic purpura because of pancytopenia, LDH elevation, haptoglobin decline, and renal dysfunction. He was treated with plasmapheresis. On day 20, he had bleeding from rectum ulcer. Despite of intensive care, he died of multiple organ failure on day 28. An autopsy revealed alveolar bleeding, microvasculitis from skin dermis and rectum ulcer. These findings indicated the possibility of systemic vasculitis, not SjS. [Discussion] In this case, anti-SSA/Ro antibody which binds epitope PEP08 were positive. This antibody can be related with morbidity and severity of intestinal pneumonia in connective tissue disease. Further accumulation of such cases is needed.

## P46-26

### Association between novel coronavirus infection (COVID-19) and relapse of Granulomatosis with polyangiitis (GPA): a case report

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Conflict of interest: None

[Case] A 60-year-old Japanese man came to our hospital 8 years ago with left ear pain, skin rash, and fever, and was diagnosed with Granulomatosis with polyangiitis (GPA) based on the results of cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) 63.4 U/ml and skin biopsy. He was treated with oral prednisolone (PSL) 40 mg/day and intravenous cyclophosphamide for remission induction therapy. Since then, the patient has been in remission with 2.5 mg of PSL every other day for 4 years. This time, the patient presented with left ear pain and fever. The antigen and PCR of SARS-CoV-2 were positive. There was an elevation of C-ANCA to 14.8 U/ml. Therefore, the GPA was considered to have relapsed due to COVID-19. Methylprednisolone 500 mg was administered intravenously for 3 days starting on the 8th hospital day. Thereafter, the ear pain improved considerably and PSL 40 mg/day was continued. [Discussion] This is a case of GPA relapse caused by SARS-CoV-2 infection. It has been shown that COVID-19 may be involved in the development and exacerbation of autoimmune diseases. Similarly, there have been several reports of relapse of ANCA-associated vasculitis caused by COVID-19. We report a case of GPA relapse caused by COVID-19.

## P46-27

### A rare case of anti-GBM disease complicated with thrombotic microangiopathy

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Aino Hospital

Conflict of interest: None

A 67-year-old male was admitted to previous hospital for high fever, lower leg edema and decreased urine output in March X-1. Acute renal dysfunction, urinary occult blood, and protein were observed, and rapidly progressive glomerulonephritis was suspected. PR3-ANCA and anti-GBM antibody in his serum were found to be positive. There were no obvious granulomatous lesions, and he was diagnosed with anti-GBM disease. He was treated with prednisolone and plasma exchange. Hemodialysis could be avoided, but renal dysfunction remained. He was admitted to our hospital in July of the same year for the purpose of continuous treatment and rehabilitation. Consciousness was observed from the beginning of August, and blood tests showed decreased thrombocytopenia, decreased hemoglobin, increased LDH, decreased haptoglobin, worsening BUN / Cr, crushed red blood cells, etc. He was diagnosed with thrombotic microangiopathy (TMA). ADAMTS13 activity or anti-ADAMTS13 antibody were not observed. He was treated with steroid pulse therapy and PE. And, TMA was improved. TMA in association with anti-GBM antibody disease is rare, and we report this case with some literature review.

## P46-28

### A case of granulomatosis with polyangiitis associated with ulcerative colitis with persistent ANCA positivity after treatment

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Conflict of interest: None

The patient was a 56-year-old man with ulcerative colitis (UC). He was aware of a headache for half a month and developed fever. Blood test showed a high level of PR3-ANCA and he was referred to our hospital on suspicion of granulomatosis with polyangiitis (GPA). Blood tests showed a high CRP level. CT showed sinusitis, and MRI showed diffuse dural thickening with contrast enhancement. We diagnosed GPA. High-dose prednisolone (PSL) was introduced on the third day, and headache and inflammatory response improved. On the 11th day, the patient had a fever, re-elevation of the inflammatory response, and increase the frequency of diarrhea, so rituximab was introduced on the 12th day. Lower gastrointestinal endoscopy showed active UC, and symptoms improved as the UC achieved remission. Although PR3-ANCA elevated 1 month after hospitalization and remained positive, the PSL was reduced to 3 mg/day without recurrence of GPA. It was reported that PR3-ANCA may be positive in UC, and correlated with UC activity. The activity of UC after treatment, and the elevation of PR3-ANCA after treatment were suspected that PR3-ANCA related to UC in this case. GPA associated with UC is uncommon, and we discuss an association of UC with PR3-ANCA and ANCA-related vasculitis based on previous reports.

## P46-29

### A case of microscopic polyangiitis associated with retrobulbar neuritis

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Conflict of interest: None

[Case] Retrobulbar neuritis in microscopic polyangiitis (MPA) is a rare complication. We present a case of MPA complicated with retrobulbar neuritis due to hypertrophic pachymeningitis. The patient was a 76-year-old woman who was diagnosed as MPA with myeloperoxidase-antineutrophil cytoplasmic antibodies positivity and rapidly progressive glomerulonephritis. She felt blurry vision in the left 4 months after induction therapy as methylprednisolone pulse therapy and cyclophosphamide. Since her ophthalmoscopy was normal, a retrobulbar neuritis which was associated with MPA was suspected. Based on the findings of pachymeningitis thickening and high intensity area in left optic nerve on MRI, she was diagnosed as retrobulbar neuritis due to hypertrophic pachymeningitis. We treated with 50 mg of prednisolone with 1000 mg of daily i.v. methylprednisolone pulse therapy for three consecutive days, and Rituximab. Although her left blurry vision was not improved, it was not exacerbated after second induction therapy. [Clinical Significance] Physicians should consider the possibility of retrobulbar neuritis in patients with MPA complaining of eye symptoms.

## P46-30

### A case of eosinophilic granulomatosis with polyangiitis developed aortic lesion

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Conflict of interest: None

Case: A 70-year-old man who had a history of asthma presented with fever, weight loss, numbness of limbs, eruption 6 years ago. Physical findings revealed livedo reticularis of lower extremity and facial nerve palsy.

Laboratory findings showed elevated CRP level, renal dysfunction, eosinophilia and positive MPO-ANCA. NCV indicated mononeuritis multiplex finding. Skin biopsy revealed eosinophil infiltration around small artery. Renal biopsy demonstrated destruction of Bowman's capsule basement membrane by granuloma and crescentic glomerulonephritis. These findings suggested the diagnosis with eosinophilic granulomatosis with polyangiitis (EGPA). Multimodal therapy with PSL, IVCY and RTX ameliorated the clinical and laboratory findings. Since the last 1 year, he developed myalgia and re-elevation of MPO-ANCA, and then, CT showed abdominal aortitis finding. Increased PSL dose and RTX dramatically improved aortitis finding. Conclusion: ANCA-associated vasculitis has been rarely reported to cause vasa vasorumitis like aortitis on imaging, and therefore our case is thought to be developed by similar mechanism. We herein report EGPA associated with aortic lesion with previous literature review.

## P46-31

### Eosinophilic Sinusitis followed to Eosinophilic Granulomatous with Polyangiitis, with Eosinophilic Myocarditis

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Conflict of interest: Yes

Clinical significance: It is important to differentiate EGPA in heart failure cases with characteristic symptoms, history, and eosinophilia. Case report: A 57-year-old male with histories of depression and eosinophilic sinusitis (ES) was referred to the department of cardiology in our hospital for an abnormal ECG. He had 1 year history of difficulty swallowing, body weight lost 15 kg/3-year, 4-month history of papules, 2-month history of dyspnea consulting an otorhinolaryngology made him diagnosed with ES and treated with PSL, then occurring his steroid-psychosis (SP). On admission, his laboratory data showed high inflammation, elevated CK, troponin I, and his eosinophil (9860 / $\mu$ L) levels and his diffuse hypomotility on UCG. Therefore, he was admitted in CCU. CAG was normal. The finding of eosinophil infiltration into the myocardium made a pathological diagnosis of EM. We diagnosed EGPA. He was started PSL 0.5 mg/kg/day since day 8; however, his complaints were not decreased. Thereafter, PSL was up to 1.2 mg/kg/day on day 12, and added 6-time IVCY/2 week from day 17. He was discharged on day 30. he had been tapering taking PSL and was started mepolizumab/4 week for sparing the dose of PSL, further. Now, his cardiovascular condition has been stable.

## P46-32

### A case report of polyangiitis overlap syndrome: eosinophilic granulomatosis with polyangiitis (EGPA) and granulomatosis with polyangiitis (GPA)

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Conflict of interest: None

[Case] A 63-year-old man. [Chief complaint] Joint pain. [Present illness] He presented with acute pericarditis in July X. Acute pericarditis was improved, but eosinophilia was persisted. In August X, he reported multiple joint pain and purpura on lower legs. His medical history was allergic rhinitis. Laboratory tests revealed eosinophilia, elevated CRP, positive for PR3-ANCA. A skin biopsy of purpura showed EGPA. After treatment with mPSL, eosinophil count and CRP decreased and symptoms were diminished. However, Cr was elevated. Renal biopsy showed GPA like lesion. Moreover, a granulomatous mass in the nasal cavity and a mass-like lesion on the pleural surface were detected. Then he diagnosed with polyangiitis overlap syndrome of EGPA and GPA. After steroid pulse therapy, the dosage of mPSL was increased and MMF were started. Consequently, renal function was improved. [Clinical significance] The treatment and prognosis



sis are different for EGPA and GPA. It is important to identify the type of vasculitis. However, there are very few case reports of polyangiitis overlap syndrome. Some report showed that most of polyangiitis overlap syndrome were positive for PR3-ANCA. When we diagnose PR3-ANCA-positive EGPA, it is important to keep in mind that GPA may overlap.

### P46-33

#### **A case of panniculitis as the first clinical manifestation of microscopic polyangiitis**

Chihiro Saiki<sup>1</sup>, Naoyasu Ueda<sup>1</sup>, Sanshiro Inoue<sup>2</sup>, Genichi Tanaka<sup>1</sup>, Koichi Mashiba<sup>1</sup>

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Conflict of interest: None

A 70-year-old woman was admitted to our hospital with persisting fever and firm skin on the right gluteal area. She presented with a double-palm-sized subcutaneous induration accompanied by mild tenderness and warmth, but no skin erythema. The histological diagnosis was lobular panniculitis. Many IgG4-positive plasma cells were observed, but with elevated inflammatory markers, her clinical features did not correspond with IgG4-related disease (IgG4RD). The serum titer of MPO-ANCA was high. She presented with proteinuria and hematuria along with progressive renal dysfunction, and crescentic glomerulonephritis was proven on renal biopsy. She was diagnosed as microscopic polyangiitis, and was treated with prednisolone and rituximab. The subcutaneous induration disappeared. It is reported that 35% of ANCA-associated vasculitis (AAV) patients have cutaneous manifestation. To our knowledge, only 10 cases of panniculitis have been reported. In this case, no evidence of small vessel vasculitis was observed on skin biopsy, which suggested that panniculitis did not result from regional vasculitis but occurred secondary to systemic inflammation. Histological findings in AAV cases can sometimes resemble those of IgG4RD, and differential diagnosis should be made based on clinical features.

### P46-34

#### **Microscopic polyangiitis occurred as a complication in a patient with ulcerative colitis treated with Risankizumab**

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Conflict of interest: None

[Clinical significance] We experienced a case of microscopic polyangiitis (MPA) in a patient with ulcerative colitis (UC) after treated with Risankizumab (RIS). It was very important case suggesting which Risankizumab producing MPA or just being overlapped. [Case report] A 49-year-old female. She has 9 year-history of UC. Two years ago, she was treated with Golimumab (GLM); however, at the 7 months, there was no efficacy of GLM. Then, azathioprine (AZA) was started; however, the hepatic failure was occurred as a complications of AZA. Thereafter, she participated in the 3<sup>rd</sup> phase clinical trial for RIS against the patients with middle or sever active cases of UC. The 8 months late, erythema multiform and arthralgia which was thought as an extra-intestinal lesions was occurred and the trial was continued. The intestinal lesions were improved though the erythema multiform and arthralgia were stayed. Thus, the trial was validated, and she was referred to our hospital. The laboratory data detected elevated serum level of MPO-ANCA, and the skin biopsy was shown fibrinoid necrotizing vasculitis. Thus, we diagnosed that she had a MPA. We selected PSL and cyclosporine A therapy because she was a patient with UC which made her compliances improve.

### P46-35

#### **An atypical case of eosinophilic granulomatosis with polyangiitis presenting as multiple mass lesions of liver**

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Conflict of interest: Yes

Case: A 63-year-old female with no history of allergy. She had undergone surgery for cervical cancer (stage IIB) three years ago, followed by radiation chemotherapy. A contrast-enhanced CT scan for follow-up revealed multiple hepatic masses. PET-CT showed four localized intrahepatic accumulations and no other findings suggestive of recurrence. Liver biopsy showed eosinophilic infiltration, deposition of eosinophilic granular components, obstruction of vessels with eosinophilic infiltration, and coagulative necrosis of hepatocytes. 3 months later, contrast-enhanced CT showed an enlarged multiple hepatic masses, and the patient was referred to our department. She showed no vasculitis symptoms. Laboratory examinations revealed an elevated eosinophilic count (1430/ $\mu$ l) and IgE (9820 IU/ml), but both PR3-ANCA and MPO-ANCA were negative. After re-liver biopsy from a different mass, we clinically made a diagnosis of eosinophilic granulomatosis with polyangiitis. Since starting Prednisolone (50 mg/day), eosinophil count, ESR, and CRP quickly improved negatively, and the liver mass was continuously reducing. Discussion: It is difficult to differentiate ANCA-negative EGPA from hypereosinophilic syndrome. We report our experience with a borderline case.

### P46-36

#### **A case of remission induction therapy with rituximab for granulomatosis with polyangiitis relapsing with hypertrophic pachymeningitis and cavitary lung lesions**

Tomoko Sano, Eisuke Takamasu, Nanae Okimoto, Eisuke Kanematsu, Daisuke Asatori, Kazusa Saegusa, Naoki Tanomogi, Masahiro Iida, Yoshitaka Ueda, Kae Onishi, Takayasu Kise, Masako Utsunomiya, Yuji Miyoshi, Naoto Yokogawa, Kota Shimada

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

[Case] A 57-year-old man presented with otitis media and sinusitis in February. PR3-ANCA was positive, pathology of the middle ear showed granulomatous lesions, and the diagnosis of granulomatosis with polyangiitis (GPA) was made, and the patient was treated with prednisolone 60 mg (1 mg/kg). From early May, left facial nerve palsy, hoarseness, and dysphagia appeared. Contrast-enhanced MRI scan showed dural thickening of the bilateral middle cranial fossa, and CT scan showed two cavitary pulmonary lesions in the left upper lobe. Tissue culture was negative for antimicrobial and fungal organisms. A transbronchial lung biopsy showing granulomas with multinucleated giant cells, we diagnosed thickened dura mater and cavitary pulmonary lesions due to relapsing GPA. The patient was treated with glucocorticoid pulses followed by prednisolone 1 mg/kg for remission induction, and rituximab 375 mg/m<sup>2</sup> was administered once a week for four times, and the dural thickening and lung cavity shadow improved on imaging. [Clinical implication] The effect of rituximab on hypertrophic pachymeningitis in the induction of remission in ANCA-related vasculitis is not established. We report this case as a suggestive example.

### P46-37

#### **A case of microscopic polyangiitis for which the addition of tacrolimus was effective during maintenance therapy**

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Conflict of interest: None

A 67-year-old man visited our department with complaints of bloody sputum and dyspnea. He was admitted to the hospital because of suspected alveolar bleeding on CT. MPO-ANCA was strongly positive on blood test, and we diagnosed microscopic polyangiitis (MPA). We started treatment with PSL 80 mg/day in combination with cyclophosphamide intermittent intravenous therapy (IVCY) after steroid pulse therapy. Treatment was successful and PSL was gradually reduced to 25 mg/day and the patient

was discharged from the hospital. After completing IVCY, azathioprine (AZA) was used as remission maintenance therapy. MPO-ANCA decreased from 290 to 19.4 U/ml, but at the start of AZA, MPO-ANCA increased to 203 U/ml due to gradual decrease in PSL. PSL was increased from 17.5 to 25 mg/day and MPO-ANCA decreased to 76.3 U/ml, but increased to 210 U/ml while PSL was gradually decreased to 17.5 mg/day again. Tacrolimus (TAC) was added because it was difficult to maintain remission by AZA. After the addition of TAC, MPO-ANCA has been steadily declining. We experienced a case of MPA in which MPO-ANCA re-elevated during maintenance therapy with AZA. In this case, MPO-ANCA decreased with the addition of TAC, which was considered to be one of the effective treatment options.

#### P46-38

##### **A case of polyarteritis nodosa diagnosed by liver biopsy after difficulty in treatment**

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Yodogawa Christian Hospital

Conflict of interest: None

76-year-old man came to our hospital in December of X due to fever and dyspnea. Blood test showed high levels of CRP, and simple CT scan showed pericardial effusion, so the patient was admitted to the hospital for further investigation and treatment. A contrast CT scan showed renal infarction. At the same time, liver damage appeared, so liver biopsy was performed considering intravascular lymphoma. The liver biopsy showed fibrinoid necrosis and neutrophil infiltration with nuclear fragments in the hepatic artery, leading to the diagnosis of polyarteritis nodosa. Treatment with cyclophosphamide 500 mg and methylprednisolone 500 mg/day was started. After the start of treatment, liver enzymes and CRP showed rapid improvement, symptoms disappeared, and the patient was in remission. Therefore, prednisolone was gradually decreased, and azathioprine was introduced and gradually increased to 50 mg/day. The patient remained in remission, and was discharged from the hospital in February of X+1. We have experienced a case of polyarteritis nodosa, which was diagnosed by liver biopsy after difficult treatment. There are no specific markers for polyarteritis nodosa in blood tests, and it is difficult to diagnose it in many cases as in this case. We report with a review of the literature.

#### P46-39

##### **ANCA-associated vasculitis recurring with necrotizing scleritis**

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Saku Central Hospital

Conflict of interest: None

(Case) A 72-year-old woman developed dyspnea following fatigue. Based on skin rash and multiple nodular lesions in both lungs on CT with an elevated level of MPO-ANCA (113 IU/ml), she was diagnosed as having ANCA-associated vasculitis (AAV) in a neighboring hospital although biopsy was not performed. After starting oral prednisolone (PSL) at a dose of 60 mg/day following methylprednisolone pulse therapy respiratory symptoms and nodular lesions in lungs improved and decrease in MPO-ANCA (6.8 IU/ml). When PSL was tapered to 14 mg/day, left ocular pain due to necrotizing scleritis developed with worsening of lung lesions and a reincrease in MPO-ANCA (29.1 IU/ml) suggestive of an exacerbation of AAV. An increase in PSL (60 mg/day) following methylprednisolone pulse therapy subsequently with intravenous cyclophosphamide relieved her clinical symptoms. She has been in good general condition with no exacerbation under 17.5 mg/day of PSL with methotrexate. (Discussion) AAV causes a variety of ocular lesions. Scleritis is a common complication of AAV, but a necrotizing type shows poor prognosis in ocular function including a high risk of blindness. Early treatment should actively be considered in AAV patients with ocular pain and/or a decrease in visual acuity suggestive of scleritis.

#### P46-40

##### **A case of microscopic polyangiitis complicated by acute kidney injury due to thrombotic microangiopathy**

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Conflict of interest: None

[Case] 74-year old woman [History of present illness] She developed a fever of 38°C, with elevated CRP and leukocytes. Thereafter, abnormal sensation and muscle weakness in both lower limbs appeared, and she was admitted to our hospital. She was transferred to our hospital for renal biopsy because of oliguria, positive urine protein and occult blood, decreased renal function, and positive MPO-ANCA. [Passage] The diagnosis of microscopic polyangiitis (MPA) was made based on the presence of rapidly progressive glomerulonephritis, polyneuritis, and MPO-ANCA positivity. After steroid pulse therapy, prednisolone 1 mg/kg/day was started. However, progression of anemia and thrombocytopenia and appearance of crushed red blood cells were observed. A renal biopsy revealed acute kidney injury associated with thrombotic microangiopathy (TMA). After the introduction of rituximab and plasma exchange, the inflammatory reaction, thrombocytopenia, and MPO-ANCA tended to improve, and the crushed red blood cells disappeared. After tapering off steroids, she remained without exacerbation. [Objective] TMA may be secondary to autoimmune diseases or malignancies, but it is relatively rare in MPA. We report a case of TMA secondary to MPA diagnosed by renal biopsy.

#### P46-41

##### **A case of ANCA-related vasculitis mimicking IgG4-related disease**

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Conflict of interest: None

A 70-year-old man with vision loss and exophthalmos of the right eye presented to our clinic. Magnetic resonance imaging revealed a mass from the right orbit to the paranasal sinuses. Histological findings of the intra-orbital tumor biopsy specimen showed IgG4-positive plasma cell infiltration (IgG4-positive plasma cell: 80/HPF, IgG4/IgG ratio: 45%), flower sac fibrosis, and neutrophil infiltration on the blood vessel wall, suspecting IgG4-related disease. Laboratory tests revealed the elevated levels of CRP and MPO-ANCA (32 IU/mL). IgG, IgG4, and IgE were 2200 mg/dL, 76.5 mg/dL, and IgE 245.5 IU/mL, respectively. Based on the above findings, he was diagnosed as ANCA associated vasculitis. Treatment with PSL 40 mg/day was initiated and his symptoms improved. The size of intraorbital and paravertebral tumors gradually decreased, and the high intensity lesion of DWI on MRI disappeared rapidly. This is a case of ANCA-related vasculitis with IgG4-positive plasma cell infiltration in the affected organ tissue. In our case, although the histological findings mimic the features of IgG4-related diseases, the elevated MPO-ANCA levels and leukocytoclastic vasculitis were observed. It was difficult to distinguish between ANCA associated vasculitis and IgG4-related diseases.

#### P47-1

##### **Clinical characteristics of patients with granulomatosis with ulcerative colitis**

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Department of Rheumatology, Saga University Hospital

Conflict of interest: None

[Objective] We have experienced two cases of granulomatosis with polyangiitis (GPA) during the course of ulcerative colitis (UC). The aim of this study is to clarify the clinical characteristics of GPA associated with UC by a literature review. [Methods] Thirteen cases of GPA associated with UC, combining 11 cases reported in Japan and 2 cases from our hospital, were included in this study. The clinical features were compared to

those of general Japanese GPA patients. [Results] The mean age at the time of GPA diagnosis was 49.2 years (19–60 years), which was younger than that of general Japanese GPA. There were 9 males and 4 females, which is more common in males than in general GPA. Pulmonary involvement was observed in 8 patients out of 13, while only 2 patients (15%) developed renal disease, which was much less than that of general GPA. Ten patients were PR3-ANCA positive and 1 patient was MPO-ANCA positive. All patients were treated with corticosteroids, 8 patients with cyclophosphamide pulse therapy, and 2 patients with rituximab. [Conclusions] Japanese patients with GPA and UC were characterized by a higher prevalence of male, younger age at onset, and a lower incidence of renal involvement, compared to those of general GPA.

## P47-2

**The efficacy of mepolizumab (MEP) as as sparing corticosteroid agency in patients with eosinophilic granulomatosis with polyangiitis (EGPA)**  
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Conflict of interest: None

[Objective] The aim of this study is to evaluate the efficacy and the safety of MEP as co-treatment in the standard therapy of EGPA. [Methods] Eleven patients receiving the maintenance therapy of EPGA were enrolled in this study. Dose of prednisolone (PSL), Birmingham vasculitis activity score (BVAS) and blood eosinophil count were examined retrospectively at baseline and 12 months after administration of MEP. [Results] The mean age was 60 years old (n=11), and 91% were female. The mean disease duration was 5.6 years and 27% were relapse cases. The mean dose of PSL was significantly reduced (mean±S.E) (pre-administration of MEP: 5.9±1.0 mg/day, 12 months after administration of MEP: 0.8±0.4 mg/day,  $p<0.001$ , respectively). Furthermore, 64% (n=7) could achieve the cessation of PSL after 12 months. Blood eosinophil count also significantly decreased after 12 months ( $485\pm124/\mu\text{l}$  vs  $29\pm5/\mu\text{l}$ ,  $p<0.01$ ) There was no statistical significant change in BVAS ( $4.7\pm0.9$  vs  $4.1\pm0.8$ ,  $p=0.60$ ). As for adverse event, rheumatoid arthritis (n=1) was revealed. [Conclusions] Our study suggested that co-treatment with MEP on standard EPGA therapy could prevent the flare of EPGA and reduce the dose of PSL with statistical significance among the patients under the maintenance treatment of EPGA.

## P47-3

**The clinical features of otitis media with ANCA-associated vasculitis (OMAAV) treated with steroid monotherapy in our hospital**

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Conflict of interest: None

[Background] The efficacy of treatment with a combination of corticosteroids and immunosuppressant therapy in otitis media with ANCA-associated vasculitis (OMAAV) have been recently reported. However, there are some patients having good hearing prognosis by steroid monotherapy. [Objective] To investigate efficacy of steroid monotherapy against OMAAV in our hospital. [Methods] We retrospectively examined 15 OMAAV patients treated with steroid monotherapy at Ehime University Hospital from 2010 to 2021. [Results] Mean age was 72.8-year-old. The median duration from the onset to the diagnosis was 4 months. MPO- and PR3-ANCA were positive in 11 and 2 cases, respectively. The air-conduction (AC) hearing threshold at diagnosis was 64dB (range 43–111). Lung lesion, renal lesion, and facial palsy were observed in 7, 4 and 2 cases, respectively. All patients were treated with prednisolone (0.63 mg/kg/day), 11 with methylprednisolone pulse therapy. According to the hearing outcome, patients were divided into two groups: good and poor prognosis groups at one year after treatment. The AC hearing level at diagnosis (56 dB) was suggested as an indicator for good prognosis. [Conclusions] This

study suggests that the AC hearing level at diagnosis might be important for steroid monotherapy of OMAAV.

## P47-4

**Treatment and outcome of elderly-onset microscopic polyangiitis in daily clinical practice: a two-center study in Fukushima, Japan**

Shuzo Sato<sup>1</sup>, Makiko Furuya<sup>1</sup>, Kohei Yokose<sup>1</sup>, Shuhei Yoshida<sup>1</sup>, Haruki Matsumoto<sup>1</sup>, Jumpei Temmoku<sup>1</sup>, Yuya Fujita<sup>1</sup>, Naoki Matsuoka<sup>1</sup>, Tomoyuki Asano<sup>1</sup>, Eiji Suzuki<sup>2</sup>, Takashi Kanno<sup>2</sup>, Hiroshi Watanabe<sup>1</sup>, Kiyoshi Migita<sup>1</sup>

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<sup>2</sup>Rheumatology, Ohta-Nishinouchi Hospital

Conflict of interest: None

[Objective] To investigate clinical features, therapy and outcome of newly diagnosed elderly-onset (75 years old or older) microscopic polyangiitis (MPA) compared to younger patients in Fukushima region, Japan. [Methods] We collected newly-diagnosed MPA patients treated in Fukushima Medical University hospital and Ohta-Nishinouchi hospital between 2004 and 2019. We retrospectively investigated the clinical features, immunosuppressive treatments including rituximab (RTX), and outcome (using Kaplan-Meier analysis) in MPA patients, especially in the elderly MPA. [Results] Among 44 MPA patients, 25 patients (56.8%) were male and the mean age of MPA patients were 68.8 years old (range: 52–81). The mean BVAS scores at initial hospitalization were 15.8. Three-year survival rates were 73.8% and elderly-onset MPA patients showed significantly lower 1-year survival rates than younger group (72.2% vs 95.2%, respectively) ( $P=0.03$ ). RTX was administered in 11 MPA patients, and 1-year survival rates were similar compared to conventional therapy group (33 patients). Infection-free survival rates (1-year) were also similar between the 2 groups. [Conclusions] Elderly-onset MPA may be worse survival rates, therefore, immunosuppressive therapy including RTX should be considered in early timing.

## P47-5

**Clinical features and risk factors in patients with eosinophilic granulomatosis with polyangiitis: a retrospective cohort study**

Yuko Shirota<sup>1</sup>, Tomomi Tsutsumi<sup>1</sup>, Yumiko Oka<sup>1</sup>, Tomoki Takeda<sup>1</sup>, Miki Takeshita<sup>1</sup>, Ryo Kuwata<sup>2</sup>, Naruhiko Takasawa<sup>1</sup>, Takao Kodera<sup>1</sup>, Junichi Kameoka<sup>1</sup>

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Conflict of interest: None

[Objective] It is reported that peripheral nerve, respiratory, and skin symptoms are common, and central nervous system involvement is uncommon in EGPA. We investigated the clinical features, and risk factors in EGPA. [Methods] We studied 41 patients who attended our hospital between 2000 and 2021. The ANCA positivity rate was examined for each organ. The association between lifestyle-related diseases and vaccination was also examined. Relative risk (95% confidence interval) was used for analysis. [Results] MPO-ANCA positive, PR3-ANCA positive, both positive, both negative, and unknown were 11, 1, 1, 1, 27, and 1 case, respectively. Peripheral nerve, respiratory, and skin lesions were common (more than 50%), and cerebrovascular, cardiovascular, renal lesions, cerebral neuropathy were found in 22, 15, 6, and 3%, respectively. MPO-ANCA positive cases had significantly more peripheral nerve, renal, and cerebrovascular lesions than negative cases. Lifestyle-related diseases were not a risk factor for cerebrovascular disease. In addition, one patient with prior asthma developed severe mononeuropathy multiplex and nephritis after the COVID-19 vaccination. [Conclusions] Central nervous system involvement is life-threatening and occurs relatively frequently during the active phase of EGPA.

## P47-6

**Clinical benefit of IVR for intra-abdominal arterial bleeding in patients with vasculitis**

Motoko Kanemoto, Misako Uehara, Taro Karahashi



Conflict of interest: None

[Objective] To clarify the clinical courses of intra-abdominal arterial bleeding in patients with collagen disease as well as the indications and effects of IVR for the bleeding. [Methods] We examined the symptoms, lesions, and courses of treatment of 3 patients who underwent IVR in these 5 years due to intra-abdominal arterial bleeding. [Results] Case 1: A 61-year-old man with microscopic polyangiitis MPA. He was taking prednisolone PSL10 mg and azathioprine. He was once taken to the emergency department presenting with sudden hematemesis and vital sign of shock. Therefore, he underwent IVR with massive blood transfusions, which stopped bleeding from a duodenal aneurysm. Case 2: A 50-year-old woman. She was receiving PSL50 mg and tacrolimus for dermatomyositis. CT was performed for abdominal pain and melena, and it revealed active bleeding from the middle colic artery. Hemostasis was performed with IVR. Case 3: A 78-year-old woman. She started taking PSL40 mg for MPA. She underwent CT for abdominal pain, which revealed bleeding from a pseudoaneurysm of the omental artery and underwent IVR. [Conclusions] By identifying indications with radiologists, it is desirable that IVR, which is a less invasive option, will become more widespread among patients with vasculitis having bleeding.

#### P47-7

##### **Associated factors with diastolic dysfunction of the left ventricle in patients with acute phase of microscopic polyangiitis**

Takashi Nawata, Makoto Kubo

Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine

Conflict of interest: None

[Objective] We previously reported that acute-phase microscopic polyangiitis (MPA) patients revealed diastolic dysfunction of the left ventricle (LV). We investigated the factors associating with diastolic dysfunction of the left ventricle in patients with MPA. [Methods] This single-center case-control study included 15 MPA patients who underwent echocardiography before or within 2 weeks of starting steroid for induction or reinduction therapy. The echocardiography parameters of the patients were compared with those of the 30 age- and sex-matched controls. [Results] MPA group showed significantly higher left atrial (LA) diameter and LA volume index, as well as higher early diastolic filling velocity, trans-tricuspid pressure gradient, and a shorter deceleration time. Serum C-reactive protein (CRP) levels were positively correlated with E wave, E/A, and deceleration time. [Conclusions] LV diastolic dysfunction in patients with acute-phase MPA had relationship with serum levels of CRP. This finding indicates the importance of cardiac assessment in patients with MPA, especially in patients with a strong inflammatory reaction.

#### P47-8

##### **Clinical features of anti-glomerular basement membrane antibody-positive cases**

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Kurobe City Hospital, Kurobe, Japan

Conflict of interest: None

We examined clinical features of anti-glomerular basement antibody (anti GBM antibody) positive cases diagnosed in our hospital during 15 years. Result: Positive cases are observed 11 cases (5 male and 6 female). Average antibody titer of antibody was 161.5 U/mL (8.9-794.0) and the average age was 79.5 years old. Four cases were positive for MPO-ANCA and other four cases were positive for PR3-ANCA at the same time, and two of them were positive for both MPO and PR3-ANCA. There were six cases of limited renal disease and four case had lesion in both kidneys and lungs, so called Goodpasture syndrome. There was only one case of limited lung. Prognosis is very poor. Seven cases died within one year after diagnosis. Two cases rapidly developed end stage renal failure, but no recurrence of vasculitis was observed. Conclusion: Most of anti GBM antibody positive case have renal lesion and it is difficult to recover from rapidly progressive glomerulonephritis and prognosis of is very poor. On the

other hand, there were many cases with low titer and simultaneous high titer of ANCA. So, it is not necessary reflect anti GBM disease, and several case might occur in association with other disease.

#### P47-9

##### **Four cases of microscopic polyangiitis complicated with diffuse alveolar hemorrhage successfully rescued by treatment with plasma exchange**

Haruna Sunakawa, Reina Yonamine, Masaki Uehara, Kazushi Kinjo  
Department of Nephrology and Rheumatology, Nakagami Hospital

Conflict of interest: None

(Cases) We had 4 patients with microscopic polyangiitis (MPA) complicated with diffuse alveolar hemorrhage (DAH) treated with plasmapheresis between 2016 and 2021. Case 1: A 84-year-old female was admitted for MPA with DAH. MPO-ANCA was 86.3 IU/mL. On day 3 of admission double filtration plasmapheresis (DFP) was initiated, however DFP was changed to plasma exchange (PE) using FFP because of progressive anemia. Case 2: A 73-year-old male with end stage renal disease due to MPA was on hemodialysis. He was hospitalized because of DAH and on day 2 PE was started. MPO-ANCA was 1385 IU/mL. Case 3: A 84-year-old female was admitted for DAH caused by MPA. MPO-ANCA was 282 IU/mL. On day 2 PE was introduced. Case 4: A 88-year-old female had been admitted for MPA, who was on PSL and AZA. One month after admission she developed DAH, and was immediately treated with mPSL pulse therapy and PE simultaneously. MPO-ANCA was 69.5 IU/mL. The present four patients were rescued by successful treatment with PE. (Clinical significance) We introduce plasmapheresis early for treatment of DAH complicating MPA, and considering alveolar hemorrhage, prefer plasma exchange using FFP. We could rescue all four patients, so it is suggested early introduction of PE is important for treatment of DAH caused by MPA.

#### P47-10

##### **The treatment-efficacy and safety of RTX for ANCA associated vasculitis (AAV)**

Moemi Yabe<sup>1,2</sup>, Yusuke Tarutani<sup>1,2</sup>, Mako Yamamoto<sup>1,2</sup>, Kenshi Inoue<sup>1,2</sup>, Naofumi Dobashi<sup>1,2</sup>, Kenta Misaki<sup>1,2</sup>, Yasuhiko Imaizumi<sup>2</sup>

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Conflict of interest: None

[Objective] We analyzed the efficacy and adverse events of RTX for AAV. [Methods] We retrospectively analyzed 24 AAV patients under the treatment of RTX from April 2016 to May 2020. [Results] Twenty-one cases were Microscopic polyangiitis (MPA) and 3 cases were Granular polyangiitis (GPA). The average age was 69.6 years old, and the average observation period was 36.1 months. RTX was administered as the first induction therapy in 15 cases, and as the treatment for flare in the rest cases. The baseline average BVAS was 11.7. BVAS 0 was achieved in 18 cases (75%: MPA (n=16), GPA (n=2)), and glucocorticoid (GC) was tapered and withdrawn in 9 cases (37.5%: all MPA). Adverse events occurred in 10 cases: infectious disease (n=7: including 5 severe infectious disease), sore throat (n=1), exacerbation of interstitial lung disease (ILD) (n=1), and lung cancer (n=1). Six deaths occurred: severe infectious disease (n=4), lung cancer (n=1), and ILD (n=1). Other immunosuppressive agents for rheumatoid arthritis were prescribed in two dead cases. [Conclusions] AAV remission, even glucocorticoid-free remission, can be achieved with RTX treatment. Infectious disease should be watched for in AAV patients with RTX therapy.

#### P47-11

##### **Association Between Renal-limited Vasculitis and Incidence of Relapse in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis**

Makoto Yamaguchi, Hironobu Nobata, Shiho Iwagaitsu, Takayuki Katsuno, Takuji Ishimoto, Shogo Banno, Yasuhiko Ito  
Aichi Medical University

Conflict of interest: None

**Background:** Although several previous studies have evaluated the predictors for relapse in antineutrophil cytoplasmic antibody-associated vasculitis (AAV), the association between renal-limited vasculitis (RLV) and relapse has not been evaluated. **Methods:** This single-center retrospective cohort study included 94 consecutive AAV patients newly diagnosed with RLV (n = 36, RLV group) and microscopic polyangiitis (MPA) with renal and extra-renal involvement (n=58, non- RLV group) at the Aichi Medical University Hospital in Japan between 2004 and 2019. **Results:** During the median follow-up period of 30 (range, 9-54) months, 30 (34.9%) patients had at least one relapse. Multivariate Cox proportional hazards model identified that lower estimated glomerular filtration rate (adjusted HR=1.15, 95% CI: 1.00-1.32; P=0.042) and RLV (adjusted HR=0.32, 95% CI: 0.12-0.84; P=0.021) were associated with a decreased risk of relapse. The steroid dose during the observation period was lower in the RLV group than in the non-RLV group. **Conclusion:** RLV was associated with a lower risk of relapse than non- RLV. Our data may contribute to the formulation of clinical practice guidelines for RLV that minimize the adverse effects of immunosuppression therapy.

## P47-12

### A study of 40 cases of eosinophilic granulomatosis with polyangiitis in our hospital

Yuichiro Sato, Kaoru Minegishi Takase, Ryusuke Yoshimi, Hiroki Mizuno, Yohei Kirino, Hideto Nagai, Naoki Hamada, Kana Higashitani, Yutaro Soejima, Takaaki Komiya, Natsuki Sakurai, Lisa Hirahara, Ayaka Maeda, Chiharu Hidekawa, Yuki Izuka, Yuji Yoshioka, Soichiro Adachi, Naomi Tsuchida, Hideaki Nakajima  
Hematology, Rheumatology and Infectious Disease Internal Medicine, Yokohama City University Hospital

Conflict of interest: None

[Objective] To clarify the clinical characteristics at the time of onset and the course of treatment of EGPA diagnosed or initially treated at our hospital. [Methods] We retrospectively analyzed the clinical findings at the time of onset and the course of treatment in 40 patients with EGPA who had attended our hospital between January 2000 and June 2021. [Results] Of the 40 patients, 6 had cardiac lesions, 11 had gastrointestinal lesions, 1 had renal lesions, 19 had ENT lesions, 13 had pulmonary lesions, and 31 had peripheral neuropathy. FFS 0,1,2,3,4 are as follows, n=5,20,9,5,1. The mean eosinophil ratio at diagnosis was 41%, the mean CRP was 6.22 mg/dl, and the mean PSL dose during initial treatment was 47 mg/day. Steroid pulse was administered in 13 patients, IVCY in 12, and IVIG in 9. Mepolizumab was introduced in 14 patients. There were 4 deaths, and 4 patients (10.0%) achieved steroid-free status. Two of the four patients who achieved steroid-free status were treated with mepolizumab. [Conclusions] Steroid-free status was achieved mainly in patients with an FFS score of 1, but not in patients with an FFS score of 3 or higher. In addition, control with mepolizumab alone was considered an option for maintaining steroid-free status.

## P47-13

### Examination of lung lesions associated with microscopic polyangiitis

Motochika Asano, Ayaka Kato, Masayuki Fuwa, Koichiro Taguchi, Ichiro Mori, Hiroyuki Morita  
Gifu University Hospital

Conflict of interest: Yes

[Objective] To clarify the clinical picture of lung lesions with microscopic polyangiitis (MPA) [Methods] From January 2014 to March 2021, 36 patients with microscopic polyangiitis diagnosed at our department were retrospectively investigated, and lung lesions at the time of diagnosis were examined. MPA Was diagnosed using the 1998 Ministry of Health and Welfare diagnostic criteria, and lung lesions were diagnosed by CT. [Results] We found in 21 of 36 (58%). 8 males and 13 females, and normal interstitial pneumonia (UIP) 9 and UIP +pulmonary nodule, UIP + lung cancer, nonspecific interstitial pneumonia (NSIP) 3, NSIP + pulmonary nodule, pulmonary nodules, pulmonary nodule + pleural inflammation / pleural effusion, pleural ulcer / pleural effusion, organizing pneumonia (COP) 2. All lung nodules disappeared after administration of prednisolone (PLS), and mediastinal emphysema developed in 2 UIP patients after

administration of PSL. [Conclusions] Interstitial pneumonia of MPA occurred in 36 to 47%, it was more common in men over 70 years old and more in UIP. It reported that cases of interstitial pneumonia combined with mediastinal emphysema are extremely rare, but 2 patients were found in our department. There are no reports of inflammatory lung nodules, but 4 patients in our department.

## P48-1

### Effect of Mepolizumab in Eosinophilic Granulomatosis with Polyangiitis

Takeshi Shoda<sup>1</sup>, Hideyuki Shiba<sup>1</sup>, Yumiko Wada<sup>1</sup>, Takao Kiboshi<sup>1</sup>, Takayasu Suzuka<sup>1</sup>, Junichi Konma<sup>2</sup>, Youhei Fujiki<sup>2</sup>, Kenichiro Hata<sup>1</sup>, Takuya Kotani<sup>1</sup>, Tohru Takeuchi<sup>1</sup>

<sup>1</sup>Rheumatology, Osaka Medical and Pharmaceutical University, <sup>2</sup>Rheumatology, Yodogawa Christian Hospital

Conflict of interest: None

[Objective] Evaluate the effect of polizumab (MEPO) in EGPA. [Methods] Consecutive cases of EGPA treated in our department and Yodogawa Christian Hospital between 2002 and 2020 were included. The clinical data, treatment, and course of EGPA were investigated, and the use of mepolizumab was evaluated. [Results] 54 pts were available for EGPA, with age of onset of 63 years. ANCA was positive in 19 pts (35%). The lesions affected 19% of central nerves, 37% of lung, 24% of heart, 13% of digestive organs, and 17% of kidney. Remission induction therapy consisted of PSL pulse in 24 pts (44%), IVCY in 26 pts (48%), RTX in 5 pts (9%), IVIG in 27 patients (50%), AZA in 26 patients (48%), MTX in 4 patients (7%), MEPO in 2 patients (4%), and maintenance therapy in 27 patients (50%) on AZA, 6 patients (11%) on MTX, and 17 patients (31%) on MEPO. Of the 17 patients with mepolizumab, ANCA positivity was 7 (40%), and many of them used it in the course of severe disease. The median pre-treatment PSL was 11 mg and the median post-treatment PSL was 6 mg. There were no EGPA relapses or adverse events in patients treated with mepolizumab. [Conclusions] Mepolizumab treatment of GPA was effective in reducing steroid use and was well tolerated in patients with severe injuries.

## P48-2

### Comparison of risk of remission and mortality in ANCA-associated vasculitis at our hospital with different remission induction therapies

Yutaka Shinkawa<sup>1</sup>, Hideaki Tsuji<sup>1</sup>, Mirei Shirakashi<sup>1</sup>, Hideo Onizawa<sup>2</sup>, Ryosuke Hiwa<sup>1</sup>, Koji Kitagori<sup>1</sup>, Shuji Akizuki<sup>1</sup>, Ran Nakashima<sup>1</sup>, Akira Onishi<sup>2</sup>, Hajime Yoshifuji<sup>1</sup>, Masao Tanaka<sup>2</sup>, Akio Morinobu<sup>1</sup>

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Conflict of interest: None

[Objective] To investigate the effectiveness of cyclophosphamide (CY) and rituximab (RTX) in induction therapy for ANCA-associated vasculitis (AAV). [Methods] AAV cases treated with CY (54 cases) and RTX (16 cases) as induction therapy at our hospital from September 2006 to July 2021 were divided into the early group (28 cases, 2006-2014) and the late group (33 cases, 2015-2021). The 1-year survival rate (1y-SR) and remission rate (1y-RR) were retrospectively analyzed. [Results] The mean age was 62.4 years in the early group and 66.3 years in the late group. Microscopic polyangiitis / granulomatosis with polyangiitis were 21/7 cases in the early group and 16/17 in the late group, respectively. CY/RTX were 26/2 cases in the early group and 18/15 cases in the late group, respectively. 1y-SR was 96.4% in the early group and 96.2% in the late group (p = 0.88). The 1y-RR (no relapse that needs escalation of glucocorticoid dose) was 85.3% in the early group and 83.6% in the late group (p = 0.82). In addition, there was no significant difference in 1y-SR/RR between CY and RTX group (p = 0.54, p = 0.43, respectively). [Conclusions] Similar therapeutic effects were observed with the induction therapy for AAV between before and after RTX was covered by health insurance.

### P48-3

#### Background, efficacy, safety, and course in patients with eosinophilic granulomatosis with polyangiitis treated with mepolizumab

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Rheumatology & Clinical Immunology, Jichi Medical University Hospital, Japan

Conflict of interest: None

[Objective] Mepolizumab, an anti-IL-5 antibody, maintains remission and reduce steroid dose in eosinophilic granulomatosis with polyangiitis (EGPA). In this study, we examined the course of mepolizumab administration in EGPA. [Methods] We retrospectively reviewed the background and course of EGPA patients who received mepolizumab at our hospital and affiliated hospitals after May 2018. [Results] Of the 21 patients with EGPA, 6 patients (29%) were treated with mepolizumab. The age ranged from 21 to 69 years, and the men to women ratio was 5:1. The reasons for mepolizumab use were asthma exacerbation in 2 patients, reincrease in eosinophil count during prednisolone (PSL) dose reduction in 2 and EGPA relapse in 2. PSL was administered in 6 patients and discontinued in 3 because of remission. The PSL dose decreased from 9 to 2.5 mg/day and the eosinophil count from 619 to 46/ $\mu$ L after mepolizumab administration. In 2 patients, the dose of mepolizumab was reduced and administration intervals were extended because remission was maintained. [Conclusions] Mepolizumab was given to 29% of EGPA patients and was effective in maintaining remission and reducing steroid dose. It will be necessary to study the appropriate dosage after remission and the background of EGPA that requires mepolizumab.

### P48-4

#### Long-term Outcome of Rituximab Treatment in Japanese Patients with ANCA-Associated Vasculitis in daily clinical practice: A Two-Center Study in Fukushima, Japan

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Conflict of interest: None

[Objective] Rituximab (RTX) efficacy for Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has been reported in large randomized studies; however, the long-term efficacy of RTX in Japanese AAV patients is not well known. We aimed to determine the long-term clinical efficacy of RTX in Japanese AAV patients. [Methods] This study included 78 AAV patients who newly diagnosed and treated in Fukushima Medical University Hospital or Ohta-Nishinouchi Hospital from April 2004 to September 2019. Clinical records were retrospectively reviewed, and clinical efficacy and outcome (three-year survival) between the RTX treatment group (23 cases) and the conventional therapy group (immunosuppressive therapy other than RTX, 55 cases) were compared. [Results] No major differences in clinical characteristics between RTX group and conventional therapy group were found. The RTX group showed similar three-year survival and relapse rates compared to the conventional therapy group. In contrast, after 6 months of treatment, prednisolone doses significantly decreased in the RTX group compared to the conventional therapy group ( $p < 0.01$ ). [Conclusions] RTX was effective in Japanese AAV patients and may be beneficial for prompt tapering of prednisolone doses.

### P48-5

#### Effect of mepolizumab on steroid reduction in patients with MPO-ANCA positive eosinophilic polyangiitis granulomatosis

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Conflict of interest: None

[Objectives] To clarify the effect of mepolizumab on steroid reduction in patients with MPO-ANCA positive eosinophilic polyangiitis granulomatosis (EGPA). [Methods] We retrospectively investigated the medical records of 27 EGPA patients who used MEP at our hospital. [Results] The mean age at the start of MEP was 53.9 years, the mean morbidity was 54.8 months, the ANCA positive rate was 25.9%, the prednisolone (PSL) dose rate was 100%, and the mean dose was 12.7 mg/day. The rate of concomitant immunosuppressive therapy was 29.6% ( $n=8$ ). The PSL withdrawal rate was 41.2% ( $n=7$ ) in 17 patients who were followed up to 72 weeks after initiation of MEP. In patients with immunosuppressive agents, 66.7% ( $n=4$ ) of the 6 patients followed up to 72 weeks were able to reduce their dose. The PSL withdrawal rate at 72 weeks was 75% in the MPO-ANCA-positive group and 30.7% in the MPO-ANCA-negative group ( $p=0.25$ ). Among the 2 patients in the MPO-ANCA-positive group and 5 patients in the MPO-ANCA-negative group with concomitant immunosuppression, the percentage of dose reduction was 50% ( $n=1$ ) and 60% ( $n=3$ ). [Conclusions] The addition of MEP to EGPA patients can be expected to result in PSL withdrawal and immunosuppressive drug reduction in both MPO-ANCA positive and negative patients.

### P48-6

#### Effectiveness of Mepolizumab administration in patients with eosinophilic polyangiitis granulomatosis

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Conflict of interest: None

[Objective] To investigate the effect of mepolizumab (MEP) against the patients with eosinophilic polyangiitis granulomatosis (EGPA). [Methods] We enrolled 14 (35%) EGPA patients who had started MEP out of 40 (28.5%) who met the Japanese EGPA diagnostic criteria; in our hospital, 1403 patients visited from April to June 2021. [Results] The patients backgrounds were as below; male/female ratio: 1/1, average age: 49.5 y/o (IQR: 39, 62), preceding allergic symptoms: 14 (100.0%), fever and weight loss: 6 (42.9%), multiple mononeuritis: 12 (85.7%), gastrointestinal lesions: 5 (35.7%), joint lesions: 5 (35.7%), muscle lesions: 3 (21.4%), skin lesions: 8 (57.1%), heart lesions: 4 (28.6%), lung lesions: 9 (64.3%), renal lesion: 1 (7.1%), tissue infiltration of eosinophil cells: 11 (78.6%), fibrinoid necrotizing vasculitis: 4 (36.4%), anti-neutrophil cytoplasmic antibody positive: 3 (21.4%), the pulse intravenous methylprednisolone: 6 (42.9%), intravenous cyclophosphamide: 8 (57.1%), intravenous immunoglobulin: 7 (50.0%), immunosuppressive drug combination (azathioprine, cyclosporin A, methotrexate): 8 (57.1%). Three patients (21.4%) who achieved steroid-free administration with MEP were found, while 2 (14.3%) relapsed with MEP. [Conclusion] MEP may can withdraw EGPA patients from steroids.

### P48-7

#### The comparison of glucocorticoid (GC) tapering strategy between the recommendations and real world (RW) in ANCA-associated vasculitis (AAV)

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Conflict of interest: None

[Purpose] For GC tapering target 12 weeks after induction therapy in AAV, 15 mg or 7.5-10 mg per day are recommended (BSR/BHRP/EULAR), however, it is ambiguous whether the recommendations correspond to clinical practices in RW. In this study, we analyze the characteristics of cases deviating from the recommendations to reveal clinicians' decision in RW and their validities and errors. [Method] Twenty-four cases with newly diagnosed AAV and consecutive induction therapy for more 12 weeks in our hospital between January 2017 and June 2021 were enrolled. Based on dosage of GC 12 weeks after induction therapy, they were divided into 2 groups; (1) rapid tapering group ( $GC \leq 15$  mg/day) and (2) slow tapering group ( $GC > 15$  mg/day). Patients with anti-glomerular basement membrane antibody were excluded. [Results] Six cases (6/24, 25%) were rap-



idly tapered and 18 cases (18/24, 75%) were slowly. Although baseline characteristics in slowly tapered cases tended higher CRP and WBC, there were no significant differences in the BVAS at the baseline, 24 and 48 weeks after induction therapy, the frequency of relapsing or adverse events of GC. [Conclusion] GC tapering strategy in RW tends slower than the recommendations and baseline higher inflammatory reaction might affect clinicians' decision.

#### P48-8

##### **Efficacy of rituximab for remission induction and maintenance therapy in patients with ANCA-associated vasculitis**

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Conflict of interest: None

[Objective] This study examined the efficacy of RTX for remission induction and maintenance in patients with ANCA-associated vasculitis (AAV). [Methods] We retrospectively recruited 16 patients with AAV treated with rituximab (RTX). The primary endpoint was remission induction and maintenance rate (BVAS 0) 1 year after introducing RTX. [Results] The mean age and BVAS of the 13 patients who received remission induction therapy were 65 years and 7.9, respectively. RTX was administered at 375 mg/m<sup>2</sup> for 4 consecutive weeks in 3 patients and once in 10 patients. Except for one patient who died of severe infection during remission induction, RTX was continued once every 6 months thereafter. The mean age of the 3 patients who received maintenance therapy was 73 years, and all patients had a BVAS of 0. They received a single dose of RTX 375 mg/m<sup>2</sup> every 6 months. At 1 year, 92% (12 patients) in remission induction and 100% (3 patients) in maintenance achieved and maintained remission. The mean PSL dose in patients with remission induction decreased from 23 mg/day to 8 mg/day after 1 year, and from 23 mg/day to 6 mg/day in patients with maintenance, with a reduction rate of 64% and 74%, respectively. [Conclusions] Most cases achieved and maintained remission one year after introducing RTX.

#### P48-9

##### **Feasibility of the reduced-dose oral glucocorticoid regimen of PEXIVAS trial for microscopic polyangiitis**

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Conflict of interest: None

[Objective] To investigate feasibility a reduced-dose oral glucocorticoid regimen of PEXIVAS trial for microscopic polyangiitis (MPA) in daily clinical practices. [Methods] Characteristics of the patient at baseline and outcomes were retrospectively analyzed. The primary outcomes were disease flares and a composite of end stage kidney diseases (ESKD) and death. [Results] Eight patients (female 5, male 3) were enrolled. The average age was 72.3 (34-90) yr. All patients had glomerular nephritis, and 3 patients had rapidly progressive glomerular nephritis. One had diffuse alveolar hemorrhage and COVID-19. The average Birmingham Vasculitis Activity Score (BVAS) v3 was 18.8. None underwent plasma exchange, and all were administered with rituximab as a remission induction therapy. After 8 weeks, 4 patients withdrew from the regimen; 2 were due to pleuritis and organizing pneumonia, respectively, regarded as a vasculitis flare. ESKD occurred in 3 patients; all had developed at baseline. One patient died from sepsis following withdrawal from the regimen. [Conclusions] The reduced-dose oral glucocorticoid regimen was not associated with ESKD and death. Thus, it is a feasible protocol for attempting to reduce glucocorticoid toxicities in daily practices.

#### P48-10

##### **Clinical course of 14 cases of eosinophilic granulomatosis with polyangiitis EGPA treated with mepolizumab in our department**

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Conflict of interest: None

[Objective] We will discuss the efficacy of mepolizumab, a humanized anti-IL-5 monoclonal antibody in eosinophilic granulomatosis with polyangiitis (EGPA) in our department. [Methods] We retrospectively reviewed 14 EGPA patients who treated with mepolizumab among between October 01, 2019 and September 30, 2021. [Results] 8 males and 6 females EGPA patients, their ages ranged from 30 to 85 years (mean 59.8 years). All patients had bronchial asthma, 11 had peripheral neuropathy, 3 had skin rash, and 4 had pulmonary infiltration. Prednisolone use ranged from 2 mg/day to 60 mg/day (mean 23.3 mg/day). The reasons for induction were difficulty in reducing steroid dose in 7 patients, relapse in 6, and persistent eosinophilia during remission in 1. The duration of treatment ranged from 1 month to 28 months (mean 12.4 months). In patients with difficulty in reducing steroid dose, all achieved reduction. 2 patients relapsed after mepolizumab introduction, 1 of which was discontinued at the patient's request and 1 of which was self-interrupted. 2 patients had serious adverse events, 1 case of pneumonia and 1 case of drug rash. [Conclusions] In EGPA patients in our department, mepolizumab showed a steroid dose-reducing effect and was considered to be highly safe. Conflict of interest: No

#### P49-1

##### **A usability survey of mouth rinse using sodium bicarbonate water on dry mouth symptoms in patients with Sjögren's syndrome**

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Conflict of interest: None

[Objective] To assess influences of mouth rinse using sodium bicarbonate water on dry mouth in patients with Sjogren's syndrome (SS). [Methods] Twenty-seven patients with SS who rinse their mouth with homemade sodium bicarbonate water were enrolled. Usage conditions and changes of subjective symptoms regarding dry mouth were investigated by a questionnaire. [Results] 15 patients (55.6%) did not know the mouth rinse using homemade sodium bicarbonate water. The mouth rinse was used mainly twice a day (9 patients; 33.3%), and before sleep (18 patients; 66.7%) and after meals (17 patients; 63.0%). 20 (74.1%) of the patients answered that feeling in use of the sodium bicarbonate mouth rinse was good or very good. Questionnaire revealed an improvement of dry mouth symptoms in 18 patients (66.7%). The most common answer was "the feeling in the mouth is refreshing" (14 patients; 51.9%). No serious adverse event was found. 20 patients (74.1%) wished to continue using the mouth rinse. [Conclusions] Mouth rinse using sodium bicarbonate water is a useful self-care tool for the management of dry mouth in patients with SS.

#### P49-2

##### **Sjogren's syndrome with transverse myelitis preceded by lymphocytic interstitial pneumonia; a case report**

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Conflict of interest: None

We report a 40-year-old woman with Sjogren's syndrome (SS) who developed transverse myelitis (TM) preceded by lymphocytic interstitial pneumonia (LIP). Five years ago, she was diagnosed as SS based on positive of anti-SS-A and anti-SS-B antibodies, saliva test, Schirmer test, corneal conjunctival disorder, and lip biopsy findings. She had been treated for dry symptoms. In October year X-1, her chest CT showed a pattern of LIP. About four months later, prednisolone and tacrolimus were started for

the worsening of CT finding. Because of the good treatment response of LIP, PSL had been gradually reduced to low dose. In July year X, she began to suffer from numbness and weakness in her upper limbs expanding from both hands. MRI showed longitudinally extended transverse myelitis in the upper cervical spinal cord, so she was diagnosed as TM associated SS. Aquaporin 4 antibody was negative. After the combination therapy of high-dose glucocorticoid, intravenous cyclophosphamide, and high-dose immunoglobulin, her neural symptoms were gradually improved. A previous report showed that lung lesions were at risk of developing TM in SS. In our case, LIP developed shortly before the onset of TM, so it suggests an association between LIP and TM.

#### P49-3

##### **Association between CD8 positive regulatory T cells and clinical features in patients with primary Sjögren's syndrome (pSS), and the induction of CD8 positive regulatory T cells differentiation in vitro**

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Conflict of interest: None

[Objective] To clarify pathogenic roles and therapeutic potential of CD8 positive regulatory T cells (CD8<sup>+</sup>Treg) in pSS. [Methods] 1) The population of CD8<sup>+</sup>Treg (CD8<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup>) and CD4<sup>+</sup>Treg (CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup>) in peripheral blood were compared by flow cytometry, between patients with pSS (N=10) and age gender-matched healthy controls (HC) (N=10). 2) In pSS patients, the association between the population of peripheral CD8<sup>+</sup> and CD4<sup>+</sup>Treg and clinical features were examined. 3) We examined the effects of CDK8/19 inhibitor against the induction of CD8<sup>+</sup>Foxp3<sup>+</sup>T cells differentiation from peripheral memory CD8<sup>+</sup>T cells derived from HC by IL-2 and TGF- $\beta$  stimulation, in vitro. [Results] 1) CD8<sup>+</sup>Treg population was significantly lower in pSS ( $0.27 \pm 0.17\%$ ) than in HC ( $0.56 \pm 0.30\%$ ), while CD4<sup>+</sup>Treg population was similar between pSS ( $5.56 \pm 2.69\%$ ) and HC ( $4.23 \pm 0.86\%$ ). 2) In pSS patients, there was no significant association between the population of CD8<sup>+</sup> and CD4<sup>+</sup>Treg and the clinical features (age, ESSDAI, ESSPRI, IgG, RF, and anti-SS-A/B antibody). 3) The induction of CD8<sup>+</sup>Foxp3<sup>+</sup>T cells were significantly enhanced by CDK8/19 inhibitor (from  $28.5 \pm 2.7\%$  to  $55.4 \pm 2.7\%$ ). [Conclusion] Peripheral CD8<sup>+</sup>Treg population decreased in pSS, and CDK8/19 inhibitor could enhance CD8<sup>+</sup>Treg differentiation in vitro.

#### P49-4

##### **Two cases of acute encephalitis in primary Sjögren's syndrome**

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Conflict of interest: None

<Case 1>A 33-year-old woman was admitted to our hospital for fever, vomiting, and disturbance of consciousness. Acute encephalitis was diagnosed based on the results for cerebrospinal fluid (CSF) test with the increase of interleukin-6 (IL-6) level, and magnetic resonance imaging (MRI). Serum anti-SSA antibody was positive. The biopsy specimen of her labial salivary gland revealed a focal lymphocytic sialadenitis. She was diagnosed with primary Sjögren's syndrome (pSS) complicated with acute encephalitis and successfully treated with immunosuppressive therapy. <Case 2>A 84-year-old man was admitted to our hospital for fever, seizure, and disturbance of consciousness. Acute encephalitis was diagnosed based on the results for CSF test with the increase of IL-6 level, and MRI. Serum anti-SSA antibody was positive. The biopsy specimen of his labial salivary gland revealed a focal lymphocytic sialadenitis. He was diagnosed with primary pSS complicated with acute encephalitis and successfully treated with immunosuppressive therapy. <Discussion>Acute encephalitis can be the initial manifestation of pSS and treatable by the immunosuppressive therapy. In acute encephalitis of unknown origin, pSS should be included in the differential diagnosis.

#### P49-5

##### **A Case of cerebellar atrophy associated with Sjogren's syndrome with dramatic responses to steroids and mycophenolate mofetil**

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Conflict of interest: None

[Background] Sjogren's syndrome develop extraglandular symptoms such as central nervous system symptoms, but there are a few reports of cerebellar symptoms, and is no established treatment. [Case] A 51-year-old man acutely developed wobble and dizziness. He visited hospital and was identified cerebellar atrophy by head MRI. He had leftward nystagmus, but there was no abnormalities in the semicircular canals. Cerebrospinal fluid examination showed no increase in cell number / protein and no appearance of oligoclonal band. Although there were no symptoms of dry mouth or eyes, blood test for autoimmune diseases revealed anti-SS-A antibody positivity. After that, lip biopsy revealed lymphocyte infiltration around the gland, and he was Sjogren's syndrome was diagnosed. After he was treated with Prednisolone (PSL) 30 mg, his cerebellar symptoms disappeared completely. However, the symptoms recurred during the PSL tapering process, and when mycophenolate mofetil (MMF) was added, the symptoms disappeared again. [Discussions] It has been suggested that the central the causes of nervous system symptoms of Sj were vasculitis and vasculopathy. Because steroids and MMF were effective for this case, so it was considered that reversible vasculitis and vasculopathy were present.

#### P49-6

##### **A case of sarcoidosis complicated with Sjogren's syndrome**

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Conflict of interest: None

A 68-year-old woman was admitted to our hospital because of skin rashes suspicious for sarcoidosis. She had been diagnosed with Sjogren's syndrome at the age of 47 without any organ damages. One year ago, erythema had appeared on her face and fingers, and gradually worsened. She had been treated at her local doctor without improvement. She had referred to the dermatology department of our hospital. Skin biopsy had revealed non-necrotizing granulomas in the dermis. A full-body examination revealed enlarged hilar and mediastinal lymph nodes and multiple granular and nodular shadows in both lungs, which were considered to be sarcoidosis lesions. Ophthalmological examination revealed mutton-fat keratic precipitates, chorioretinal atrophy and snowball vitreous opacity, indicating ocular sarcoidosis. She was treated with prednisolone 0.6 mg/kg. There have been reports of combined cases of these two diseases. In most cases, the diagnosis of sarcoidosis is made at the same time or within a few years after the diagnosis of Sjogren's syndrome. However, there are also case reports of sarcoidosis occurring after a prolonged period of time, as in this case. We would like to discuss the relationship between the two diseases by comparing this case with previous reports.

#### P49-7

##### **A case report regarding a patient died from pulmonary hypertension associated with Sjögren syndrome and portal hypertension**

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Conflict of interest: None

A 67 year-old female with liver cirrhosis, esophageal varices and portal thrombosis, was referred to our hospital to treat recurring esophageal varices. Besides anti-SSA and SSB antibodies positive, further examina-

tion proved primary Sjögren syndrome. Later, echocardiography showed right heart strain (TRPG 68.3 mmHg). She was admitted to our hospital for further examination and treatment against pulmonary hypertension. Despite aggravation of interstitial lung disease and portal thrombosis, CTD-PAH was considered as a lead condition with the evidence of vasculitis. Corticosteroid (CS) was started, but as portal thrombosis and ascites increased, we added Tadalafil to reduce the dose of CS. However, Tadalafil was discontinued due to remained ascites, sepsis and DIC. CS was required to decrease because of steroid-induced psychosis resulting in restart of Tadalafil. She developed sepsis again and died by rapid respiratory and cardiovascular failure. Autopsy showed both right and left heart failure as a direct cause of death. From autopsy findings, it could be considered that CS accreted portal thrombosis and pulmonic vasodilator caused ventilation-perfusion mismatch. Utilizing CS and pulmonic vasodilator for CTD-PAH should be carefully discussed based on complicated conditions.

## P49-8

### Anti-Ku antibody positive Sjögren syndrome

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Conflict of interest: None

A 56-year-old woman was admitted to our department due to elevated levels of creatine kinase (CK) and nonspecific interstitial pneumonia. She developed shortness of breath on exertion with asymptomatic elevated levels of CK 2 years earlier, but definitive diagnosis could not be made because the specific findings for the diagnosis of connective tissue disease was not observed. She had no Raynaud's phenomenon, skin thickening nor erythema, and autoantibodies in systemic sclerosis and inflammatory myopathies were negative. Since mild sicca symptoms and positive for anti-SS-A antibody was observed, labial salivary gland biopsy was performed, indicating Sjögren syndrome (SjS). Moreover, her serum was positive for anti-Ku antibody. She was diagnosed with anti-Ku antibody positive SjS, and prednisolone 40 mg per day with intravenous cyclophosphamide therapy was improved her respiratory symptoms and serum CK levels. The clinical symptoms in patients with anti-Ku antibody are mainly muscular, articular and Raynaud's phenomenon, and the antibody have been reported in the patients with not only overlap syndromes with systemic sclerosis and myositis but also SjS. Anti-Ku antibody may be observed in case of SjS with muscular symptoms or interstitial pneumonia.

## P49-9

### Coexistence of heterozygous Fabry disease, membranous nephropathy, and primary Sjögren syndrome

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Conflict of interest: None

Fabry disease is an X-linked lysosomal storage disorder in which mutations in *GLA* cause deficiency in the lysosomal hydrolase, alpha-galactosidase A. Heterozygous females may be affected. Here, we report a rare case of Fabry disease in a heterozygous 70-year-old female who also displayed membranous nephropathy and previously diagnosed Sjögren syndrome. Urinary proteins were elevated. Alpha-galactosidase activity and the concentration of globotriaosylsphingosine in blood were normal. Genetic analysis of all exon/intron junctions in *GLA* showed no pathological variants. Kidney biopsy and electron microscopy showed stage II-III membranous nephropathy and myelin bodies, leading to a diagnosis of Fabry disease. As a result of treatment, the patient's serum albumin has increased, and she is now on enzyme replacement therapy. Diagnosis of Fabry disease should involve detection of myelin bodies with electron microscopy. Negative results of *GLA* mutation analysis are insufficient to exclude the diagnosis of Fabry disease. In Fabry disease, globotriaosylceramide accumulates due to decreased  $\alpha$ -galactosidase activity and is recognized by antigen-presenting cells as a Damage associated molecular pattern (DAMP), which can induce autoimmunity.

## P49-10

### A case of Sjögren's syndrome that developed neuromyelitis optica after administration of COVID-19 vaccine

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Rheumatology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital

Conflict of interest: None

<Case> 49-year-old man <Chief complaint> Neuropathy <Current medical history> The patient was diagnosed with Sjögren's syndrome (SS) in her thirties and had been going to the hospital for about two years. She received the COVID-19 vaccine on April 26 and May 17, 2020. She became aware of her lower body desensitization on May 25 and consulted her former doctor on May 26. She was positive for anti-SS-A antibody and was referred to our department on the 28th on suspicion of neuropathy due to SS. She started steroid pulse therapy with a diagnosis of transverse myelitis on that day, but her neuropathy worsened. She was found to be positive for her anti-aquaporin 4 antibody (AQP4 Ab), and started plasmapheresis on the 3rd. She received a total of 4 steroid pulses, 7 plasmaphereses, and 1 high-dose immunoglobulin therapy, and she recovered. <Clinical significance> SS is known to be associated with transverse myelitis, but SS has been reported in anti-AQP4 Ab-positive patients characteristic of neuromyelitis optica (NMO), and SS is suspected to be associated with myelitis. It is desirable to measure anti-AQP4 Ab. It is also known that NMO develops after vaccination, and it is necessary to keep in mind that patients with SS may develop NMO especially after vaccination.

## P49-11

### A case of Sjögren's syndrome associated with Sweet's syndrome

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Conflict of interest: None

We describe a 30-years-old female with a 16 years history of Sjögren's syndrome (SS) with recurrent annular erythema associated with fever and swelling of parotid glands. Hydroxychloroquine (HCQ) was started for her symptoms. One month later, she presented with erythematous, maculopapular skin lesions on her back associated with fever, stomatitis, and swelling of lips. Skin biopsy revealed a diffuse infiltrate of mature neutrophils in the papillary dermis, consistent with Sweet's syndrome. After therapy with 100 mg/day prednisone and HCQ withdrawal, her symptoms disappeared. One month later, HCQ was reintroduced while receiving colchicine and tapering doses of prednisone, but there was no recurrence. Sweet's syndrome is an acute neutrophilic dermatosis characterized by the systemic inflammation, which is associated with autoimmune disease, neoplasm, and drugs. Its etiology remains unknown, but it can be mediated by a hypersensitivity reaction in which cytokines, followed by infiltration of neutrophils, may be involved. In this case, SS and HCQ could cause unusual hypersensitivity and immune reactions involving proinflammatory cytokines. Although various skin manifestations are involved in SS, Sweet's syndrome is one of the important differential diagnosis to be considered.

## P49-12

### A case report of primary Sjögren syndrome (SjS) complicated with pulmonary arterial hypertension (PAH) improved by induction therapy with Rituximab (RTX) and moderate dose of prednisolone (PSL)

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Conflict of interest: None

[Case] A 70 years-old woman with liver cirrhosis (LC) and autoimmune hepatitis (AIH) visited our hospital because of systemic lymphadenopathy. Physical examination showed loud S2 in apex area, nail fold capillary change. She had sicca and was positive for Schirmer, fluorescent, and gum test. Laboratory test: C3 58 mg/dL, C4 4.7 mg/dL, IgG 5861 mg/dL, ANA x1280 (speckle), anti-dsDNA Ab 239 IU/mL, anti-Sm Ab (-),



anti-U1RNP Ab > 550 IU/mL, anti-SS-A Ab 729 IU/mL, anti-SS-B Ab 29.7 IU/mL. UCG: RVSP 57 mmHg. RHC: mPAP 40 mmHg, PAWP 12 mmHg, PVR 5.5 wood. 6 min walk test 405 m. Lymph node biopsy didn't suggest Castleman's Disease, IgG4 related Disease, and lymphoma. She lacked Raynaud's phenomenon and photosensitivity. We assumed that hypocomplementemia and high titer of anti-dsDNA Ab were associated with LC and AIH. Our pretreatment diagnosis was only SjS. Because of her anemia, we chose PSL 0.8 mg/kg/day and RTX (500 mg four times, weekly) instead of cyclophosphamide. A month after the induction therapy, her RVSP was improved to 29 mmHg. [Discussion] PAH related to non-systemic sclerosis connective tissue diseases was reported to be reactive to immunosuppressive therapy, but effectiveness of RTX is not well-known. We herein report a successful case, with a review of literature.

## P50-1

### Factors related to serum IgG4 elevation and development of IgG4-related disease: data from resident examination

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Conflict of interest: None

[Objective] This study aimed to investigate the frequency of serum IgG4 elevation in the general Japanese population and its associated factors using data from resident examinations. [Methods] We measured the serum IgG4 levels in 1,201 residents who underwent a general medical examination in Ishikawa prefecture. Logistic regression analysis was used to search for factors related to serum IgG4 elevation. Secondary examinations were conducted for participants in whom elevation was identified. [Results] The mean serum IgG4 level was 44 mg/dL, and serum IgG4 elevation was observed in 42 patients (3.5%). Univariate logistic regression analyses showed that male sex, older age, lower eGFR-CysC, lower serum HDL-Chol levels, and higher serum HbA1c levels were associated with serum IgG4 elevation. Subgroup analyses in men showed that older age, lower eGFR-CysC levels, and higher serum HbA1c levels were associated with serum IgG4 elevation. In contrast, the analyses in women found no significant factors. One of the 10 residents who underwent secondary examinations was diagnosed with possible IgG4-related retroperitoneal fibrosis. [Conclusions] In the general population, serum IgG4 elevation is more common in older men, which is similar to the epidemiological features of IgG4-RD.

## P50-2

### A case of IgG4-related disease suggested the potential treatment with IL-4/IL-13 inhibitor (dupilumab)

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Conflict of interest: None

<Case> 51-year-old woman presented with swelling on the outside of her upper eyelid. She was treated for asthma and rhinitis with corticosteroid inhalation and nose drops. CT and MRI showed bilateral lacrimal gland enlargement and retroperitoneal mass. Laboratory findings demonstrated that the serum IgG and IgG4 levels were 1895 and 768 mg/dL, respectively. Biopsies of the left lacrimal gland showed storiform fibrosis with infiltrations of 100 IgG4-positive cells per high power field and an IgG4+/IgG+ cells ratio of 50%. She was clinically diagnosed with IgG4-RD. She was followed up without any treatment because of her few symptoms, however, the eyelid and retroperitoneal swelling gradually worsened. Her otolaryngologist started treatment with dupilumab for refractory

eosinophilic sinusitis. Her eyelid and retroperitoneal swelling significantly improved 9 months after dupilumab treatment with a decrease of serum IgG4 level. <Discussion> This case suggests that dupilumab may be a novel alternative or additional therapeutic agent for IgG4-RD. The inhibition of IL-4/13 signaling by dupilumab could suppress IgG class switch and fibrosis, and therefore it could account for the decrease of serum IgG4 level and shrink of lacrimal gland enlargement in our case.

## P50-3

### A case of childhood onset IgG4-related disease treated with dupilumab for chronic sinusitis

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Conflict of interest: None

[Objective] IgG4-related disease is a disease for which glucocorticoid (GC) is highly effective, but there are cases of refractory or frequent exacerbation, and the side effect of GC is a problem. We report a case of intractable IgG4-related disease complicated with sinusitis for whom anti-IL-4/13 receptor antibody markedly improved the findings of IgG4-related disease. A 17-year-old girl noticed exophthalmos at 12 years old. She was diagnosed as IgG4-related disease and GC was started that resulted in transient effect and GC related glaucoma. Exophthalmos, lacrimal gland swelling, submandibular gland swelling and eosinophilic pustular folliculitis on trunk was observed, and she complained marked nasal obstruction, olfactory disturbance, and headache due to chronic sinusitis associated with nasal polyps. Blood examination showed WBC 12700/ $\mu$ L, eos 33%, IgG4 1090 mg/dL, IgE 52343 IU/mL. Mycophenolate mofetil and rituximab improved partially. Bronchial asthma developed at the age of 16, arthralgia, myalgia, numbness and mastoiditis also appeared at the age of 17 in which course ANCA-negative eosinophilic granulomatosis with polyangiitis was suspected. Mepolizumab was not effective for sinusitis and she requested to switch to dupilumab which also lead the improvement of both diseases.

## P50-4

### A rare IgG4-related disease case complicated with cardiovascular lesions

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Conflict of interest: None

BACKGROUND: Few cases of IgG4-related disease (IgG4-RD) complicated with cardiovascular (CV) lesions are reported. CASE: A 55-year-old man presented with bilateral swelling of submandibular glands without sicca syndrome. Bilateral lower-leg edema and rashes on the extremities were also noted. Laboratory data showed an elevated level of serum IgG4 at 1240 mg/dL. In addition to a set of salivary glands, the imaging studies revealed an enlarged pancreas and prostate; abnormal mass around the bile duct, bilateral renal pelvis, and upper ureters. Further investigation exhibited pericardial effusion and soft tissue hyperplasia around the coronary arteries, ascending aorta, and pulmonary arteries. The histopathological study of the left submandibular gland showed lymphocytic infiltrate and storiform fibrosis. A diagnosis of IgG4-RD was made based on the 2019 ACR/EULAR classification criteria. Combination therapy of 1 mg/kg oral prednisolone plus rituximab was started for remission induction because CV diseases were potentially life-threatening. A significant response was shown after 10-days of treatment. DISCUSSION: This is one of the few cases of IgG4-RD with CV lesions, and is notable for its successful treatment course with the combination of high-dose glucocorticoid and rituximab.

## P50-5

### Cases of IgG4-related retroperitoneal fibrosis and Hydronephrosis

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Conflict of interest: None

[Objective] IgG4-related disease often causes retroperitoneal fibrosis and hydronephrosis. We focus on the cases of hydronephrosis caused by IgG4-related retroperitoneal fibrosis experienced at our hospital. [Methods] We examined 6 cases of hydronephrosis due to IgG4-related retroperitoneal fibrosis treated at Kansai Electric Power Hospital from August 2014 to March 2021. [Results] Patients ranged in age from 58 to 77 years. The patients were all male. There were 3 cases of unilateral hydronephrosis and 3 cases of bilateral. Ureteral stents were placed in 5 cases. Steroid treatment was started with PSL 30-40 mg in all cases. Hydronephrosis improved in all cases, and ureteral stent was removed. Two patients became steroid-free, but one had a recurrence of hydronephrosis and another had a relapse with a pancreatic mass and sclerosing cholangitis. As a maintenance dose, all patients were taking low doses of prednisone and immunosuppressants (such as azathioprine and brexinin). [Conclusions] Steroids are effective against IgG4-related retroperitoneal fibrosis and hydronephrosis, but it might be difficult to discontinue immunosuppressive therapy.

## P50-6

### Co-occurrence of glomerulonephritis due to microscopic polyangitis (MPA) and interstitial cystitis and bilateral hydronephrosis caused by IgG4-related disease (IgG4-RD)

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Conflict of interest: None

A 74-year-old woman was referred to our division for further investigation of the cause of interstitial cystitis and dysuria. Contrast-enhanced CT showed circumferential wall thickening of the bladder and ureters and hydronephrosis. Blood tests revealed polyclonal hyperglobulinemia, high IgG4 and high MPO-ANCA. The 24-hour urine protein level was 1.8 g/day. Renal biopsy disclosed fibrocellular glomerular crescent formation with pauci-immune type. The bladder mucosal biopsy showed no findings suggestive of vasculitis in EVG staining. The Immunohistochemistry revealed IgG4-positive plasma cells infiltrating the bladder wall, which was consistent with IgG4-RD. The patient was diagnosed with co-occurrence of MPA and IgG4-RD, and induction therapy with rituximab 375 mg/m<sup>2</sup> and prednisolone 1 mg/kg/day was started. The dysuria quickly disappeared, and urinary protein also decreased. Though IgG4-RD has been reportedly accompanied by elevated ANCA titer, ACR/EULAR 2019 classification criteria of IgG4-RD put ANCA positivity into one of the exclusion criteria. Our case underscores the possibility that IgG4-RD may co-occur with ANCA-associated vasculitis, thus present with multi-organ involvements which cannot be explained by IgG4-RD or ANCA-associated vasculitis only.

## P50-7

### Clinical Features of IgG4-Related Dacryoadenitis and Sialadenitis

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Conflict of interest: None

[Object] IgG4-related disease (IgG4-RD) is recognized as a systemic disease that may affect various organs. Dacryoadenitis and sialadenitis (DS) are one of the main disease features of IgG4-RD. The aim of this study was to clarify the characteristics of IgG4-RD with DS. [Methods]

Patients with IgG4-RD who diagnosed at our hospital and Kagawa University Hospital after 2008 and underwent FDG-PET/CT were included. We classified the patients into two groups: those with lacrimal and salivary gland inflammation (DS group) and those without (non-DS group), and retrospectively reviewed age, gender, serum biomarkers, imaging findings, and clinical course. [Results] Thirty five patients were included in the study. The DS group was younger than the non-DS group. Compared to the non-DS group, the DS group had lower CRP, serum IgA, and complement level. The number of organ involvements was not significantly different between the two groups. Retroperitoneal fibrosis was more common in the non-DS group. During the course, there were many cases followed up without treatment in the DS group. [Conclusions] Clinical features, including serum biomarkers, of IgG4-RD with dacryoadenitis and sialadenitis have been clarified. In addition, the prognosis of IgG4-RD patients with DS may be relatively good.

## P50-8

### Characteristics and clinical course of patients with IgG4-related disease presenting to our department

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Conflict of interest: None

[Objective] We will review characteristics and clinical course of patients with IgG4-related disease (IgG4-RD) presenting to our department. [Methods] We evaluated clinical findings, treatment details, and serial Responder Index (RI) of IgG4-RD patients who visited our department. [Results] There were 12 patients with IgG4-RD (6 females, 6 males), and the median age was 58 years. Salivary glands were involved in 8 cases and orbital/lacrimal glands in 8 cases. The median time since onset (range) was 16 (1-120) months. Three patients were followed up without treatment. Three patients received prednisolone (PSL) 0.2-0.3 mg/kg/day, and indicated lesions were orbit/lacrimal glands. After 4 months (median), RI tended to decrease from 9 to 3, but relapsed in 1 patient. Six patients received PSL 0.6 mg/kg/day, and indicated lesions were pancreas in 4 patients, retroperitoneum in 3 patients, orbit/lacrimal gland in 1 patient, and pituitary gland in 1 patient. After 2 months (median), RI decreased from 12 to 4 (p=0.034). There were no differences in age, sex, time since onset, or serum IgG4 levels among the 3 groups. [Conclusions] RI was useful for evaluation of responses to treatment. Further examinations are warranted to clarify predictors for development of lesions requiring treatment.

## P50-9

### A case of IgG4-related disease associated with pancreaticobiliary duct and skin lesions successfully treated with mycophenolate mofetil

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Conflict of interest: None

A 60-year-old male with swollen lacrimal and salivary glands and high serum IgG4 levels was diagnosed as having IgG4-RD based on the results of submandibular gland biopsy 3 years ago. The patient was treated with PSL (1 mg/kg/d) and improved. 1 and a half years ago, while the patient was maintained on low doses of PSL and cyclosporine, itchy and erythematous plaques appeared on both cheeks. Skin biopsies revealed IgG4-related skin lesions. Due to elevated pancreatic enzymes and exacerbation of skin lesions, the patient was admitted to the hospital. PSL was increased to 0.7 mg/kg/day and MMF (1000 mg/d) was started. The pancreatic enzymes promptly decreased, and the facial rash gradually disappeared. IgG4-RD complicated by skin lesions has been reported to occur in 4.2 to 6.3% of patients. The appearance of systemic organ manifestations often precedes the skin lesions, and lesions of the head and neck lymph nodes, orbits, lacrimal and salivary glands are prominent, while those of the pancreaticobiliary tract are relatively rare. Therefore, we re-

port this rare case of IgG4-related skin disease in which pancreaticobiliary duct involvement was confirmed at the time of initial presentation.

## P50-10

### **A case of IgG4-related disease with marked eosinophilia and predominantly gastrointestinal symptoms**

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Conflict of interest: None

[Case] 66 years old, female Since X-2, he has had chronic diarrhea accompanied by eosinophilia. She had an examination, but there was no particular change. However, after that, frequent diarrhea symptoms recurred, and blood tests pointed out RF and ANA positive, and hypergammaglobulinemia, and there was a suspicion of collagen disease. In year X, he was referred to our department. Colonoscopy was performed, and the gross findings were only mild polyps, but pathological examination revealed IgG4-positive plasma cells were 10/HPF or higher, and IgG4/IgG-positive cell ratio was 40% or higher. SLE was differentiated due to low complement and positive anti-dsDNA antibody. Renal biopsy was performed to detect renal dysfunction. It did not meet the SLE classification criteria and met the criteria for IgG4-RKD. Satisfying IgG4-RKD and histopathological findings of the intestine considered the possibility of IgG4-related gastroenteritis. Starting with prednisolone 0.8 mg/kg, improvement of gastrointestinal symptoms was observed. The concept of IgG4-related gastroenteritis has not been established, there are several reports on the concept of disease and cases. A small number of cases of IgG4-RD with gastrointestinal symptoms are reported, including a review of the literature.

## P50-11

### **A case of pericarditis suspected of having IgG4-related disease**

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Conflict of interest: None

[Case] 66-year-old man [Chief complaint] Chest pain [medical history] Chest pain appeared from the end of July X, and pericardial fluid retention was observed on CT. He was diagnosed with pericarditis and NSAIDs and colchicine were started. His symptoms improved once, but in October they worsened again. He was admitted to the cardiology department for detailed examination and treatment. He had high serum IgG and high serum IgG4 levels and was associated with submandibular adenitis and mediastinal lymphadenopathy. Therefore, he underwent pericardial and lymph node biopsy in November on suspicion of IgG4-related disease. Histological examination ruled out infections and malignancies. Pericarditis associated with IgG4-related disease was suspected. He was admitted to our department in December and started treatment with PSL 0.6 mg / kg / day. The treatment was immediately effective and the pericarditis improved. [Discussion] Among the complications of IgG4-related diseases, pericarditis is much less frequent than autoimmune pancreatitis, retroperitoneal fibrosis, and Mikulitz's disease, but it can be fatal. When you discover pericarditis of unknown cause, it is important to recall IgG4-related disease as one of the differential diseases.

## P50-12

### **A case of diffuse large B-cell lymphoma that presented as superior vena cava syndrome and required differentiation from IgG4-related disease**

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Conflict of interest: None

The patient is 72-year-old male and he admitted to hospital with complaint of facial edema. Computed tomography (CT) showed a mass in the anterior and middle mediastinum and supraclavicular and mediastinal lymphadenopathy. After a biopsy of the left subclavian lymph node, mPSL pulse was performed. Histological examination of the lymph nodes showed no findings of malignancy, on the other hand, IgG4 (+) plasma cells were found. Next month, facial edema worsened. After another mPSL pulse, PSL45 mg/day with suspicion of IgG4-related disease (IgG4-RD) based on serum IgG4 elevation. And biopsy was reperformed under a transvenous catheter, but we didn't get a diagnosis. After that, there was a lull, but in June, the patient was readmitted with worsening facial edema and bilateral pleural effusions. We performed another biopsy from the left subclavian lymph node, but failed to reach a diagnosis, so we submitted the pleural fluid cytology and performed a CT-guided biopsy from the mediastinal mass. That search led to a diagnosis of Diffuse Large B-Cell Lymphoma. Since existing reports suggest that peri-tumor tissues rich in IgG4 plasma cells may be misdiagnosed as IgG4-RD, we report this case as a reminder of the importance of collecting a large number of tissues for diagnosis.

## P50-13

### **A case of IgG4-related disease with concurrent eosinophilic gastroenteritis that required differentiation from lymphocyte-variant hyper-eosinophilic syndrome**

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Conflict of interest: None

A 75-years old man who presented 2 months prior with submandibular gland swelling visited our hospital. Laboratory investigation revealed both elevated serum IgG and IgG4 levels, and slightly increased eosinophils count. Histopathological findings of the submandibular gland included an increased number of IgG4 plasma cells without conspicuous eosinophil infiltration. Since he was anorexic, an esophagogastroduodenoscopy was performed. Eosinophil infiltration was observed by gastric mucosal biopsy. After admission, he developed abdominal pain along with a rapid increase in eosinophils. Contrast-enhanced CT showed thickening of the gut wall, multiple lymphadenopathy, and a wedge-shaped parenchymal low-density lesion in the kidney. We made a diagnosis of IgG4-related disease (IgG4-RD) concurrent with eosinophilic gastroenteritis. Treatment with prednisolone (40 mg/day) resulted in rapid improvement of submandibular gland swelling and abdominal pain, and a decreased eosinophil count. Bone marrow examination and genetic screening for PDGF-RA, PDGF-RB, FGFR1, and clonal T-cell receptor rearrangement was normal. As submandibular swelling due to IgG4-RD had been observed earlier, we assumed that hyper-eosinophilia was effected by IgG4-RD.

## P50-14

### **A case of IgG4-related disease with multiple organ involvement including gastric polyposis**

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Conflict of interest: None

[Case Report] A 53 year-old man noticed swelling of the bilateral submandibular glands in February X. A blood test showed a high IgG4 level of 699 mg/dL and he was admitted to our hospital in July. Blood examination revealed elevated hepatobiliary enzymes. CECT showed diffuse enlargement of the pancreas, wall thickening of the common bile duct, perirenal nodular shadows. MRCP revealed an irregular diameter of the main pancreatic duct and stenosis. Upper gastrointestinal endoscopy revealed gastric polyposis. Tissue biopsy was performed from the renal and gastric



lesions, and infiltration of IgG4-positive plasma cells was observed, leading to the diagnosis of IgG4-related disease. The subjective symptom and rise in the hepatobiliary enzyme recognized the rapid improvement, when the administration of prednisolone 40 mg/day was started. [Consideration] This case showed the gastric polyposis as a characteristic lesion, but polyposis was reported as IgG4-related disease could not be recognized as far as we searched. The disease concept of the IgG4-related digestive tract lesion has not yet been established, and the storage of future cases is desired region, and the digestive tract scanning as a screening seems to be important in the case which suspects the IgG4-related disease.

## P50-15

### **A case of IgG4-related Mikulicz disease complicated with lung diseases and lymphoma**

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Conflict of interest: None

Eighty-five years old man, who was diagnosed as IgG4-related Mikulicz disease by lip biopsy and elevated serum IgG4 ten years ago. He had both enlarged eyelids and submandibular glands, and a decrease in saliva production at the same time. We treated with prednisolone (PSL) and used immunosuppressants in conjunction with tapering PSL. Six years ago, he had an abnormal shadow in his left upper robe, so we decided to remove it with video-associated thoracoscopic surgery because of lung cancer suspicion by PET-CT. The diagnosis was fibrosis. Four years ago, we quitted PSL and treated with methotrexate (MTX) alone. Three years ago, he had subcutaneous tumors at the top and back of the head. Skin biopsy showed T cell lymphoma and there were some lymphadenopathies in several parts of his body. We quit MTX and restarted PSL. The subcutaneous tumors and lymphadenopathies were shrunk in a half year. We treated with low dose PSL, but one year ago, he fought for breath because of pleural effusion in left lung and also had an abnormal shadow in his right upper robe. We drained bloody effusion; the cytology was class II. We treated with increased prednisolone, so symptoms are improving. In this case, there are diverse symptoms for ten years, so we report and consider on basis of literature.

## P51-1

### **A case of pemphigus vulgaris with folliculitis-like skin rashes, vulvar ulcers, and oral aphthae difficult to differentiate from Behcet's disease**

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Conflict of interest: None

[Case presentation] A 45-year-old man was aware of swelling of the posterior nailfold of his fingers. He was also aware of painful ulcerative lesions on his penis, folliculitis-like skin rashes, and oral aphthae. Although he was treated with prescribed valacyclovir, the ulcerative lesions on his penis did not improve. He was referred to our hospital on the suspicion of Behcet's disease. Although the folliculitis-like skin rash, vulvar ulcers, and oral aphthae raised the possibility of Behcet's disease, the oral aphthae were not recurrent, and the nailfold lesions seemed atypical for Behcet's disease. Biopsy of the nailfold lesion was done and he was diagnosed as pemphigus vulgaris. Vulvar ulcers and oral aphthae were also consistent with pemphigus vulgaris, and we started treatment for pemphigus vulgaris. [Discussion] Behcet's disease shows various clinical manifestations, and is necessary to be diagnosed with excluding other diseases. Although the main differential diseases are listed in the diagnostic criteria of Behcet's disease in the Ministry of Health, Labor and Welfare, pemphigus vulgaris is not included. Here, we report pemphigus vulgaris similar to symptom of Behcet's disease, showing folliculitis-like skin rash, vulvar ulcers, and oral aphthae.

## P51-2

### **A case of intestinal Behcet's disease complicated by cutaneous diffuse large B cell lymphoma during TNF inhibitor therapy**

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Hatakeyama, Shogo Furukawa, Kenji Yamazaki, Kumiko Shimoyama  
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Conflict of interest: None

[Case] 23 year-old, male. The patient developed oral aphthae and pharyngeal ulcer at the age of 17 years (X-6 year). He was diagnosed as intestinal Behcet's disease because of ileocecal ulcers. HLA-A26 or B51 were negative. A TNF inhibitor therapy was started, and his intestinal Behcet's disease reached remission. X-1 year, a cutaneous nodule in the right thigh appeared, and the diagnosis of diffuse large B cell lymphoma was made, in which the clinical stage was 1EA. After rituximab-CHOP therapy, the B cell lymphoma attained remission. This is a rare but important complication occurred in a patient with intestinal Behcet's disease treated with a TNF inhibitor. Here, we report this case with some literature review.

## P51-3

### **A case of intestinal Behcet's disease-like lesion with Trisomy8-positive MDS successfully treated with ustekinumab**

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Conflict of interest: None

A 50s' woman was diagnosed with trisomy8-positive myelodysplastic syndrome 12 years ago and had repeated genital ulcers, stomatitis, and abdominal pain for about 10 years. MDS is a low-risk group with no clinical symptoms and is being followed up. In year X-1, lower gastrointestinal endoscopy revealed multiple ulcers in the ileocecal region, and immunosuppressive treatment was started for intestinal Behcet's disease (BD) like lesion. After the diagnosis, adalimumab, infliximab, and golimumab were administered in combination with methotrexate and corticosteroids (CS), but ulcers remained and CRP did not become negative. Three types of anti-TNF- $\alpha$  blockers were not effective for intestinal BD like lesion and we couldn't reduce CS. When ustekinumab was started in year X after increasing the dose of CS, the ulcer disappeared on gastrointestinal endoscopy and CT scan, and CRP had normalized. Currently, the dose of CS is gradually reduced, but the intestinal lesions have not recurred. We report a case in which three types of anti-TNF  $\alpha$  inhibitors were ineffective and relapsed repeatedly, but changing to ustekinumab was effective and a stable course of intestinal lesion was obtained.

## P52-1

### **A study of covid-19 pneumonia secondary to rheumatoid arthritis and other autoimmune diseases treated in our hospital**

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Conflict of interest: None

[Objective] The course and prognosis of COVID-19 in autoimmune diseases such as RA are often unclear. [Methods] Of the 358 patients with COVID-19 admitted to our hospital between April 2020 to September 2021, 12 patients with RA and autoimmune diseases were evaluated. [Results] Patients with COVID-19 admitted to the hospital, 6 had RA, 2 had interstitial pneumonia with autoimmune features (IPAF), and 1 each had psoriasis, autoimmune hepatitis, sarcoidosis, and EGPA. While 57 out of 358 patients were discharged with exacerbation or death, one patient with IPAF and one patient with autoimmune hepatitis had exacerbation and was transferred to a higher hospital, while the remaining 10 patients recovered and were discharged. The remaining 10 patients recovered and were discharged from the hospital. However, one patient which used MTX for RA was readmitted to the hospital on disease occur day 16 after discharge because of recurrent fever and the appearance of ground glass opacity shadows in both lungs. [Conclusions] In RA and autoimmune diseases, COVID-19 does not trend to cause severe disease. However, with the use

of immunosuppressive drugs, prolonged viral elimination and consequent continuation of infection and delayed onset of symptoms may be observed, which requires attention.

## P52-2

### Effects of SARS-CoV ORF3a on ASC variant-dependent inflammasome function

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Conflict of interest: None

[Objective] It has been reported that SARS-CoV derived ORF3a activates NLRP3 inflammasome by promoting ASC ubiquitination (Siu KL et al. FASEB J, 2019). In addition, we have previously found the ASC splicing variant lacking exon2 ( $\Delta$ exon2 ASC) which increases IL-1 $\beta$  production compared to wild type in patients with palindromic rheumatism (Suganuma Y et al., Asian Pac J Allergy & Immunol, 2019). Here we investigated the effects of ORF3a on wild type and  $\Delta$ exon2 ASC-dependent inflammasomes. [Methods] THP-1 cells were transfected with wild type or  $\Delta$ exon2 ASC and ORF3a expression vectors alone or simultaneously. The cells were stimulated with LPS (5  $\mu$ g/mL), and monosodium urate (MSU) (100  $\mu$ g/mL) or Poly (dA: dT) (3  $\mu$ g/mL). Secreted IL-1 $\beta$  in the culture supernatant was quantified by using ELISA. [Results] By using LPS and MSU stimulation, secreted IL-1 $\beta$  showed increasing trend in the case with  $\Delta$ exon2 ASC and ORF3a as compared to the case with wild type ASC and ORF3a. No differences were observed by using LPS and Poly (dA: dT) stimulation. [Conclusions] Our results suggest that SARS-CoV ORF3a may enhance IL-1 $\beta$  secretion via  $\Delta$ exon2 ASC-dependent NLRP3 inflammasome as compared to wild type ASC.

## P52-3

### A study of psychological stress caused by novel coronavirus infection in rheumatoid and collagen disease patients in Gifu Prefecture

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Conflict of interest: None

[Objective] Mental stress has been shown to be a factor in the onset and exacerbation of autoimmune diseases. In this study, we evaluated the impact of the new coronavirus on the daily lives of patients with systemic autoimmune diseases and its effects on mental stress and disease activity. [Method] Patients with systemic autoimmune diseases who visited our hospital during the declaration of a state of emergency in Gifu Prefecture in April 2020 were included in the study. The results of clinical examinations, physical examination data, and outpatient questionnaire surveys were cross-sectionally analyzed. [Results] The subjects were 20 males and 62 females. Regarding the activity of the disease under treatment, 3 responded that it had worsened, 76 responded that it had not changed, and 3 responded that it had improved. The mean value of POMS2, which evaluates the amount of stress, was 80.7 in the exacerbation group, 42.8 in the no change group, and 20.0 in the improvement group, and tended to be higher in the exacerbation group. The most common causes of stress were reduced opportunities to go out (31), avoiding eating out (21), and wearing a mask (20). [Conclusion] In this study, the amount of stress tended to have an effect on the exacerbation of the disease.

## P52-4

### A Study of Patients with COVID-19 Positive Rheumatoid Arthritis

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Conflict of interest: None

[Objective] To examine the background and course of patients with rheumatoid arthritis (RA) who have been positive for COVID-19. [Methods] The period from March 2020 to October 2021, when COVID-19 positive patients were reported for the first time in the prefecture, was investigated. The case which became COVID-19 positive in the patient who was carrying out RA treatment in our department and related hospital was made to be an object. [Results] There were 5 cases, all of which were female. The average age was 49.4 years (38-60) and the history of RA was 17.4 years (6-26). Biologics (ETN 2, TCZ 2) were used in 4 out of 5 cases, and MTX (average 8.5 mg / week) was used in 4 cases. At the time of the positive understanding, the vaccination was not inoculated in 4 cases. After the positive findings, Biologics and MTX indicated that the rest was taken. Three patients were hospitalized and two patients were in a medical institution, and antibody cocktail therapy was performed in one case. All cases were mild and improved. [Conclusions] No cases were severe even in COVID-19 infections using Biologics and MTX and unvaccinated.

## P52-5

### Three cases of connective tissue diseases developed after COVID-19 vaccination

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Conflict of interest: None

[Case 1] 77-year-old woman was under treatment for bronchial asthma. Facial edema appeared after the first COVID-19 vaccination, and worsened and numbness and weakness appeared after second vaccination. On the 23rd day after the second vaccination, she visited our hospital. She was hospitalized and was diagnosed with EGPA due to eosinophilia, elevated serum level of CRP and MPO-ANCA. She was treated with PSL and AZA. [Case 2] 72-year-old man had palpitation and shortness of breath during his walking on the 12<sup>th</sup> day after second vaccination. When he revisited 46<sup>th</sup> day, he had skin sclerosis and proximal muscle weakness. He was diagnosed with systemic sclerosis and polymyositis. He was successfully treated with high dose PSL and Tacrolimus. [Case 3] 62-year-old, male had general malaise 14 days after the first COVID-19 vaccination. On the 19th day, he was hospitalized with a complaint of fever over 38 degrees and respiratory distress. He was diagnosed with anti-ARS antibody-positive interstitial pneumonia. He was refractory to treatment. [Discussion] Cases who developed connective tissue diseases after COVID-19 vaccination should be accumulated.

## P52-6

### SARS-CoV-2 vaccination responses in patients with immune-mediated inflammatory diseases under the ACR guideline

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Conflict of interest: None

[Objectives] To assess the influence the humoral immune response to vaccination against SARS-CoV-2 in patients with immune-mediated inflammatory diseases (IMiD) who followed the American College of Rheumatology (ACR) vaccination guideline. [Methods] Patients visiting outpatient clinic in JR Tokyo General Hospital and Azuma Rheumatology Clinic with (1) no previous history of COVID-19, (2) negative baseline anti-SARS-CoV-2 IgG test, (3) SARS-CoV-2 vaccination between 2 to 4 weeks before serum collection were measured for anti-SARS-CoV-2 IgG, and (4) following ACR COVID-19 vaccine Clinical guidance. Demographic, disease-specific and vaccination-specific data were recorded. Immune responses against the vaccination were divided into weak (W), moderate (M), and strong (S). The results were statistically non-significant; bsDMARDs (W20%, M53.3%, S26.7%/n=30), csDMARDs (W16.7%, M42.9%, S40.5%/n=84), MTX (W15.2%, M47.8%, S37.0%/n=46), TAC (W8.8%, M50.0%, S41.2%/n=34). [Results] Vaccination responses from 99 patients (men 30/female 69, ave 58 years-old) were analysed. [Conclusions] Immune responses against the SARS-CoV-2 were not

significant in patients with IMID under the ACR vaccination guideline.

## P52-7

### Clinical features and outcomes of patients with SARS-CoV-2 infection (COVID-19) in patients with rheumatic diseases and systemic autoimmune diseases

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Division of Rheumatology, Yodogawa Christian Hospital

Conflict of interest: None

[Object] To investigate the characteristics of patients with COVID-19 among patients with rheumatic diseases and systemic autoimmune diseases. [Method] Among the 1247 patients visiting our hospital, the clinical features and outcomes of patients with COVID-19 by October 2021 were examined retrospectively. [Results] The study patients were 9. Age was 52 years, 4 males. 5 are receiving steroids. In all cases, immunosuppressants were used (biological drug in 2 cases, JAK inhibitor in 1 case, rituximab administration history in 2 cases). Rheumatoid arthritis 3 cases (487 patients at our hospital), systemic lupus erythematosus 3 cases (116 patients), ANCA-associated vasculitis (AAV) 2 cases (50 patients), Sjogren's syndrome 2 patients (67 patients), Bechet's disease 1 patient (43 patients). Hospitalized 7 cases, no treatment follow-up 3 cases, oxygen administration 4 cases, artificial respirator management 2 cases. There were two deaths, both 62-year and 82-year-old men. All of them were smokers and were patients with AAV who had coexisting lung disease and CKD and did not respond to the combined treatment of steroids and antiviral drugs. [Conclusion] The fatal case in our department was an elderly man of a systemic autoimmune diseases with a history of smoking and comorbidity.

## P52-8

### Treatment results of Apremilast for Behcet's disease in our hospital

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Conflict of interest: None

[Objective] To determine the therapeutic efficacy and safety of Apremilast for refractory oral ulcers (OU) in Behcet's disease (BD). [Methods] We retrospectively evaluated the therapeutic efficacy and safety up to 24 weeks in patients who were treated with Apremilast for refractory OU of BD at our hospital from September 2019 to September 2021. [Results] 12 patients with BD were enrolled in the study. All patients had active OU. Other active lesions were found in 6 patients with joint symptoms, 1 patient with a genital ulcer, and 4 patients with skin lesions. There were no cases with active major organ involvement. After 24 weeks, Apremilast was continued in 11 patients (91.7%), and OU improved in 9 patients (75%,  $p = 0.003$ ). Joint symptoms improved in 2 patients (33.3%,  $p = 0.16$ ), but genital ulcers and skin lesions did not improve. PSL was continued in 5 patients at a dose of 3.8 mg/day (2.1 - 5.0 mg/day,  $p = 0.94$ ). Adverse events were observed in 4 patients (33.3%), all of which were abdominal symptoms: 1 patient discontinued Apremilast; 1 patient was treated with a reduced dose of Apremilast; the other 2 patients improved with symptomatic therapy only. [Conclusions] Apremilast is effective and well-tolerated in the treatment of refractory OU in BD.

## P52-9

### Changes in SARS-CoV-2 neutralizing antibody over time due to vaccination in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Neutralizing antibody by vaccination against SARS-CoV-2 virus may be insufficiently produced in patients with rheumatoid arthritis (RA) due to disease and drugs used, and changes over time should

be compared and observed with healthy subjects. [Methods] Neutralizing antibodies against the spike protein of SARS-CoV-2 of our hospital staff and RA patients who were vaccinated with Pfizer vaccine between April and July 2021 were quantified. Peripheral venous blood was collected before the first vaccination, at the time of the second vaccination, and 1 month and 3 months after the end of vaccination. There was a pause of medicine for the use of methotrexate, abatacept, and Janus kinase inhibitors. [Results] A study of 54 RA patients found that 49 were positive for antibodies 3 months after vaccination. The antibody titer was inversely correlated with age. The ratio of antibody titers 3 months and 1 month after the end of vaccination was  $0.29 \pm 0.12$  for RA patients and  $0.26 \pm 0.07$  for staff. [Conclusions] Both RA patients and healthy subjects have similar fluctuations in antibody titers, and it is possible that the antibody titers one month after the end of vaccination can be expected to fluctuate thereafter.

## P52-10

### Effect of immunosuppressive therapy on post-immunization antibody titer of coronavirus vaccine

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Conflict of interest: None

[Objective] A broadly targeted vaccine program against the COVID-19 pandemic is underway. The vaccine currently in use is still in its infancy, and its impact in immunosuppressed patients has not been fully explored. [Methods] We measured antibody titers serially in the remaining sera of patients who had blood drawn at the rheumatology department. Elecsys SARS-COV2 and Elecsys SARS-COV2 S were used as test kits. [Results] 898 measurements were performed. Of these, 575 (552 patients) were at least 10 days post second vaccination. Of these, 74 were untreated and 478 were receiving some form of immunosuppressive therapy. When the cutoff value was set at 133, 6 (8.1%) of the untreated group and 200 (41.8%) of the treated group did not meet the cutoff value. Even when the cutoff value was 49.8, 1 patient (1.4%) in the no treatment group and 143 patients (29.9%) in the treatment group did not meet the cutoff value. Multivariate analysis showed that Jak-I, MMF, RTX, TNF-i, ABA, CNI, MTX, and age, in that order, had the greatest effect on antibody titer decline; LEF, csDMARD, AZP, and anti-IL-6 therapy had no effect. [Conclusions] Multiple immunosuppressive treatments affect the ability to produce antibodies after coronavirus vaccination.

## P52-11

### Treatment for patients with rheumatoid arthritis in outbreak of COVID-19

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Conflict of interest: None

[Objective] The rate of new COVID-19 infected patients had become the worst of Japan since April 2021 in Okinawa prefecture. For that reason, governor had announced declaration of state of emergency for long time. So rheumatoid arthritis (RA) patients seemed to have lived staying at home, fearing the risk of infection. This study was carried out how disease activity and treatment of RA patients changed due to outbreak of COVID-19. [Methods] We researched 194 RA patients from April to September 2021, and compared the disease activity, therapeutic agents, enhancing the treatment from October to December 2019. [Results] For RA therapy, methotrexate (MTX), biologics DMARDs (Bio.), and Janus kinase inhibitors were used in 73 (37.6%), in 66 (33.5%), in 2 (1.0%) respectively. There were 12 new RA cases. 53 patients (29.1%) were progressed of disease activity and enhancing the treatment, with age of 64.9 y-o, and disease duration of 13.6 years. 13 were increased MTX, 13 were started Bio, and 27 were added DMARDs. 3 patients infected with COVID-19, and 5 were close contact. [Conclusions] RA Disease activity has increased by about 30%. It is expected that RA patients were staying at home and taking good measures against infection as a reason for the low number of COVID-19 infections.



## P52-12

### Casirivimab-Imdevimab for COVID-19 in patients with rheumatic disease

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Conflict of interest: None

[Objective] There have been reported only a few cases of Casirivimab-Imdevimab (REGN-COV2) use in patients with rheumatic disease (RD). We herein reported our division's experience. [Case] We extracted data of patients with RD who had admitted our hospital and had been prescribed REGN-COV2 for the treatment of COVID-19. Case 1 was a 64-year-old female with RA. Case 2 was a 54-year-old female with SLE, LN, APS and RA. Case 3 was a 33-year-old, 33 weeks pregnant female with SLE and LN. Disease activity of all cases were stable. All cases were diagnosed with COVID-19 based on fever, respiratory symptoms and positive SARS-CoV-2 PCR test. The severity of COVID-19 was moderate in case 1 and 2, and mild in case 3. All patients were on treatment with GCs, and case 3 had a risk factor for progression (i.e., late pregnancy). All patients responded well to REGN-COV2 without any serious AEs. Only case 1 had a flare of RA due to discontinuation of DMARDs, but the two SLE cases remained in remission and case 3 was able to deliver normally. [Clinical implication] Despite results from a small number and short observation period, our experience suggests that REGN-COV2 is effective and safe for RD patients with COVID-19. In addition, REGN-COV2 did not exacerbate the disease activity.

## P52-13

### COVID-19 vaccination under continuous JAK inhibitor: case reports

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Conflict of interest: None

[Purpose] Although the effects of RA and DMARDs on the production of neutralizing antibodies are unknown. In this study, we report the antibody levels of SARS-CoV-2S in three patients who were vaccinated while on JAK inhibitors due to severe RA. [Case 1] A 79-year-old woman was vaccinated with filgotinib because of a recent history of relapsing arthritis in the large joints. DAS28-CRP was 1.7/1.71/1.42 just before vaccination, 3 weeks after vaccination, and 3 weeks after the second vaccination, and IgG S antibody 86.2 AU/ml was confirmed. [Case 2] A 76-year-old woman had a history of RA flare after 3 days of withdrawal of Upadacitinib (UPA) due to infection. DAS28-CRP was 2.59/3.04/3.69. No antibody was detected. [Case 3] A 31-year-old woman was vaccinated 3 months after the introduction of UPA due to a flare-up of hand arthritis. DAS28-CRP was 1.75/2.25/2.22 and IgG S antibody was 113.9 AU/ml. [Conclusion] The mRNA vaccine is a potent inducer of type 1 IFN, and there is concern that continued use of JAK inhibitors may theoretically reduce the production of neutralizing antibodies. However, the antibody production was confirmed in two of our cases under continuous JAK1-selective inhibitors. It is possible that the disease activity at the time of vaccination affected antibody production.

## P52-14

### COVID19 vaccine antibody titer in rheumatoid arthritis during immunosuppressive therapy

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Utazu Hospital

Conflict of interest: None

[Objective] COVID19 vaccination is recommended for rheumatic diseases during immunosuppressive therapies. We examined COVID19 vaccine antibody titer during immunosuppressive therapy. [Methods] Rheumatoid arthritis (RA) treated with MTX, Abatacept (ABT), JAK inhibitors and healthy volunteers (HC) were included. Antibody titers (U/mL) at 2, 8, 16 and 24 weeks after vaccination were measured with Elecsys® Anti-SARS-CoV-2 S RUO (Roche Diagnostics). Fifteen (U/mL) or more were positive. [Results] RA135 (MTX83, ABT37, JAK10), HC44. Antibody titers increased from 2 to 8 w for both RA and HC. The antibody titer at 8 w was HC> RA, and in RA, MTX, JAK>ABT. The results of 16 w or later are under investigation when making this abstract. [Conclusions] It was suggested that MTX, ABT, and JAK inhibitors, especially ABT inhibitors may have an inhibitory effect on antibody production of the COVID19 vaccine. Appropriate infection control were required even after the vaccine.

## P52-15

### A report of a married couple with rheumatoid arthritis who developed COVID-19 simultaneously

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Conflict of interest: None

[Case 1] a 74-year-old male with a history of RA for 25 years. He had received abatacept and MTX for 9 years and DAS28-CRP was 1.9 one month before the onset of COVID-19. Fever emerged with sore throat in April 2021. PCR test was positive and chest radiographs showed mild pneumonia. He recovered well without oxygen therapy. [Case 2] a 70-year-old female with a history of RA for 17 years. Infliximab biosimilar and MTX were started 6 years ago. The patient discontinued the biosimilar in December 2020. Thereafter, joint symptoms worsened. She was transferred to the ER 3 days after the admission of her husband. SpO2 was 68% and chest radiographs revealed pneumonia. She was immediately given ventilator treatment in the ICU. She was treated with dexamethasone, remdesivir, and tocilizumab and saved from death. [Clinical significance] Recent studies reported that baseline use of specific medications for RA and disease activity are associated with COVID-19 severity and mortality in patients with RA. In this report of a married couple with RA, a husband with disease remission did not worsen and a wife with high disease activity after stopping infliximab biosimilar progressed to severe COVID-19. Discontinuation of biologic DMARDs should be considered carefully in the COVID-19 pandemic.

## P52-16

### A case of rheumatoid arthritis who showed exacerbation of arthritis after COVID-19 vaccination

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Conflict of interest: None

83 year old female was diagnosed as rheumatoid arthritis (RA) eight years ago because she had polyarthritis with both rheumatoid factor (RF) and anti-CCP antibody positivity. Methotrexate (MTX) 8 mg / week was initiated and her joint symptoms improved. Since the next day after the second COVID19 vaccination in June, polyarthralgia and general pain appeared throughout the body. She showed elevated serum CRP and RF on blood sampling. Although she was given celecoxib 200 mg / day and dexamethasone 2.5 mg / day, her symptoms gradually worsened and she was hospitalized due to difficulty moving. on Ultrasonography revealed that she had biceps tendon sheath synovitis and deltoid bursitis. Her blood culture and tumor markers examinations were negative. CT also detected any abnormal findings. She was diagnosed as the exacerbation of RA due to COVID19 vaccination 7.5 mg daily of prednisolone (PSL) was effective to improve her joint symptoms and serum CRP and RF levels. Although many cases of exacerbation of RA after vaccination have been reported, the reports of RA exacerbation due to COVID19 vaccination is rare. We herein report a RA patient who were exacerbated by COVID19 vaccination and discuss in relation to the literature review.

## P52-17

### Two cases of polymyalgia rheumatica that occurred after COVID-19 vaccination

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Conflict of interest: None

Polymyalgia rheumatica (PMR) is an inflammatory disease that affects the shoulder and pelvic girdles in aged persons. We experienced two cases of PMR that occurred after COVID-19 vaccination. Case 1 is an 81-year-old man. He experienced shoulder girdle pain, finger joint pain, and peripheral edema after COVID-19 vaccination. Blood tests showed WBC 8100/ $\mu$ l, CRP 13.1 mg/dl, and rheumatoid factor and anti-CCP antibody were negative. In ultrasonography, synovitis of the biceps tendon and the finger and wrist joints were observed. The patient was diagnosed with PMR and RS3PE syndrome and received prednisolone (PSL) and salazopyridine (SASP). Case 2 is an 81-year-old woman. She felt pain in the shoulder girdle and pelvic girdle after vaccination and was unable to walk. Blood tests showed high inflammatory findings and negative serum reaction. Ultrasonography revealed synovial fluid in the biceps tendon and synovitis in the fingers and wrists. The patient was diagnosed with polymyalgia rheumatica and RS3PE syndrome. After being treated with PSL and SASP, she soon became able to walk. We report on the association between PMR and COVID-19 vaccines.

## P52-18

### A case of RS3PE syndrome that developed after COVID-19 vaccination

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Conflict of interest: None

An 81-year-old woman received COVID-19 vaccination (BNT162b2) in June of year X. The next day, she developed fever; on the ninth day after vaccination, she noticed oedema in all four limbs and bilateral arthralgia in the hands and feet. Neither swelling nor tenderness was observed in the small to large joints. However, marked oedema on the dorsa of both hands and feet and limited elevation of the shoulder joints were noted. Blood tests showed elevated levels of CRP and MMP-3. She tested negative for rheumatoid factor and anti-CCP antibody. Ultrasonography did not show synovitis and bone erosion in the joints, but showed tenosynovitis in the finger flexor tendon and posterior tibial muscle tendon. No complications of malignant tumours were observed. We diagnosed the patient with RS3PE syndrome and started prednisolone therapy. The oedema and arthralgia improved rapidly, and the patient was discharged from the hospital. The mRNA vaccine BNT162b2 is expected to have adjuvant effects mediated by Toll-like receptors (TLR)-7 and TLR-9 in the mRNA itself. Although a relationship between the onset of a related disease, polymyalgia rheumatica, and TLR has been suggested, the details are yet to be clarified. Herein, we report our case with a review of the literature.

## P52-19

### Two Cases of Rheumatic Disease Exacerbated by COVID-19 mRNA Vaccination

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Conflict of interest: None

[Case 1] A 79-years old man. He was diagnosed as microscopic polyangiitis 2 years and 1 month later, Steroid pulse therapy combined with MTX induced remission. 7 months ago, the MPO-ANCA turned positive again, but there was no rise in CRP or symptoms. However, he developed fever and night sweats 10 days after vaccination with mRNA vaccine (Pfizer). He was diagnosed as recurrence of vasculitis, and hospitalization

and increase of steroid and MTX were required. [Case 2] A 77-years old woman. She developed RA 2 years ago. The combination of interstitial pneumonia was also recognized. The activity was very high, and the subcutaneous injection of tocilizumab was initiated 1 year and 10 months ago, which lowered the disease activity. However, exacerbation occurred 3 months ago, and tocilizumab was switched to peficitinib 2 months ago. Peficitinib was remarkably effective, and the disease activity rapidly became low. However, when peficitinib was withheld for 7 days while receiving the mRNA vaccine (Pfizer) twice, the disease worsened again, and could not be controlled even if peficitinib was resumed. [CLINICAL SIGNIFICANCE] The mRNA vaccines elicits a very strong immune response, and should be permitted after careful consideration of indications for the patients of rheumatic diseases.

## P52-20

### Coronavirus disease 2019 (COVID-19) in patients with rheumatic disease: a case series

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Conflict of interest: None

[Objective] To evaluate clinical characteristics and outcome of COVID-19 hospitalized patients with rheumatic diseases. [Methods] COVID-19 hospitalized patients were assessed by a retrospective chart review. [Results] There were 12 COVID-19 patients with rheumatic diseases in our hospital. Rheumatic diseases were Rheumatoid arthritis (N=5), Polymyositis/dermatomyositis (N=2), Polymyalgia rheumatica (N=2), systemic lupus erythematosus (N=1) and Behcet disease (N=1). The mean age was 68.1 years, 41.6% were male. The severity was 3 mild, 8 moderate and 1 severe. The most common route of infection was household transmission (41.7%) and 91% patients had risk factors for COVID-19. Five patients were on DMARDs (1 on bDMARD) and corticosteroids were used in 9 patients (mean dose 5.8 mg/day). Rheumatic disease was stable in all patients. However, one patient with severe interstitial pneumonia deceased. [Conclusions] Households are important venues for transmission, and the underlying medical conditions and corticosteroid use are at risk for COVID-19 in the patients with rheumatic diseases.

## P52-21

### A case of SLE in which the condition deteriorated due to the relapse of COVID-19

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Conflict of interest: None

[Case] 39 y.o. F [medical history] Lupus nephritis was diagnosed 8 months ago, and 6 months ago, after a steroid pulse, remission was induced with PSL 60 mg / day, tacrolimus 3 mg, and mycophenolate mofetil 3 g. Two months ago, he became a close contact with COVID-19, and PCR was performed, and the diagnosis of COVID-19 was made and the patient was isolated from the negative pressure chamber. Two weeks after the positive confirmation, the patient was released from quarantine and discharged. Loss of appetite appeared from 1 month ago, and dysgeusia and olfactory dysfunction appeared from 2 weeks ago, and oral intake gradually became difficult. Since she also had difficulty moving, she was admitted to the hospital outside the appointment. She was admitted to the hospital because of difficulty in moving, and was diagnosed with a recurrence of COVID-19. [Progress] At the time of admission, renal dysfunction worsened, electrolyte abnormalities, and anemia progressed, PSL increased. His dysgeusia and olfactory dysfunction gradually improved, and he was discharged after adjusting the drug. [Conclusions] It should be noted that the relapse of COVID-19 may exacerbate the current disease.

## P52-22

### A case of severe COVID-19 in elderly rheumatoid arthritis successfully treated with tocilizumab

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Conflict of interest: None

[Case] A female in her 80s was treated for rheumatoid arthritis (RA) and systemic sclerosis for 24 years. She hadn't been vaccinated against coronavirus. She had contact with a coronavirus-positive patient and suffered from cough 3 days before her transfer to our hospital. Chest HRCT showed diffuse ground glass opacities (GGO) in both lungs. She was positive for SARS-CoV-2 PCR and PaO<sub>2</sub> was 51.9 mmHg under a 6 L/min O<sub>2</sub> mask. Based on the imaging findings, she was diagnosed severe COVID-19. Intravenous methylprednisolone pulse and remdesivir were started and oxygen demand improved temporarily, but on her 6th hospital day, oxygen saturation deteriorated again to 93% SpO<sub>2</sub> under 15 L/min O<sub>2</sub> mask. Chest HRCT showed new GGO in both lungs, which was judged to be another exacerbation of COVID-19. Intravenous tocilizumab (8 mg/kg) was administered for 2 days. Oxygen demand improved and chest X-ray showed diminishing GGO. Remdesivir was administered for 10 days and corticosteroids for 25 days. She was discharged on her 36th hospital day. [Clinical Significance] Usefulness of tocilizumab was suggested against severe COVID-19 complicated with elderly RA.

## P52-23

### A case of polyarthritis that developed and persisted after administration of COVID-19 mRNA vaccine

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Division of Rheumatology, National Hospital Organization Disaster Medical Center

Conflict of interest: None

An 87-year-old woman, who was vaccinated with Pfizer-BioNTech COVID-19 vaccine, presented with numbness of the left finger and left wrist joint pain that appeared 7 days after vaccination. She developed pain in the right shoulder 45 days after vaccination. Ultrasonographic study revealed synovial thickening of the left wrist joint and synovial fluid retention in the right subdeltoid bursa. Nerve conduction study revealed the findings of left carpal canal syndrome. Immunology findings were negative, including for rheumatoid factor, anti-cyclic citrullinated peptide, and antinuclear antibody. Serum CRP was high as 2.16 mg/dl. HLA-B27 was negative. Intra-articular injection of triamcinolone acetonide into the left and right shoulder joints improved the symptoms, however, her symptoms relapsed and swelling of the left 2nd MCP joint also appeared. Initiation of oral methotrexate improved her symptoms. Although the exact causal relationship is unknown, arthritis in this case developed after the vaccination and affected joints expanded. It has been reported that some cases of arthritis after other vaccinations such as HBV vaccine had a persistent course, suggesting that similar caution may be required in treatment in our case.

## P52-24

### A case of *Pneumocystis pneumonia* referred as COVID-19

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Department of Rheumatic Disease, Tama-Hokubu Medical Center, Tokyo Metropolitan Health and Medical Treatment Corporation

Conflict of interest: None

[Background] The care of critically ill patients with fever tended to be delayed, emerging COVID-19 in early 2020. [Case] An 85-year-old woman with a history of rheumatoid arthritis was started on etanercept six months ago. On day X-3, she had a fever of 38°C with chills and no improvement. She saw her family doctor on day X, who referred her to our hospital for suspected COVID-19. She was admitted to our hospital as an emergency on the same day. Although the chest CT image implied COVID-19, the differential diagnosis included *pneumocystis pneumonia*

(PCP), atypical pneumonia, and pulmonary tuberculosis. The test result showed that SARS-CoV-2 PCR negative and *Pneumocystis jiroveci* PCR positive, and ST combination and glucocorticoid were continued. The patient's respiratory condition improved, and she was extubated on day X+9. Soon after, her respiratory failure deteriorated as lung candidiasis, and she passed away on day X+13. [Discussion] In the COVID-19 epidemic, the diagnosis of diseases that generally require urgent treatment might be delayed. In immunosuppressed patients, other infectious diseases should be considered, especially PCP, for which a delay in treatment can be fatal.

## P52-25

### A case of giant cell arteritis and polymyalgia rheumatica that developed after COVID-19 vaccination

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Conflict of interest: None

A 74-year-old man received COVID-19 vaccination (BNT162b2) in June of year X. After vaccination, he developed fever and experienced left temporal pain and arthralgia in both shoulders, fingers, and knees. The symptoms were exacerbated, therefore, he was referred to our hospital. Distension of the frontal branch of the superficial temporal artery, tenderness of the whole scalp, and tenderness and limited flexion of the shoulder joints were observed. Ultrasonography revealed thickening of the vascular walls of the left common carotid artery and superficial temporal artery as well as synovitis of the biceps tendons on both sides. Contrast-enhanced CT revealed vascular wall thickening at the origins of the brachiocephalic artery, common carotid artery, and subclavian artery. We diagnosed the patient with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) and initiated prednisolone therapy. After the medication was started, headache and arthralgia resolved quickly. The mRNA vaccine BNT162b2 is expected to have adjuvant effects mediated by Toll-like receptors (TLR)-7 and TLR-9 in the m-RNA itself. The relationship between GCA/PMR and TLR has been suggested, however, the details are yet to be clarified. Herein, we report our case with a review of the literature.

## P53-1

### Analysis of inflammatory biomarkers in patients with septic and non-septic knee arthritis

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Conflict of interest: None

[Objective] We analyzed clinical inflammatory biomarkers in patients with septic and non-septic knee arthritis. [Methods] We retrospectively reviewed medical records of 24 patients with septic and 97 patients with non-septic knee arthritis, treated between May 2018 and September 2021. [Results] Non-septic knee arthritis included osteoarthritis, pseudo-gouty, gouty, and rheumatic arthritis. Hematological examination showed the white blood cell (WBC) count, neutrophil sequestration, CRP, and procalcitonin levels were higher in the septic arthritis group. Joint fluid analysis revealed a higher WBC count and neutrophil sequestration in the septic arthritis group. The articular glucose concentration and ratio between the articular and hematic glucose concentrations were lower in the septic arthritis group. Receiver operating characteristic curve analysis showed that the ratio between the articular and hematic glucose concentrations was the best potential diagnostic predictor of septic arthritis. [Conclusions] The ratio between the articular and hematic glucose concentrations, which was the best potential diagnostic indicator to distinguish between septic and non-septic arthritis, may effectively estimate the probability of septic knee arthritis in emergency medical practice.



### P53-2

#### The effect of periodontitis severity on the clinical response to biological disease-modifying antirheumatic drug therapy for 1 year in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] The present study aimed to assess whether periodontitis severity affects the clinical response to biological disease-modifying antirheumatic drugs (bDMARDs) therapy for 1 year in patients with rheumatoid arthritis (RA). [Methods] We conducted a retrospective study that collected data from 50 patients with RA who had received corticosteroid, conventional synthetic DMARDs, or non-steroidal anti-inflammatory drugs before (baseline) and after 1 year of bDMARD therapy. Rheumatologic conditions were compared between the groups, as classified by the Centers for Disease Control Prevention (CDC)/ American Academy of Periodontology (AAP) case definitions. [Results] Twenty-eight patients with no or mild periodontitis showed significantly greater decreases in changes in the Clinical Disease Activity Index (CDAI) and tender and swollen joint count than 22 patients with moderate and severe periodontitis ( $p = 0.02$ ,  $p = 0.01$ , and  $p = 0.03$ ). Both bivariate and multivariate analyses revealed a significantly positive association between the baseline CDC/AAP definitions and CDAI changes ( $p = 0.005$  and  $p = 0.002$ ). [Conclusions] Baseline periodontitis severity according to the CDC/AAP definitions is associated with the clinical response to bDMARDs therapy for 1 year in patients with RA.

### P53-3

#### Analysis of cytomegalovirus infection in our department and comparison of cytomegalovirus antigenemia assay with blood cytomegalovirus DNA PCR

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Conflict of interest: None

[Objective] To evaluate the clinical usefulness of cytomegalovirus (CMV) antigenemia assay and blood CMV DNA polymerase chain reaction (PCR) in patients with collagen tissue disease (CTD), and to assess the incidence of cytomegalovirus infection in our patients. [Methods] Medical records of the hospitalized patients who were treated in our department after February 2021 were reviewed retrospectively. Whole blood samples from the patients were analyzed by CMV antigenemia assay and CMV DNA PCR. Clinical outcome according to the results were analyzed. [Results] A total of 148 patients are enrolled in this study and 324 samples were analyzed. The median age was 64 years, and the male-female ratio was about 1: 2.5. When the antigenemia assay and the PCR results were compared, the positive and negative concordance rates were 97.9% (47/48) and 72.8% (201/276), respectively. While the results of the antigenemia assay were highly correlated with that of the PCR, the results of PCR relatively deviated from the results of the antigenemia assay when the number of positive cells in the antigenemia assay was small. [Conclusions] It is important to detect CMV infection at an early stage. To treat them at an appropriate time, further analysis for CMV detection is required.

### P53-4

#### Examination of 24 patients with rheumatoid arthritis with nontuberculous mycobacterial disease

Hironobu Kosugiyama

Department of Orthopaedic Surgery, Nagoya University Hospital

Conflict of interest: None

[Object] To investigate the clinical feature of patients with rheumatoid arthritis with nontuberculous mycobacterial disease (NTM). [Methods]

Subjects were 24 RA patients who have nontuberculous mycobacterial disease. We retrospectively investigated patient background, clinical course, and disease activity. [Results] The patient background was 69.9 years on average, 20 females (83.3%), and the average duration of RA was 11.3 years. 9 methotrexate (MTX) and 10 PSL, 4 biologics (3 cases of ABT, 1 case of TCZ), 1 molecular target drugs (BAR) were used, and 1 case introduced a biologics after lung resection. Mean DAS28-CRP averaged 2.3 (remission to low disease activity: 16 cases, medium to high disease activity: 8 cases). The average duration of NTM disease was 6.5 years. Anti-MAC antibody was positive in 6 cases, and the identified bacterial species were *M. avium* in 12, *M. intracellulare* in 8, *M. abscessus* in 3, and *M. goodii* + *avium* in 1 case. In a case of NTM (*M. abscessus*) with interstitial pneumonia, death due to the onset of pulmonary aspergillosis. [Conclusion] Many reports suggest biologics and molecular-targeted drugs can be used in RA patients with NTM, but it is necessary to pay attention to the risk assessment of patients with other complications.

### P53-5

#### Recurrence of *Pneumocystis jirovecii* Pneumonia after the restart of the biologics in patients with rheumatoid arthritis who recovered from *Pneumocystis jirovecii* Pneumonia

Shin-ichiro Omura<sup>1</sup>, Toshiaki Miyamoto<sup>1</sup>, Daisuke Shichi<sup>2</sup>

<sup>1</sup>Seirei Hamamatsu General Hospital, <sup>2</sup>Seirei Mikatahara General Hospital

Conflict of interest: None

(Object) To investigate the recurrence of PCP after the restart of the biologics in patients with RA who recovered from PCP. (Methods) We retrospectively analyzed consecutive patients with RA who recovered from PCP during biologic treatment. The primary outcomes were the recurrence of PCP and development of the other severe infections after the restart of biologics. (Results) Twenty-two patients could be analyzed in this study. Seventeen patients restarted biologics (Restart group) and 5 patients did not restart (non-Restart group). Twenty-one patients received secondary PCP prophylaxis. The median follow-up duration was 3.7 years. There were no significant differences regarding clinical characteristics including age, gender, chronic lung disease, and other immunosuppressive therapy. The development of PCP rate in the Restart group and non-Restart group was 5.9% and 0.0%, respectively and the development of the other severe infections in the Restart group and non-Restart group was 41.7% and 0.0%, respectively. (Conclusions) Biologics might be able to restart after the recovery of PCP if patients receive secondary PCP prophylaxis but the other severe infection rate was high compared to the non-restart biologics.

### P53-6

#### A case of varicella-zoster virus meningoencephalitis and vasculopathy requiring differentiation from central nervous system lupus

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Showa University Northern Yokohama Hospital

Conflict of interest: None

A 61-year-old woman who had been treated with prednisolone 10 mg/day and tacrolimus 2 mg/day for systemic lupus erythematosus. One day she noticed weakness in her extremities, difficulty walking and speaking. Her symptoms gradually worsened, and she was taken to our hospital because of disorder of consciousness with GCS3 (E1V1M1) and fever of 39°C. FLAIR images of head MRI showed diffuse high-signal areas in whole cerebrum. Spinal fluid examination showed an increased cell count of 53/ $\mu$ l and protein of 190 mg/dl. We suspected central nervous system lupus, and started steroid pulse, high-dose steroid therapy and acyclovir (ACV) for viral meningitis. Plasma exchange was performed due to prolonged unconsciousness, but she subsequently developed a right subcortical hemorrhage with compression to the brain trunk and underwent emergency craniotomy to remove the hematoma. Subsequent spinal fluid examination revealed varicella-zoster virus (VZV)-DNA (deoxyribonucleic acid) positivity, so we diagnosed the cerebral hemorrhage due to VZV encephalomyelitis and VZV vasculopathy. Steroids were tapered, and she was treated with ACV for 21 days. Cranioplasty was performed, and her level of consciousness improved to GCS9 (E4VTM5), but she still had higher-order functional disability.

## P53-7

### Longitudinal trends of herpes zoster associated with rheumatoid arthritis patients in NinJa

Takao Yamanaka<sup>1</sup>, Toshihiro Matsui<sup>1</sup>, Shigeto Tohma<sup>2</sup>

<sup>1</sup>National Hospital Organization Sagami Hospital, <sup>2</sup>National Hospital Organization Tokyo National Hospital

Conflict of interest: None

[Background] It is well known that herpes zoster (HZ) risk is elevated in Rheumatoid arthritis (RA) compared with the general population, and JAK inh. increased HZ risks on clinical trials. [Objective] To investigate the incidence for HZ in RA in daily clinical practice after approval of JAK inh. [Methods] Using data of NinJa (National database of rheumatic diseases in Japan) between Apr 2015 and Mar 2021, incidence rate of HZ in RA patients were calculated and performed risk for each drug used. [Results] The usage rate of JAK inh. was 1.03% in 2015 (valid responses: 13859 cases), and then increased over time to 5.25% in 2020 (valid responses: 11703 cases). Although there has been a slight increase and a slight decrease from year to year between 2015 and 2020, the age-adjusted incidence rate of HZ was 10.27, 10.35 per 1000 patients-years in 2015, 2020 respectively. Of the 1000 patients who received the JAK inh., it occurred 8.57% of 144 patients in 2015. Despite the yearly increase of patients receiving the drug, the incidence of HZ decreased year by year. Only 3.64% of the 614 patients who received JAK inh. developed HZ. [Conclusions] While the usage rate of JAK inh. was increasing year by year, the incidence of HZ among these drugs administers was decreasing year by year.

## P53-8

### A case of multiple pulmonary nodules and disseminated central nervous system lesions due to *Nocardia farcinica* after remission induction therapy for systemic lupus erythematosus leading to dialysis kidney

Mayumi Nonaka, Yumiko Wada, Katsumasa Oe, Ayana Okazaki, Takeshi Shoda, Tohru Takeuchi

Osaka Medical and Pharmaceutical University

Conflict of interest: None

[Case] 57-year-old woman. She was diagnosed as systemic lupus erythematosus (SLE) in October X-1 with positive antinuclear antibody and anti-ds-DNA antibody, and renal pathology, in the wake of acute kidney injury. She was refractory to multiple immunosuppressive agents and was placed on maintenance dialysis. Rituximab was added and we tapered off steroid. Airway symptoms and elevated CRP were observed from April X, chest CT showed multiple nodules in the right lung, and sputum culture showed *Nocardia*. Head MRI showed a small nodule in the right brain, which was diagnosed as multiple pulmonary nodules and central nervous disseminated lesions due to *Nocardia*. We started treatment with meropenem (MEPM) and sulfamethoxazole/trimethoprim (SMX/TMP). MEPM was changed to sulbactam/ampicillin (SBT/ABPC) after identification of species *Nocardia farcinica* and susceptibility. In July, clavulanic acid/amoxicillin (CVA/AMPC) and SMX/TMP started, and as of October, the disease has passed without relapse. [Discussion] We have experienced 7 cases of Nocardiosis, and this is the third case of SLE. Nocardiosis is often associated with lung involvement, with hematogenous dissemination in about one third of cases. We reviewed the clinical features of seven cases of Nocardiosis and report them.

## P53-9

### A case of cervical pyogenic lymphadenitis caused by *Mycobacterium haemophilum* during treatment for rheumatoid arthritis (RA)

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Conflict of interest: Yes

[Chief complaint] neck swelling [History of present illness] A 69-year-old woman with methotrexate and etanercept for RA came to our hospital with slowly progressive swelling of the left anterior neck. She denied pain,

fever, weight loss, and sweating. [Clinical course] We suspected lymphoproliferative disease and tuberculosis (TB) infection due to treatment with methotrexate and etanercept. Three sputa acid-fast bacillus (AFB) cultures were negative. A contrast-enhanced CT scan showed necrotic lymph nodes in the left mandible and supraclavicular lymph nodes. Pathology of the neck lymph node showed no malignant findings, and Ziehl-Neelsen Stain showed AFB. TB and MAC PCR tests, cultures were negative. Since the cervical lymph nodes were enlarged again, we performed another biopsy and sent it to the Research Institute of Tuberculosis for further examination. We identified *M. haemophilum* by genetic analysis. [Clinical significance] *M. haemophilum* is an AFB that requires specific conditions for culture and causes skin infections in immunocompromised patients. The clinical course and causative organisms of AFB are becoming more diverse.

## P53-10

### A case of disseminated nontuberculous mycobacteriosis secondary to anti-Jo-1 antibody-positive antisynthetase syndrome treated as seronegative rheumatoid arthritis

Eisuke Kanematsu, Naoki Tanomogi, Nanae Okimoto, Tomoko Sano, Daisuke Asatori, Kazusa Saegusa, Masahiro Iida, Yoshitaka Ueda, Eisuke Takamasu, Kae Onishi, Yuji Miyoshi, Masako Utsunomiya, Naoto Yokogawa, Kota Shimada

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

[Case] A woman in her 70s with a history of tuberculosis, was treated with prednisolone for antisynthetase syndrome with positive anti-Jo-1 antibody, which developed 15 years ago as her symptoms were myositis and interstitial pneumonia. Two years ago, seronegative rheumatoid arthritis was diagnosed from polyarthritis. She was treated with biologic drugs, but arthritis was uncontrollable. She was referred to our hospital and Baker's cysts were punctured, which *Streptococcus anginosus* and *Mycobacterium avium* (*M. avium*) were identified; CT showed cavitation of lungs and abscesses on buttocks and left lower leg. Bronchoscopy identified *M. avium* and *Mycobacterium intracellulare*. Disseminated nontuberculous mycobacteriosis (NTM) infection was diagnosed and drainage of the abscess and antibiotic treatment were started. She will receive antimicrobial therapy for more than 2 years. [Discussion] Symptoms improved after starting antibiotics, suggesting that polyarthritis was caused by disseminated NTM infection. This is a novel case of disseminated NTM infection in a non-HIV patient, which required differentiation from antisynthetase syndrome and rheumatoid arthritis.

## P53-11

### Influence of intramuscular injection of Shingrix for the disease activity of RA

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Department of Immuno-Rheumatology Center, Amanokawa Hospital

Conflict of interest: None

[Objective] Purpose of this study was to examine whether intramuscular injection of Shingrix (recombinant zoster vaccine) affect the disease activity of rheumatoid arthritis (RA). [Methods] We evaluated DAS28-ESR before and after intramuscular injection of Shingrix. Patients, who started or added new treatment before 3 months, were excluded. [Results] Two patients were male and 23 patients were female. The mean age was 74.2±8.8 years, the mean disease duration was 10.3±12.2 years. Seventeen patients were positive for anti-CCP antibody, and seventeen patients were positive for RF. Methotrexate was used in 7 patients, PSL in 8 patients, TAC in 7 patients. Biologic DMARDs or targeted synthetic DMARDs was used in 19 patients. The mean DAS28-ESR was 2.42±1.14. DAS28-ESR, CRP, and ESR was not significantly changed after intramuscular injection of Shingrix. [Conclusions] Intramuscular injection of Shingrix dose not affect the disease activity of RA.

## P53-12

### **A case of flexor tenosynovitis diagnosed as a combination of nontuberculous mycobacteria infection and rheumatoid arthritis**

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Conflict of interest: None

[Objective] Rheumatoid arthritis (RA) tenosynovitis is difficult to discriminate from nontuberculous mycobacteria (NTM) infection. Herein, we report a case of a patient diagnosed with RA with unilateral tenosynovitis due to NTM. [Case report] A 76-year-old woman was referred to our hospital to undergo treatment for flexor tenosynovitis with carpal tunnel syndrome. Her right hand and wrist were tender and swollen. Ultrasonography revealed synovitis at the bilateral flexor tendon and wrist joint. Blood examination showed slight elevation of the erythrocyte sedimentation rate, and the rheumatoid factor was negative. Contrast-enhanced magnetic resonance imaging of both hands showed synovitis in the flexor tendons and wrist joints as well as bone marrow edema of the carpal bones. As RA was suspected, prednisolone was administered to reduce the swelling. Tenosynovectomy with carpal tunnel release was performed to treat persistent median neuropathy. A culture of excised synovium revealed *Mycobacterium intracellulare*, which supported the decision to administer antituberculosis drugs instead of prednisolone. Polyarthritides appeared during the course of the treatment, which led to the diagnosis of combined RA. After methotrexate administration, swelling improved.

## P53-13

### **Two cases of Rheumatoid Arthritis Complicated with Legionella pneumonia**

Yumeko Taniguchi, Ryosuke Hanaoka, Toshiko Haginoya, Kohdai Konno, Satoki Anzai, Mai Yanagida

Department of Rheumatology, Kamitsuga General Hospital

Conflict of interest: None

[Case 1] A 53-year-old woman admitted our hospital complaining dyspnea. She was diagnosed that she had rheumatoid arthritis (RA), and was prescribed methotrexate (MTX) 14 mg/day, prednisolone (PSL) 5 mg/day, leflunomide (LEF) 10 mg/day. Five days before admission, she developed fever, cough, headache, general malaise, and dyspnea. Urinary antigen against *Legionella pneumophila* revealed positive. Although she was administered pазufloxacin (PZFX) 2000 mg / day and azithromycin (AZM) 500 mg / day, she required mechanical respiratory management. [Case 2] A 67-year-old man admitted our hospital presenting high fever. Nine years before, he was diagnosed that he had rheumatoid arthritis (RA), and was prescribed MTX 10 mg/day, PSL 3 mg/day. Urinary antigen against *Legionella pneumophila* revealed positive. Although he was administered PZFX 500 mg / day and azithromycin (AZM) 500 mg / day, he required mechanical respiratory management and continuous hemodiafiltration. [Clinical significance] *Legionella pneumonia* is significantly frequent among RA patient who are received biologic agent. However, it is rarely developed among those without biologic agent.

## P53-14

### **Clinical study of pneumocystis pneumonia in patients with rheumatoid arthritis in our center**

Motoko Ishida, Takafumi Tanaka, Tomoaki Iwanaga, Masataka Nakamura, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Tomoya Miyamura

Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center

Conflict of interest: None

[Objectives] To investigate the clinical features of rheumatoid arthritis (RA) patients with pneumocystis pneumonia (PCP). [Methods] Thirteen RA patients who treated PCP in our department from January 2009 to De-

cember 2020 were enrolled. [Results] The average age at onset of PCP was 64 years old, and 9 patients were woman. Steinbrocker stage was I:4, II:1, III:2, IV:4. All patients were treated with csDMARDs (MTX 12, TAC 1), 11 patients with prednisolone (PSL); average 6.6 mg /day, 7 patients with bDMARDs or tsDMARDs. Two patients had complication of interstitial lung disease (ILD), 2 patients had diabetes mellitus. All patients showed elevated level of B-D galcan (average cut off 118.3), 30% showed PCP-DNA positive. All patients treated with Co-trimoxazole. Two patients had adverse drug events and one death was observed due to PCP. Six patients had same medication before PCP onset as RA treatment post PCP, and MTX was discontinued in 6 patients. [Conclusion] Our data indicated that PCP patients with RA showed relatively good outcomes. No PCP patient was experienced who received Co-trimoxazole prophylaxis, suggesting the importance of early intervention and preventive treatment of PCP.

## P53-15

### **One case of rheumatoid arthritis in which cytomegalovirus infection and Epstein-Barr virus infection were complicated by methotrexate poisoning and caused cytopenia**

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Higashihiroshima Memorial Hospital

Conflict of interest: None

Rheumatoid arthritis (RA) is adjusted to lead to remission by administration of immunosuppressive drugs such as methotrexate (MTX). However, it should be noted that various side effects and infectious diseases may occur in the process. The case was a 71-year-old woman. She had been treated with MTX at a nearby doctor. At the age of 70, she was referred to our hospital because of fever and increased inflammatory reaction that lasted for 2 weeks. The blood test showed pancytopenia, and MTX was being taken during fever. Therefore, administration of leucovorin as MTX poisoning was started at the time of admission. Although the white blood cell count tended to improve, fever persisted and cytomegalovirus C7HRP was reported to be strongly positive. Administration of ganciclovir was started as a cytomegalovirus infection, and antipyretic and blood cell system also tended to improve. Subsequent blood test images reported abnormal findings different from owl eye. Initially, MTX-LPD was suspected, and when he visited a nearby doctor's hematology department, it was found to be due to EB virus infection, and the patient was followed up. This is an example of pancytopenia due to multiple factors rather than centralized factors, and is reported with some bibliographical considerations.

## P53-16

### **Cytomegalovirus-induced ureteral bleeding associated with rheumatoid vasculitis: a case report**

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Department of Rheumatology, Shimane University Faculty of Medicine

Conflict of interest: None

Cytomegalovirus (CMV) reactivation is a common infectious complication during immunosuppressive treatment, however CMV ureteritis is clinically rare. We report a case of CMV ureteritis following immunosuppressive treatment for rheumatoid vasculitis (RV). A 66-year-old man was diagnosed with RA at the age of 40. He admitted to our hospital with exacerbation of interstitial pneumonia (IP). IP was improved with steroid therapy, however, fever, peripheral neuropathy, and purpura on the legs appeared after 4 months. Skin biopsy revealed vasculitis. He was diagnosed with RV and treated with high-dose steroid therapy and IVCY. Fourteen days later, upper endoscopy revealed CMV gastroenteritis though his CMV PP65 antigenemia was negative. Macroscopic hematuria appeared at the same time, and bleeding from the right ureter was confirmed with a cystoscope. Contrast-enhanced CT showed wall thickening and enhanced effect in the right ureter. Urine cytology revealed intranuclear inclusions and confirmed CMV-induced ureteritis. Treatment with valganciclovir improved macroscopic hematuria and ureter lesions evident on CT. Thus, it is necessary to recall ureteral bleeding due to CMV when hematuria is observed during immunosuppressive treatment, even if CMV PP65 anti-



genemia is negative.

### P53-17

#### **A case of rheumatoid arthritis patient with multidrug-resistant *Enterobacter cloacae* purulent knee arthritis cured by local high-concentration antibiotics**

Minoru Takasaki

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Conflict of interest: None

Purulent arthritis is intractable disease, and drug-resistant bacteria are often more difficult to treat. Carbapenem-resistant enterobacteria (CREs) are multidrug-resistant bacteria that have become a clinical problem. We have intermittently performed high-concentration amikacin sulfate in the knee joint after performing endoscopic lavage for patients with rheumatoid arthritis who developed purulent knee arthritis due to CRE multidrug-resistant Carbapenem resistant *Enterobacter cloacae*, and it was cured. An 85-year-old woman was treated due to sepsis caused by Carbapenem resistant *Enterobacter cloacae* the in our hospital's internal medicine department with trimethoprim-sulfamethoxazole combination, which is the only sensitive drug. She was consulted to our department because of swelling of her left knee joint. She underwent arthroscopic lavage and catheter placement, and daily high-concentration amikacin was injected intra-articularly. Arthritis has subsided and has not recurred to date.

### P53-18

#### **Effect of sulfasalazine on the carrier state of *Pneumocystis jirovecii* in patients with rheumatoid arthritis**

Takahiro Nunokawa<sup>1</sup>, Naofumi Chinen<sup>1</sup>, Akiko Miyana<sup>1</sup>, Shino Sogabe<sup>1</sup>, Shuhei Sano<sup>1</sup>, Takuya Kakutani<sup>1,2</sup>

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Conflict of interest: None

[Objective] Since sulfasalazine is a conjugate of antimicrobial sulfonamides and 5-aminosalicylates, a preventive efficacy of the drug against *Pneumocystis jirovecii* (*P. jirovecii*) pneumonia have been advocated and have been demonstrated in several clinical studies. The aim of the present study is to clarify the effect of sulfasalazine on the carrier state of *P. jirovecii* in patients with rheumatoid arthritis (RA). [Methods] Patients with RA who were treated at Tama Nambu Chiiki Hospital were included. Those who received the prophylaxis against *P. jirovecii* were excluded. PCR detection of *P. jirovecii* was performed in sputum induced with 3% hypertonic saline inhalation. [Results] While two of 47 patients without sulfasalazine were positive for the PCR, none of 45 patients with sulfasalazine were positive for the test. [Conclusions] The result of the present study suggested that sulfasalazine may reduce the carriage of *P. jirovecii* in patients with RA.

### P53-19

#### **Allergy incidence of different prophylaxis doses of TMP/SMX for pneumocystis pneumonia (PCP) in our Rheumatic division**

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Conflict of interest: None

Object: In rheumatic disease treatment, PCP prophylaxis is important. However, many patients are forced to discontinue TMP/SMX due to allergy. It has been reported that the TMP/SMX allergy is lower when started low dose and increased gradually. To reduce the allergy, we also start with low dose. In this study, we investigated the difference between starting 0.005 g/dose (ultra-low-dose) or 0.1 g/dose (low-dose) of TMP/SMX. Method: In Aug 2018 to Jul 2021, we retrospectively investigated the sex, age, body weight, primary disease, allergy history at the start of TMP/SMX at 0.1 g/day or less in our division. EZR (ver. 1.52) was used for all statistical analyses. Result: Ultra-low-dosage group 24 / low dosage group

18 (male 7/5) cases, age 72 (41-84) / 82 (20-92) years, weight 58.8 (35.9-84.8) / 42 (33.6-82.3) kg. The primary disease varies. Allergy history 15/7 cases, the dose of PSL was 2.5 (0-90)/32.5 (2.5-55) mg, and 10 had immunosuppressive drugs. The incidence of allergy was 2 cases (8.3/11.1%) (95% CI -0.155 0.21), and there was no significant difference between groups. Conclusion: Starting at low doses can prevent losing adherence, it can also be introduced in outpatient because it reduces the dispensing time. We believe that starting with a low dose of TMP/SMX is a safe enough and effective.

### P53-21

#### **A case of cutaneous infection due to nontuberculous mycobacteria in a patient with microscopic polyangiitis**

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Department of Rheumatology, Kyoto Katsura Hospital, Kyoto, Japan

Conflict of interest: None

A 78-year-old female patient with microscopic polyangiitis was treated with low dose corticosteroid for four years and maintained remission. She presented painful nodules with erythema. Skin biopsy was performed. Histopathological examination showed the infiltration of neutrophils in epidermis and acid-fast bacilli. Culture of skin lesion identified *Mycobacterium chelonae*. We report this as a rare case with a literature review.

### P54-1

#### **A case of systemic juvenile idiopathic arthritis with persistent inflammation associated with Vitamin C deficiency**

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Conflict of interest: None

Vitamin C (VC) deficiency, which is called scurvy, causes bleeding of the skin and mucous membranes, arthralgia, and dysplasia of bone tissue. We report a case of systemic juvenile idiopathic arthritis (sJIA) with VC deficiency and persistent inflammation. A 3-year-old girl presented spiking fever, and arthralgia in her right wrist and left ankle. Blood tests showed white blood cell count of 31600/ $\mu$ l, C-reactive protein level of 27 mg/dl, and ferritin of 1649 mg/dl. She was diagnosed with sJIA because of rheumatoid rash and arthritis. She also had hypercytokinemia (IL-18 67000 pg/ml and IL-6 347 pg/ml). Although administration of dexamethasone palmitate initially improved her symptoms, her spiking fever and skin rash returned within a few days. Methylprednisolone pulse and tocilizumab improved her arthritis, but her spiking fever remained. She had unbalanced dietary habits and her serum VC level was 0.8  $\mu$ g/ml. Scurvy was also suspected on an X-ray of the metaphysis of her knee joint. Replenishment of VC improved her sJIA symptoms. It was reported that serum levels of CRP, IL-1 $\beta$ , and IL-6 are increased in osteogenic disorder Shionogi (ODS) rats that cannot biosynthesize VC. In conclusion, VC deficiency may cause persistent inflammation in sJIA with unbalanced dietary habits.

### P54-2

#### **A case of systemic juvenile idiopathic arthritis treated with Tocilizumab who experienced atypical rash, and was difficult to evaluate disease progression**

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Conflict of interest: None

To evaluate disease progression in systemic juvenile idiopathic arthritis treated with Tocilizumab (TCZ), anti-IL-6 receptor monoclonal antibody is difficult because TCZ mask medical condition. 10-year-old boy with complaint of fever and rash was diagnosed with s-JIA. Methylprednisolone pulse therapy and prednisolone (PSL) were started and these symptoms improved. However PSL dose could not decrease, therefore TCZ was started to use. Small erythema without pruritus sometimes appeared mainly in his forearm, but initially the eruption was thought that

caused by a viral infection and PSL dose was decreased. When PSL dose was 5 mg/day, the eruption appeared continually and after that s-JIA relapsed repeatedly. The PSL dose was increased and gradually decreased, however the PSL dose was difficult to be decreased under 13 mg/day. Unexpectedly, when small amount of PSL was used for patient's false recognition, the rash got worse and the level of serum IL-18 and IL-6 were 11458 and 195 pg/mL. The rash was thought that accompanied by relapse, and TCZ was switched to Canakinumab, anti-IL-1 $\beta$  monoclonal antibody. The rash disappeared promptly and it made to decrease the PSL dose. To evaluate disease progression from many direction in a case of s-JIA with atypical rash with TCZ is important.

## P54-3

### Effectiveness of tocilizumab in the treatment of skin sclerosis and joint contracture in childhood-onset scleroderma

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Conflict of interest: None

[Objective] To evaluate the effectiveness of tocilizumab (TCZ) on skin sclerosis and joint contracture in childhood-onset scleroderma. [Methods] TCZ, 8 mg/kg/4 weeks, was administered intravenously to two patients. [Results] A 7-year-old girl was diagnosed with SSc complicated with ILD with positive anti-Th/To and anti-PM-Scl at age of 5. Methylprednisolone (mPSL) pulse therapy and intravenous cyclophosphamide therapy improved skin lesions and ILD. She was maintained with azathioprine and PSL, but skin sclerosis and joint contracture gradually worsened. TCZ was started at the age of 7. During the ten-month observation, she became able to sit upright and stand on her toes. A 10-year-old-girl was diagnosed with localized scleroderma with left knee arthritis at the age of 4. After treatment with methotrexate and adalimumab, she achieved a treatment-free remission. When she was 10-year-old, localized scleroderma reappeared with restriction of flexion of the left knee joint. TCZ was introduced because of methotrexate refractoriness. After 15 months of treatment, her scleroderma and joint contracture improved to no interference with daily activities. [Conclusions] The effectiveness of TCZ in treating skin sclerosis and joint contractures in childhood-onset scleroderma was suggested.

## P54-4

### A case of polyarthritis-type juvenile idiopathic arthritis with arthritis flare-up and enthesitis on sternohyoideus after COVID-19 vaccination

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Conflict of interest: None

The number of reports on disease activity after COVID-19 vaccination in patients with collagen diseases is increasing, but further reports are required. 21-year-old female, who developed juvenile idiopathic arthritis polyarticular type (RF Positive) at age 13 years old. After the treatment with MTX, adalimumab (ADA) was induced, and MTX was switched to tacrolimus hydrate (TAC). ADA could be discontinued, however, TAC treatment was failed to stop because of the flare-up of calcaneodynia. On April 30, she got the first COVID-19 vaccination. After 19 days, fever, arthralgia, and posterior neck pain appeared. After switching TAC to MTX, she received the second vaccine on May 27. After 22 days, her neck pain worsened. She had to be hospitalized due to neck pain and poor oral intake. Her symptoms persisted, so she was referred to our hospital on July 1. Due to the pain, her head was fixed in the left rotational position, and she had pain and tenderness on the right side of the hyoid bone. Contrast-enhanced CT and echocardiography revealed enthesitis on sternohyoideus and synovitis. After admission, the DAS28ESR scores decreased from 6.75 points to 4.59 points. Our case suggested monitoring of disease

activity after COVID-19 vaccination in patients with collagen diseases is important.

## P54-5

### A case of anti-MDA5 antibody positive juvenile dermatomyositis treated with rituximab

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Conflict of interest: None

A 13 years old boy visited our department due to Gottron's signs, malar rash, knee joint pain, arthritis of the proximal interphalangeal joints of both fingers, and mild muscle weakness and myalgia. Laboratory tests showed cytopenia, elevated AST/LDH/KL-6, myogenic enzymes, ferritin, and elevated anti-MDA5 antibody titer (1100 index). MRI revealed mild myositis. Chest CT scan showed complications of interstitial pneumonia (ILD). We diagnosed as anti-MDA5 antibody positive juvenile dermatomyositis (JDM) and treated with two courses of intravenous methylprednisolone and six courses of intravenous cyclophosphamide (IVCY) followed by oral steroids (PSL) and mycophenolate mofetil. After treatment, anti-MDA5 antibody titer decreased, but with PSL tapering off, the antibody titer and KL-6 increased again. In order to prevent the progression to rapid-progressive ILD, we administered rituximab (RTX) at a dose of 375 mg/m<sup>2</sup>/dose while monitoring CD20 levels. He progressed without any adverse events and anti-MDA5 antibody titer and KL-6 titer decreased again, and chest CT scan showed no exacerbation of ILD. There are few reports on the use of RTX for anti-MDA5 antibody-positive JDM complicated with ILD. We report a case treated with RTX safely and effectively with literature review.

## P54-6

### A case of Noonan-like syndrome with aortitis syndrome

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Conflict of interest: None

[Background] Noonan/Noonan-like syndromes are rare genetic disorders characterized by short stature, congenital heart disease, mental retardation, and characteristic facies caused by genetic mutations related to the RAS/MAPK signaling pathway. Here, we present a case of Noonan-like syndrome with loose anagen hair 2 presenting as aortitis syndrome. [Case] 10-year-old girl with developmental delay, epilepsy, and chronic constipation was referred to our hospital as a two-week history of fever and right inguinal lymphadenopathy. Contrast-enhanced CT showed wall thickness in the left subclavian, right vertebral, and right femoral arteries and PET-CT showed FDG accumulation in the bilateral subclavian and brachial arteries, right inguinal lymph nodes, and right femoral artery. The patient was diagnosed with aortitis syndrome. She also showed short stature, hypertrophic cardiomyopathy, and coagulation abnormality. Genetic testing revealed a c.548A>C (p. Glu183Ala) heterozygous mutation in the *PPP1CB* gene. [Conclusion] In pediatric autoimmune/inflammatory diseases, we occasionally experience cases with hereditary diseases. It is useful to perform genetic testing based on age of onset or comorbidities, as it may be helpful in selecting treatment and predicting complications and course.

## P54-7

### A Case of Pachydermodactyly

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Conflict of interest: None

Pachydermodactyly is a benign, localized cutaneous fibromatosis that causes spindle-like swelling on the proximal interphalangeal (PIP) joints in young people. From its appearance, pachydermodactyly needs to be distinguished from juvenile idiopathic arthritis. [Case] A 15-year-old boy. At the age of 14, he noticed swelling of the PIP joints. He had no joint pain or morning stiffness. The swelling of his PIP joints gradually worsened. Although he visited several orthopedic and pediatric clinics, he was never diagnosed. On the first visit, spindle-like swelling of the bilateral PIP joints of the little, ring, middle, and index fingers were observed. There was no tenderness or limited range of motion. Rheumatoid factor and anti-CCP antibodies were negative, and there was no elevation of erythrocyte sedimentation rate or CRP. The hand radiographs showed no abnormalities in bone and joint but there was soft tissue thickening of the PIP joint. Ultrasonography showed no synovitis in PIP joints. He was diagnosed with pachydermodactyly. If arthritis has been ruled out by imaging or examination, diagnosis of pachydermodactyly is not difficult based on its characteristic appearance. Patients with pachydermodactyly need to be made known as they may be seen in multiple departments.

## P55-1

### A case of pregnant adult-onset Still's disease patient leading to emergency caesarean section due to severe liver injury

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Department of Nephrology, Kanazawa University Hospital, Kanazawa, Japan

Conflict of interest: None

[Case] Female in her 30s [Medical history] She was diagnosed with adult-onset Still's disease (AOSD) at 15 gestational weeks, presenting with fever, skin rash, sore throat, leukocytosis, elevated CRP, ferritin levels, and liver dysfunction. After 14 days of oral prednisolone (PSL) therapy, she was transferred to our hospital due to worsening liver dysfunction (the 1st hospital day). Since her disease activity was not stable, she was treated with seven times of systemic methylprednisolone pulse therapy and intravenous cyclosporine. Despite the improved fever, CRP, and ferritin levels, AST level had worsened to 2326 IU/L on the 41st day. A cesarean section was performed on the 49th day (24 gestational weeks) to prevent maternal and infant complications caused by coagulopathy. Hydrocortisone (HC) was administered as steroid therapy during the perinatal period, and after switching from PSL to HC, liver enzyme level had improved. Therefore, we considered PSL to be the suspect drug for liver dysfunction. On the 76th day, she was discharged with improved laboratory data. [Conclusion] The association between pregnancy and AOSD is not clear, but some cases are reported as refractory to treatment. In this case, the disease activity was well controlled after the termination of pregnancy.

## P55-2

### A case of adult Still's disease that relapsed with severe lumbago associated with prolonged TCZ administration

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Rheumatology, Junkohkai Kansai Medical Hospital

Conflict of interest: None

[Case] A 75 years old woman was admitted to our hospital because of fever, polyarthralgia, pharyngalgia and erythema. She was diagnosed as adult-onset Still's disease (AOSD) from appearance of the erythema, and elevation of ferritin and transaminases. Steroid pulse therapy was performed for 3 times, and cyclosporin A (CsA) was used, but the disease activity remained high. So, tocilizumab (TCZ) i.v. every 2 weeks was initiated, which resulted in a complete response. At 2 months, she was discharged. Then, PSL was gradually decreased smoothly. The interval of TCZ was prolonged to 3 weeks at 4 months, and to 4 weeks at 8 months. CsA was terminated at 11 months, and PSL, at 1 year and a month. However, strong lumbago appeared a month after the interval of TCZ was prolonged to 5 weeks at 1 year and 6 months. Although no diagnosis was made by X-ray or MRI, thrombocytopenia, and elevated levels of transaminase, LDH, and ferritin suggested exacerbation of AOSD. So, administration of steroid and CsA were resumed, and the interval of TCZ was shortened to 2 weeks. Then, the disease was well controlled. [Clinical Significance] There is no established way to stop TCZ for AOSD. Accumulation of clinical cases is necessary. And low back pain could be a symptom of hyper cytokine syndromes.

inase, LDH, and ferritin suggested exacerbation of AOSD. So, administration of steroid and CsA were resumed, and the interval of TCZ was shortened to 2 weeks. Then, the disease was well controlled. [Clinical Significance] There is no established way to stop TCZ for AOSD. Accumulation of clinical cases is necessary. And low back pain could be a symptom of hyper cytokine syndromes.

## P55-3

### A case of prolonged coma due to encephalopathy in the course of adult Still's disease

Shunpei Tsuchiya, Shin-ichiro Ogawa, Ryo Nagamata, Saeko Takeuchi, Mitsuharu Watanabe, Masao Nakasatomi, Hiroko Hamatani, Hidekazu Ikeuchi, Toru Sakairi, Yoriaki Kaneko, Keiju Hiromura

Department of Nephrology and Rheumatology, Gunma University Graduate School of Medicine, Maebashi, Japan

Conflict of interest: None

Case: Twenty-one-year-old woman was admitted to our hospital with fever, skin rash, arthralgia, and lymphadenopathy from 2 months ago. Her temperature was 39.4°C. Laboratory data showed WBC 6800/ul (neutrophils 88.0%), CRP 4.35 mg/dL, ferritin 478.5 ng/mL, and elevated liver enzymes. Skin biopsy, bone marrow aspiration, liver biopsy, and lymph node cytology showed no neoplastic disease. The patient was diagnosed as adult Still's disease. Although 60 mg/day of prednisolone was initiated, she did not improve. Steroid pulse therapy was added, but ferritin increased to 17491 ng/mL. On the 19th day, a generalized chronic convulsion appeared, followed by coma. There were no abnormalities in various imaging modalities or EEG findings, except for elevated spinal fluid pressure. Re-administration of steroid pulse therapy followed by dexamethasone and cyclophosphamide pulse gradually improved her conditions. She responded to call on the 49 day and had a conversation on the 76 day. Conclusion: In recent years, complications of aseptic meningitis and encephalitis have been reported in patients with adult Still's disease. We experienced a case of prolonged coma, possibly due to adult Still's disease-related encephalopathy, which improved with intensified immunosuppressive therapy.

## P55-4

### A case of adult-onset Still's disease with dermatomyositis-like eruptions who presented macrophage activation syndrome after administration of tocilizumab

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Conflict of interest: None

A 48-year-old woman presented pruritic erythema on her face, auricles, neck, and limbs with a fever. They occurred intermittently and pruritic erythema with pigmentation on her upper eyelids also emerged. She had splenomegaly but leukocytosis and elevated serum ferritin levels were not seen. Administration of minocycline or cyclosporine (CyA) temporarily resolved her symptoms. Eight months later, along with a fever, sore throat, and arthralgias, linear erythema and nonpruritic erythema that disappeared at the time of fever reduction also appeared. She was diagnosed with adult-onset Still's disease (AOSD). Even after the administration of prednisolone (PSL) 45 mg/day her symptoms appeared intermittently. The first administration of tocilizumab (TCZ) resolved her symptoms, but they relapsed 5 days later. After the second administration high fever and thrombocytopenia emerged. Macrophage activation syndrome was suspected and steroid pulse therapy and CyA were administered. After the activity was suppressed TCZ was re-administrated, and the dose of PSL was reduced without relapse. AOSD with dermatomyositis-like atypical eruptions was reported to be more serious. The success of the re-administration in this case is considered to be helpful to examine how to administrate TCZ.



## P55-5

### A case of adult onset Still's disease after COVID-19 vaccine injection with a significant response to baricitinib

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Rheumatology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital

Conflict of interest: None

A 40-year-old man developed acute lymphoblastic leukemia in 2014 and underwent an allogeneic peripheral blood stem cell transplant from his sister. He has not had any relapse since then. He was admitted to the hospital with persistent fever after receiving the COVID-19 vaccine in 2021. He had high grade fever, arthritis, sore throat, hyperferritinemia, and elevated transaminases, and was diagnosed with adult-onset Still's disease. Methyl-prednisolone pulse therapy was started, but the effect was temporary. Cyclosporine was also ineffective. Baricitinib was started and he improved. Since there have been few previous reports of AOSD after COVID-19 vaccine injection, and no reports that baricitinib was effective, we report this.

## P55-6

### A patient with adult-onset Still's disease complicated by acute respiratory distress syndrome

Akito Tominaga, Toshiki Ohisa, Tomohiro Suzuki, Takayuki Sawada, Yusuke Yano, Kako Kodama, Shinichi Nogi, Hirotaka Tsuno, Hideki Ogiwara, Akiko Komiya, Toshihiro Matsui  
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Conflict of interest: None

Case: 72-year-old woman. Chief complaint: fever and rashes. Medical history: Pale erythema had appeared mainly in the trunk. Fever and arthralgia then developed. The patient visited a clinic, and Antibacterial drugs were ineffective. The patient was admitted to our department for examination of fever of unknown origin 17 days after the clinic visit. On arrival, 37.9°C fever and salmon-pink rash in the precordium were noted. Blood tests showed inflammatory reaction, liver disorder, and a high ferritin level. Adult Still's disease (ASD) was diagnosed. Bone marrow puncture was indicated hemophagocytosis. Thus, the disease was diagnosed as ASD complicated by macrophage activation syndrome. Steroid pulse therapy was initiated on hospital day 10. However, reduced oxygenation rapidly progressed from day 14 and congestion in the bilateral lungs appeared on radiography, indicating complication with acute respiratory distress syndrome (ARDS). Further steroid pulse therapy and cyclosporine were initiated on day 14 and the general condition rapidly improved. The prednisolone dose was gradually reduced. Discussion: Cases of ASD complicated by ARDS are rare, and to the best of our efforts, we were only able to find 18 case reports. We report this rare case along with literature review.

## P56-1

### Pulsed oral steroid for polymyalgia

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Chiba Central Medical Center

Conflict of interest: None

[Objective] To examine effectiveness of pulsed oral steroid for polymyalgia rheumatica (PMR). [Methods] The patients who visited our hospital from Apr. 2015 to Sep. 2020, were diagnosed with PMR based on ACR/EULAR criteria, and were treated with pulsed oral steroid (oral-P) were examined for its effectiveness. One course of oral-P comprised 0.4 or 0.8 mg/kg/day prednisolone (PSL) for 3 days, followed by 0.1 or 0.2 mg/kg/day for 11 days (0.4P, or 0.8P). Three to five courses were administered; then the dose was gradually tapered off. Serum CRP level and ESR at the first visit, at the start and the end of each course were followed. [Results] Thirty-four patients (0.4P, 15; 0.8P, 19) were included. Seven patients with 0.4P and five with 0.8P had already withdrawn from steroid. CRP level and ESR were significantly higher in 0.8P group of patients than that in 0.4P group. In both groups, after the first course, CRP level and

ESR significantly decreased from that prior to oral-P, and maintained throughout follow-up. During after the first course, both CRP level and ESR showed no difference between 0.4P and 0.8P groups. [Conclusion] Oral-P brought a prompt and good therapeutic response in PMR patients.

## P56-2

### Investigation of the efficacy of methotrexate in relapses of polymyalgia rheumatica

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Conflict of interest: None

[Objective] The purpose of this study is to investigate the steroid sparing effect of methotrexate in relapses of polymyalgia rheumatica. [Methods] We retrospectively analyzed the progress of two groups of patients with polymyalgia rheumatica who had symptomatic relapses during steroid reduction at our department by November 2019: one group continued steroid monotherapy (steroid dose increase), and the other group added methotrexate in addition to steroid dose increase. [Results] The mean age was 75 years, the male to female ratio was 1:1, and the steroid dose at relapse was 5.7 mg/day of prednisolone equivalent. Methotrexate group had higher steroid dose at relapse compared to steroid monotherapy group (9.4 vs 4.0,  $p < 0.01$ ), and steroid dose at 2 years after relapses was similar (4.3 vs 4.9,  $p = 0.7$ ). The dosage increase rate of steroids was statistically significantly lower in the methotrexate group (26.5% vs 149%,  $p = 0.02$ ). [Conclusions] If a relapse of polymyalgia rheumatica is treated by increasing the steroid dose alone, it is unlikely that the steroid dose can be reduced from the time of the relapse, and the addition of methotrexate may be effective.

## P56-3

### A case of relapsing polychondritis with polymyalgia rheumatica

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Rheumatology, Tokai University Hachioji Hospital

Conflict of interest: None

A 79-years-old man was diagnosed with polymyalgia rheumatica (PMR) in x-16 and being treated by prednisolone. In August x-21 he visited a hospital because of red eye and auricles swelling, diffuse erythematous appearance with sparing of the non-cartilaginous ear lobes. Head MRI revealed he had both auricles inflammation and both Optic neuritis. By ophthalmology doctor's consultation, he was diagnosed that he has optic neuritis and uveitis too. He excluded giant cell arteritis (GCA) because he didn't have headache and jaw claudication and the other image findings that there was no aortitis and temporal arthritis by contrast-enhanced CT and ultrasonography. Sometimes relapsing polychondritis (RP) involves optic neuritis, uveitis, other autoimmune disorder. The auricle biopsy result showed infiltration of inflammatory cells into chondrocytes. He was diagnosed with RP and increased prednisolone was initiated as remission induction.

## P56-4

### A case of relapsing polychondritis diagnosed due to vestibular disorder

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Conflict of interest: None

[Patient] 64-year-old Male [Present illness] He was aware of spontaneous joint swelling and tenderness in the right fingers. A year later, he was diagnosed as scleritis with relapsing arthritis. Following improvement of scleritis, he started to suffer from rotatory vertigo with elevated inflammatory reactions and he was admitted to our hospital. [Clinical course] He had general fatigue and auricular swellings with elevated ESR 66 mm/h and CRP 9.84 mg/dL. MRI revealed high signal at the auricle to the inner ear without abnormalities in the pharyngeal trachea. He was diagnosed as vestibular disorder by horizontal nystagmus and pathology of auricle biopsy revealed inflammation with neutrophils, lymphocytes, and plasma cells in the cartilage membrane. Based on these findings, we reached to the diagnosis of relapsing polychondritis (RP) and initiated PSL 60 mg/day. General fatigue, auricular swellings and inflammatory reactions improved and concomitant methotrexate (MTX) is planned for PSL tapering. [Clinical significance] Arthritis as the initial symptom is the second most frequent following auricular pain. As within the current case, arthritis complicated by vestibular disorder needs to differentiate RP. We report this case with the efficacy of MTX and biologics in the treatment of RP.

## P56-5

### Relapsing polychondritis diagnosed by a biopsy of thyroid cartilage: A Case Report

Daisuke Nakatsubo, Yuichi Maeda, Masashi Okamoto, Hiroshi Shimagami, Tomomi Tada, Shoji Kawada, Yasutaka Okita, Takahiro Kawasaki, Takayoshi Morita, Jun Fujimoto, Yasuhiro Kato, Masayuki Nishide, Akane Watanabe, Hyota Takamatsu, Yoshihito Shima, Masashi Narazaki, Atsushi Kumanogoh

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Conflict of interest: None

A 25-year-old woman visited our hospital because of a slowly progressive hypophonia that had developed 6 years earlier. An endoscopic examination revealed shortening of the anterior-posterior diameters of the vocal cords. There was an increased level of serum C-reactive protein. Autoimmune indicators were negative. Bone scintigraphy showed high integration of bilateral arytenoid cartilages in which F-18 FDG PET also revealed marked tracer uptake. A thyroid cartilage biopsy was performed under local anesthesia and showed perichondrial infiltration of polymorphonuclear leukocytes and lymphocytes. The patient was diagnosed with relapsing polychondritis (RP). The patient started on 30 mg of oral prednisolone and showed improvement in symptoms. RP is a rare autoimmune disease characterized by episodic inflammation and destruction of cartilaginous tissues throughout the body. There is no specific test that establishes the diagnosis. If the cartilage lesion is localized, a highly invasive biopsy may be required for diagnosis. We report a case of RP diagnosed by a minimally invasive biopsy of thyroid cartilage, avoiding highly invasive laryngofissure, in which the only subjective symptom was hypophonia, there were no cartilage lesions other than bilateral arytenoid cartilages.

## P56-6

### A case of rheumatoid arthritis with palmoplantar pustulosis that improved after treatment with baricitinib

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Conflict of interest: None

[Case] A 61-year-old woman. A patient with rheumatoid arthritis was started on golimumab by a local physician in X year. After 2 years, the patient presented with skin rashes on both the palms and soles, and pain in both sternoclavicular joints. The patient visited the dermatology department of her local doctor and was diagnosed with palmoplantar pustulosis. Golimumab was discontinued and the patient was treated for palmoplantar pustulosis. Six months after the discontinuation of golimumab, pain in the joints of both hands and the left elbow appeared, and the patient was ad-

mitted to our department. The patient had pain and swelling in the joints of both hands and the left elbow, and skin rashes on the palms and the soles of the feet. The patient was started on baricitinib for rheumatoid arthritis with palmoplantar pustulosis. After 4 weeks of treatment, the skin rashes on the palms of both hands and the soles of both feet disappeared. A previous report indicated that treatment with tofacitinib led to remission in a patient with palmoplantar pustulosis caused by a paradoxical reaction to a TNF- $\alpha$  inhibitor. In this study, we reported a rare case of palmoplantar pustulosis that developed after golimumab treatment and improved after baricitinib treatment.

## P56-7

### A case of neurosarcoidosis presenting with hoarseness and dysphagia

Shunsuke Kyoda<sup>1</sup>, Tomoki Tanaka<sup>1</sup>, Keisuke Ikeda<sup>1</sup>, Yosuke Iwadata<sup>1</sup>, Nana Kinoshita<sup>1</sup>, Yosuke Sakamoto<sup>1</sup>, Eri Shishido<sup>1</sup>, Risa Shindo<sup>1</sup>, Kazuma Ino<sup>1</sup>, Yoshiro Kanayama<sup>1</sup>, Junichi Kondo<sup>1</sup>, Yasuhiro Hasegawa<sup>1</sup>, Takumi Muramatsu<sup>1</sup>, Yu Matsueda<sup>1</sup>, Takayuki Hoshiyama<sup>1</sup>, Toshihiro Tono<sup>1</sup>, Tatsuhiko Wada<sup>1</sup>, Yoshiyuki Arinuma<sup>1</sup>, Kenji Oku<sup>1</sup>, Sumiaki Tanaka<sup>1,2</sup>, Kunihiro Yamaoka<sup>1</sup>

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Conflict of interest: Yes

[Case] A 60-year-old male became aware of visual impairment and was diagnosed with bilateral panuveitis at year X-1 and referred to our hospital. ACE and lysozyme in peripheral blood were elevated and enlarged bilateral parotid gland and longitudinal lymph node were observed in CT scan. Sarcoidosis was diagnosed by skin red phase and parotid gland biopsy. Lack of pulmonary dysfunction led to drug-free observation. In March year X, dysphagia and hoarseness appeared, and the patient was admitted to our department. Endoscopy revealed left vocal fold paralysis, decreased pharyngeal sensation, and delayed laryngeal elevation, and head MRI showed an enhanced effect area in the ventral part of the left medulla oblongata. Cell count and protein were elevated in cerebrospinal fluid and he was clinically diagnosed as neurosarcoidosis. Prednisolone 70 mg/day was started with rapid improvement of the medullary lesion, dysphagia, and hoarseness. Laryngeal and pharyngeal dysfunction is reported as complications of neurosarcoidosis which could be caused by central or peripheral nerve lesions such as mediastinal lymph nodes causing recurrent nerve paralysis. Although sarcoidosis is often not eligible for treatment, careful observation and early intervention at the onset of symptoms are critical.

## P56-8

### A rare case of pustulotic arthro-osteitis accompanied with osteolysis

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Conflict of interest: None

A 50-year-old female developed pain in her left thigh on August 20XX, and was referred to our hospital. She was diagnosed with deformities of her sternoclavicular joints and palmoplantar pustulosis (PPP) on the soles of the palms and feet. She received symptomatic treatment with NSAIDs, however, her symptoms gradually got worse. As the CT examination revealed an osteolytic lesion in her left femur, which was suspected to be a bone tumor. After bone biopsy of the lesion, the pathological findings resulted in the diagnosis of osteolysis with pustulotic arthro-osteitis (PAO). She was initially treated with a combination of Methotrexate and Adalimumab (ADA), and her symptom and the osteolytic bone lesion had improved and disappeared for 6 months. However, the skin rash mainly appeared on her extremities again and spread. ADA was discontinued since paradoxical reaction was suspected. In contrast, her femur pain relapsed, suggesting the recurrence of PAO. Guselkumab has been chosen as second line treatment, thereafter, her skin and the bone lesion have improved again. PPP is characterized by aseptic pustular skin lesions on

limbs, and sometimes accompanied with PAO. Here, we have reported and discussed this rare case of PAO, which induced osteolysis in the thigh bone.

## P57-1

### Successful induction and maintenance of remission with rituximab in a patient with refractory TAFRO syndrome who re-relapsed with apparent proteinuria under anti-IL-6 therapy. A case report

Masako Utsunomiya<sup>1</sup>, Nanae Okimoto<sup>1</sup>, Kei Karakida<sup>1</sup>, Keisuke Hirobe<sup>1</sup>, Yuki Terashima<sup>1</sup>, Eisuke Kanematsu<sup>1</sup>, Tomoko Sano<sup>1</sup>, Daisuke Asatori<sup>1</sup>, Kazusa Saegusa<sup>1</sup>, Naoki Tanomogi<sup>1</sup>, Masahiro Iida<sup>1</sup>, Tatsuo Mori<sup>2</sup>, Yoshitaka Ueda<sup>1</sup>, Eisuke Takamasu<sup>1</sup>, Kae Onishi<sup>1</sup>, Takayasu Kise<sup>1</sup>, Yuji Miyoshi<sup>1</sup>, Yoshiki Nagai<sup>3</sup>, Naoto Yokogawa<sup>1</sup>, Kota Shimada<sup>1</sup>

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Conflict of interest: None

[Case] A 73-year-old woman who presented with positive anti-SS-A/Ro antibody admitted to our hospital for fever, thrombocytopenia, and elevated C-reactive protein (CRP). Lymphadenopathy, ascites, renal dysfunction, and lymph node biopsy findings were combined to diagnose her with TAFRO syndrome. She was started on prednisolone (PSL) 1 mg/kg/day and i.v. tocilizumab (TCZ) 8 mg/kg weekly, which resulted in remission. The patient had a relapse with thrombocytopenia therefore cyclosporine was added, but she had a second relapse with thrombocytopenia, proteinuria, hematuria and ascites. After renal biopsy, the dose of PSL was increased to 1 mg/kg/day, and rituximab of 375 mg/m<sup>2</sup>/week for four times was added. Renal biopsy revealed membranous glomerulonephritis-like findings. Ascites, hematuria, and proteinuria improved but thrombocytopenia persisted for ten months. With rituximab 500 mg every six months as a maintenance therapy, her PSL dose was tapered successfully. [Clinical significance] This case is of clinical significance in that 1) this case has apparent proteinuria which is uncommon in TAFRO syndrome, and 2) this case achieved and is kept under clinical remission with rituximab while management of refractory TAFRO syndrome under anti-IL-6 therapy has not yet been established.

## P57-2

### The efficacy of thrombopoietin receptor agonist (TPO-RA) in the treatment of TAFRO syndrome

PengYu Chen, Keigo Terada, Ryohei Nagata, Keigo Setoguchi  
Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Conflict of interest: None

Case 1) 73 y. o F. The patient was diagnosed with TAFRO syndrome based on thrombocytopenia, anasarca and inflammation and treated with steroid and tacrolimus. Despite the treatments, thrombocytopenia persisted and she needed blood transfusion for bleeding after lymph node biopsy and abdominocentesis. TPO-RA was started and then platelets started increasing and bleeding stopped. Consequently we could decrease steroids. Case 2) 54 y. o M. The patient was diagnosed with TAFRO syndrome based on thrombocytopenia, anasarca, inflammation, reticulin fibrosis and hepatosplenomegaly. He complicated hematoma by bone marrow biopsy and platelet count was still low despite 4 weeks of treatment with steroid and tacrolimus. TPO-RA was started and after that, platelets started increasing and we could decrease immunosuppressants. Discussion) There are still no established treatments for TAFRO syndrome yet. Among the syndrome, thrombocytopenia tend to protract and could leads to life threatening hemorrhagic complications. We think concurrent use of TPO-RA could decrease such complication and leads to faster dose reduction of immunosuppressants.

## P57-3

### A case of refractory TAFRO syndrome requiring differential diagnosis from SLE

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Osaka City General Hospital

Conflict of interest: None

(Case) 59-year-old female (Chief complaint) Bilateral leg edema (Present illness) Fever and pulmonary infiltrates were observed from Nov X-1. Hemolytic anemia appeared, antinuclear antibody and anti-RNP antibody were positive. Prednisolone 40 mg was started. The patient was referred in Apr X because of thoracoabdominal effusion and leg edema. (Clinical course) She showed thrombocytopenia, renal impairment. The CT scan showed thoracoabdominal effusion and enlarged cervical and axillary lymph nodes. The renal biopsy showed an enlarged subendothelial space and mesangiolytic. The bone marrow examination showed increased megakaryocytes and fibrosis. The diagnosis of TAFRO syndrome was made. She did not respond to corticosteroids, and tocilizumab 8 mg/kg was started. Cyclosporine was also started, but was discontinued due to posterior reversible encephalopathy syndrome. She continued to have thrombocytopenia and coagulation abnormalities. Rituximab 550 mg was started and then the patient's platelet count, renal impairment and fluid retention were improved. (Conclusion) We report a case of TAFRO syndrome with extremely diverse course including TMA. TAFRO syndrome/Castleman's disease could have lupus-like symptoms, laboratory findings including autoantibodies, so we're difficult to diagnose them.

## P57-4

### Severe cutaneous plasmacytosis of idiopathic Multicentric Castleman Disease successfully treated by tocilizumab

Junichiro Hagita, Makoto Yamaguchi, Seika Terashima, Masayoshi Toda, Akimasa Asai, Nao Asai, Asako Kachi, Fumiya Kitamura, Masako Koshino, Naoya Matsuoka, Hirokazu Sugiyama, Mayumi Ito, Shiho Iwagaitsu, Hironobu Nobata, Takuji Ishimoto, Takayuki Katsuno, Shogo Banno, Yasuhiko Ito

Nephrology and Rheumatology, Aichi Medical University

Conflict of interest: None

A 30-year-old woman presented with intermittent fever, exertional dyspnea and multiple violaceous plaques in 2010s. Chest CT scan revealed nodules and thickening perilymphatic interstitium and bronchial wall in the bilateral lungs and systemic lymphadenopathy. Laboratory data showed hyper gammaglobulinemia and inflammatory marker elevation. Lymph node biopsy revealed dense lymphocyte and plasma cell infiltration with an IgG4+/IgG+ plasma cell ratio of 40-45%, leading to the initial diagnosis of IgG4 related disease (IgG4RD). Treated with moderate dose of prednisone (PSL), her symptom once improved. But tapering PSL to 20 mg/day, her condition worsened. The patient was referred to our department for further examination and treatment. Lymph node re-biopsy and skin biopsy showed polyclonal plasmacytosis and follicular hyperplasia with no evidence of HHV-8 infection. Finally, the patient was diagnosed to idiopathic Multicentric Castleman Disease (iMCD) treated with tocilizumab (TCZ). After few times of TCZ treatments, skin lesions and systemic inflammation signs completely disappeared. IgG4RD and iMCD are confusable diseases in the point of clinical/pathological findings like this case. We report this case with some literature review.

## P57-5

### A case of neuro-Sweet disease complicated with Takayasu arteritis

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Conflict of interest: None

An 82-year-old man visited our hospital due to high levels of C-reactive protein (CRP) and refractory scleritis. Auricular cartilage biopsy due to right ear redness and swelling did not show relapsing polychondritis. Cerebrospinal fluid (CSF) examination revealed significant increases in the number of cells and interleukin 6 (IL-6) levels. After pulse therapy



with prednisolone (PSL), PSL was started at 30 mg/day. The patient was diagnosed with neuro-Sweet disease based on steroid-reactive meningitis, erythematous eruption of the auricle, scleritis, human leukocyte antigen (HLA)-B54 (+), and HLA-B51 (-). Reduction of the PSL dose to 5 mg/day increased the CRP levels. Positron emission tomography/computed tomography showed accumulation in the aortic wall, suggestive of Takayasu arteritis. The PSL dose was increased to 20 mg/day and tocilizumab (TCZ) (162 mg/week) was initiated. The CRP levels became normal, and the PSL dose was decreased to 3 mg/day. However, headache recurred, and the IL-6 levels in the CSF were increased. Thus, the PSL dose was increased to 10 mg/day and TCZ was replaced by adalimumab (40 mg/2 weeks). This regimen improved the headache and IL-6 levels in the CSF. Neuro-Sweet disease and Takayasu disease may be associated with overreaction of neutrophils.

### P57-6

#### **A case of idiopathic retroperitoneal fibrosis reached to rectus abdominis muscle**

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Conflict of interest: None

A 49-year-old woman was diagnosed with idiopathic thrombocytopenic purpura and received prednisolone 15 mg/day. After glucocorticoids were tapered off, she developed slight fever and abdominal pain. Blood tests were unremarkable except for elevated CRP. CT scan revealed a soft tissue mass surrounding the abdominal aorta and iliac arteries, which extended anteriorly to involve rectus abdominis muscles. Additional blood tests revealed weakly positive anti-dsDNA antibody but with no hypocomplementemia. A biopsy specimen from the rectus abdominis muscle revealed infiltration of lymphocytes and plasma cells and fibrous thickening of venous intima but with few IgG4-positive cells and no findings suggestive of malignant lymphoma. We diagnosed her with idiopathic retroperitoneal fibrosis and started treatment with prednisolone 60 mg/day. The abdominal pain and inflammatory responses improved rapidly and FDG-PET/CT showed a marked reduction in soft tissue lesions. Retroperitoneal fibrosis is a disease that causes inflammatory cell infiltration and fibrosis in the retroperitoneum, which can be either IgG4-related, associated with malignant tumor, or idiopathic. In any case, massive expansion that involves rectus abdominis muscle has rarely been reported in the literature.

### P57-7

#### **A case of retroperitoneal fibrosis that occurred during administration of nivolumab**

Hironori Inoue, Takuya Inoue, Shunsuke Fujieda, Risa Sagawa, Naoka Kamio, Akiko Kasahara, Shunya Kaneshita, Takuya Inoue, Kazuki Fujioka, Wataru Fujii, Takahiro Seno, Makoto Wada, Masataka Kohno, Yutaka Kawahito

University Hospital, Kyoto Prefectural University of Medicine

Conflict of interest: None

[Case] A 73-year-old man. Administration of nivolumab (3 mg/kg) was started in June 2018 for postoperative recurrence of clear cell carcinoma of the left kidney that originally developed in 1995. In August 2019, abdominal computed tomography (CT) showed a homogeneous plaque at the bifurcation of the iliac artery. The plaque gradually increased, but a laparoscopic biopsy showed no malignant cells in February 2020. In September, a new plaque was formed at the right hilum to the ureter. Based on no evidence of infection or IgG4 related disease or malignancy, retroperitoneal fibrosis (RPF) due to nivolumab was suspected. Nivolumab was discontinued in February 2021. Since no malignant cells were found in the right ureteral biopsy performed in April, prednisolone 60 mg (0.8 mg/kg) / day was started as a treatment for RPF due to an immune-related adverse event (irAE) caused by nivolumab. Abdominal CT showed a tendency for the plaque to decrease. [Discussion] RPF is caused by malignant tumors, drugs, infections, IgG4-related diseases, and so on. Adverse events caused by immune checkpoint inhibitors (ICI) are similar to collagen disease, called as irAE. However, there are few reports about RPF caused by ICI, so we present report this case with some information about previous reports.

### P57-8

#### **Minocycline ameliorated polyarthritis and pericarditis in a patient complicated with Good syndrome**

Masashi Okamoto, Hiroshi Shimagami, Tomomi Tada, Daisuke Nakatsubo, Shoji Kawada, Yasutaka Okita, Takayoshi Morita, Takahiro Kawasaki, Jun Fujimoto, Yuichi Maeda, Masayuki Nishide, Yasuhiro Kato, Akane Watanabe, Hyota Takamatsu, Yoshihito Shima, Masashi Narazaki, Atsushi Kumano

Department of Clinical Immunology, Osaka University Hospital, Osaka, Japan

Conflict of interest: Yes

A 56-year-old woman had a history of thymoma resected in X-6 year and had no recurrence. She developed organizing pneumonia in May X year and was treated with prednisolone (PSL) 30 mg/day. Her chief complaint were pain and swelling of bilateral hand and finger joints and leg edema from June, when treated with PSL 20 mg/day. White lesions were observed in her mouth. Blood tests showed CRP 20 mg/dL, IgG 130 mg/dL and C7-HRP positive, and chest CT exam revealed pericardial effusion. She was diagnosed with Good syndrome (GS), autoimmune arthritis and pericarditis, oral thrush and cytomegalovirus infection. She was treated with ganciclovir, a  $\gamma$ -globulin preparation and miconazole. However, arthritis and pericarditis were poorly improved. Minocycline was started because of its anti-inflammatory effect without immunosuppressive one. Then her symptoms improved and PSL was gradually tapered. GS is characterized by thymoma and susceptibility to infection and is associated with various autoimmune diseases. GS is often difficult to treat, since immunosuppression is required despite the immunodeficiency. Minocycline exerts a variety of biological actions including anti-inflammatory one. This case suggests a potential of minocycline for the treatment of autoimmune disease complicated with GS.

### P58-1

#### **A case of HLA-B27 positive reactive arthritis caused by chlamydial prostatitis**

Hideki Tani, Akari Miwa, Mariko Tangiku, Kei Fujioka, Tatsuo Ishizuka

Center of General Internal Medicine and Rheumatology, Gifu Municipal Hospital

Conflict of interest: None

[Case] A 48-year-old Canadian male. He noticed fever and swelling of the right knee joint. His symptoms were worsened during treatment with NSAIDs. Positive for chlamydial DNA indicated diagnosis of chlamydial prostatitis. HLA-B27 positive showed the consistent with the course of reactive arthritis. Azithromycin 2 g single dose and ceftriaxone 2 g/day were continued for 1 week. 20 mg of PSL and 500 mg of SASP were started for continued fever and joint swelling. But, arthralgia did not improve, and then the symptoms were improved after treatment with administration of 40 mg of triamcinolone acetonide to both knee joints. Two weeks later, there was a generalized skin rash, fever, and arthritis flare-up, therefore SASP was discontinued. Finally, fever and arthralgia rapidly disappeared after treatment with 40 mg /2 W ADA and 8 mg /W MTX. Switching to MTX monotherapy showed no relapsing of those symptoms. [Discussion] Reactive arthritis is a non-purulent arthritis associated with extra-articular infections. The incidence of HLA-B27 is high, and arthritis generally resolves spontaneously, but some cases progress to chronic arthritis. When severe arthritis could not be suppressed even after treatment with combined use of PSL and SASP, the combined use of MTX and ADA should be used.

### P58-2

#### **A case of granulomatous vasculitis presenting as annular erythema in neurosarcooidosis**

Kei Karakida, Shino Sogabe, Akiko Miyana, Naofumi Chinen, Takahiro Nunokawa

Department of Internal Medicine, Tamananbu Chi-iki Hospital

Conflict of interest: None

[Case] A 42-year-old female patient presented with a two-month his-

tory of annular erythema on the legs, ankle pain and fever. Skin biopsy of the erythema revealed epithelioid granuloma and necrotizing vasculitis. Computed tomography revealed bilateral hilar lymphadenopathy and Löfgren's syndrome (LS) was suspected. However, she soon developed aseptic meningitis, unilateral facial palsy and hypoalgesia of the trigeminal nerve and fourth thoracic spinal nerve. Neurosarcoidosis was diagnosed and she received intravenous methylprednisolone pulse therapy followed by high-dose prednisolone, which quickly alleviated her symptoms. She is now on methotrexate and low dose steroids. [Discussion] Cutaneous sarcoidosis is categorized into specific or non-specific types depending on the presence of sarcoid granulomas. A common, non-specific type is erythema nodosum, often presenting as part of LS. While LS is usually self-limiting, some specific cutaneous lesions can indicate specific systemic features. Annular erythema is a rare form of cutaneous sarcoidosis and several cases report of histologically confirmed granulomatous vasculitis. Cutaneous manifestations in sarcoidosis must be carefully evaluated because they can be associated with pathological conditions that require systemic treatment.

### P58-3

#### Two cases of eosinophilic fasciitis for which PET-CT was useful for evaluation of systemic lesion distribution and comparison with MRI findings

Takuya Kakutani, Kazuki Yoshizawa  
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Conflict of interest: None

[Case 1] 74 years man. He visited the outpatient for X years with the complaint of non-pitting edema of the extremities. Skin sclerosis was observed on both forearms and lower legs, and the orange peel appearance and groove sign were positive. MRI of both lower legs showed high signal on the fascia on T2 images, and PET-CT also showed FDG uptake on the fascia of the whole body. Biopsy was performed from the right lower leg, and Prednisolone 60 mg was started and improved. [Case 2] 53 years man. From March X, he became aware of non-pitting edema of the extremities, and his symptoms gradually worsened and it became difficult to flex his extremities. Strong skin sclerosis and associated movement restriction were observed in the extremities, and the orange peel appearance and groove sign were positive. MRI of both forearms and lower legs showed high signal on the fascia on T2 images, and PET-CT also showed FDG uptake on the fascia of the whole body. Biopsy was performed from the right lower leg, and Prednisolone 50 mg was administered to improve the condition. [Conclusion] A few reports have been made on the usefulness of PET-CT for eosinophilic fasciitis, it is a valuable case that was useful for understanding the lesion distribution and comparing it with MRI.

### P58-4

#### A case of muscular sarcoidosis secondary to drug induced hypersensitivity syndrome

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Conflict of interest: None

A 45-year-old female, with a 4-month history of medication with carbamazepine for bipolar disorder, was referred to our hospital presenting with generalized edema and muscle weakness. Blood examination showed eosinophilia, progressive renal dysfunction and high level of soluble interleukin-2 receptor. She also developed erythema multiforme in her trunk and arms and skin biopsy revealed drug induced hypersensitivity syndrome (DIHS) due to carbamazepine. The eruptions disappeared, but renal dysfunction and muscle weakness remained even after cessation of carbamazepine. PET-CT showed intense uptake of FDG in the whole pancreas and the left kidney, and low uptake in limb muscles. Muscle biopsy from gluteus medius revealed non-caseating epithelioid granuloma, leading to the diagnosis of muscular sarcoidosis. We started the treatment with oral prednisolone in a daily dose of 0.5 mg/kg. To our knowledge, this is the first case of sarcoidosis secondary to DIHS. They have similar pathogenetic features including the relationship with human herpesvirus-6 reactivation and the increase of regulatory T cells, suggesting pathophysiological correlation.

### P58-5

#### Two cases of arthralgia induced by Nonepisodic angioedema associated with eosinophilia (NEAE)

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Rheumatic Disease Center, Kurashiki Medical Center

Conflict of interest: None

NEAE is characterised by a single episode of persistent edema of the extremities, eosinophilia, and a benign clinical course lacking any internal organ involvement (fever, arthritis, myositis etc.). This disorder is very rare, but it is very important to consider it in differential diagnosis for rheumatologist. [Case 1] A 38-year-old woman presented with peripheral eruption and bil. wrist and ankle swelling, and lt. wrist arthralgia. She had non pitting edema of her lt. hands and no synovitis was found on ultrasonography (US). Laboratory findings showed eosinophilia (1160/ $\mu$ L). Autoantibodies including RF were negative. Her condition was diagnosed as NEAE and prednisolone (PSL) 15 mg / day was started. Symptoms improved rapidly, and after tapering off of PSL, she has not been recurrence. [Case 2] A 37-year-old woman presented with peripheral eruption and and bil. wrist and rt. ankle swelling and arthralgia. She had non pitting edema of her rt. ankle and no synovitis was found on US. Laboratory findings showed eosinophilia (2220/ $\mu$ L). Autoantibodies including RF were negative. Follow-up for 1 week, Her condition was diagnosed as NEAE and PSL 15 mg / day and suplatast tosilate were started. Symptoms improved rapidly, and after tapering off of PSL, she has not been recurrence.

### P58-6

#### Case of suspected eosinophil vascular edema after Covid-19 vaccine

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Conflict of interest: None

We report a case of suspected eosinophil vascular edema after the Covid-19 vaccine. 33 year old male The 1st Pfizer Covid-19 vaccine was administered. From the next day, he visited the hospital with awareness of pain in both feet, right middle finger, left ring finger, and ring finger, swelling of the back of the foot, and PIP swelling of the fingers from the 8th day to the 13th. WBC 20200, eosinophils 11110 (55%) LDH409 IgE467 and increased. No skin biopsy was performed and follow-up was performed without administration of steroids. The second dose of Covid19 vaccine was discontinued. Blood sampling data became normal in about one month, and swelling of fingers and back of the foot disappeared. As a mechanism, it is considered that CD4-positive T cells are activated by some mechanism and IL-5 released from the activation causes eosinophilia. A condition similar to the above symptoms was caused after the Ccovid 19 vaccine was administered this time, but TH2 caused IL-5 and Eosinophil-associated lung pathology.

### P58-7

#### 17 cases of collagen disease lung with progressive fibrosis treated with the antifibrotic medicine Nintetanib

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Conflict of interest: None

PF-ILD is a recently established concept. This is a group in which respiratory function declines due to fibrosis of the interstitium of the lungs. This group includes idiopathic pulmonary fibrosis, collagen disease lung, hypersensitivity pneumonitis. It is difficult to cure completely with current medical treatment, and it is important to control its progression. Nintetanib has been originally developed as a medicine for idiopathic pulmonary fibrosis and reported to be effective for other PF-ILDs. Nintetanib was covered by insurance for PF-ILD due to scleroderma in 2019 and PF-ILD due to other collagen diseases in 2020. Since 2019, nintetanib has been administered to a total of 17 patients with collagen disease lung and PF-ILD in 10 patients with scleroderma, 4 patients with rheumatoid arthritis, and 3 patients with myositis. This time, we evaluated the nature and course of interstitial pneumonia from 17 cases of HRCT images, respiratory func-

tion tests and blood test data. Although improvement of interstitial pneumonia was generally observed, some cases of death due to acute exacerbation of interstitial pneumonia and unexpected side effects were also observed, so some literature consideration was also included. To report.

## P58-8

### A case of migratory polyarthritis after thiamazole initiation for Graves' disease

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Conflict of interest: None

[Case] 56-year-old, female [Chief complaint] Polyarthritis, Fever [Medical history] Graves' disease [Present illness] She was diagnosed with Graves' disease 12 years ago, and after treatment she achieved remission and was followed with no treatment. On March 3, 20XX, she had tachycardia and hand tremor. She was diagnosed as relapse of Graves' disease and thiamazole was started. On March 19, fever of 38°C and migratory arthralgia (both shoulder, hand, finger, and knee joints) appeared, and she was prescribed antimicrobial agents for urinary tract infection. But her symptoms did not improve, and she was referred to our hospital on April 1. Because drug-induced arthritis caused by thiamazole was suspected, the medication was discontinued two days before admission, and fever and joint symptoms improved after admission. Laboratory data two days before admission showed CRP 5 mg/dL. But on the day of admission, we found a decreasing trend in CRP 2 mg/dL. She was discharged on the seventh day of hospitalization as her symptoms had improved. [Discussion] Thiamazole-induced arthritis is known as Antithyroid Arthritis Syndrome (AAS). The pathogenesis and treatment of AAS are not well established, and we report this case with a review of the literature.

## P59-1

### Rheumatoid meningitis during treatment with TNF-inhibitor

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Conflict of interest: None

A 69-year-old male with rheumatoid arthritis (RA) had attained remission with the combination therapy with methotrexate (MTX) and prednisolone (PSL). Following the tapering of MTX due to liver injury, symptoms worsened to require addition of TNF inhibitors for reacquisition of remission. Afterwards, he presented with intermittent episodes of fever and headache, and he was admitted because of consciousness disturbance and lower-limb weakness. Diffusion-weighted image of MRI revealed areas of high signal intensity in the left frontal lobe, parietal lobe, and cerebral falx. Elevated white blood cell, protein, rheumatoid factor (RF), anti-CCP antibody (ACPA) in cerebrospinal fluid, and elevation of antibody indexes of RF and ACPA were observed. He was diagnosed as rheumatoid meningitis (RM), and therapy with high-dose of PSL and intravenous cyclophosphamide subsequently resolved the neurological symptoms. RM is a rare, yet serious complication of RA. Elevation of antibody indexes of RF and ACPA was useful for diagnosis of RM. Since there are some reports of development of RM after treatment with MTX or TNF inhibitors, neurological manifestations emerged during treatment of RA may indicate complication of RM and suggest switch of the biologics to non-TNF inhibitors.

## P59-2

### A case of granulomatosis with polyangiitis (GPA) complicated the small intestinal perforation by lymphoproliferative disorder (LPD) during maintaining the remission with mycophenolate mofetil

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Conflict of interest: None

[Case] A 79-year-old woman was referred to our department 4 years ago for evaluating vasculitis. She had been pointed out otitis media with effusion (OME) and pharyngeal ulcers. ANCA for both ELISA and IIF were negative. PET showed FDG accumulation (FDG-a) in naso-pharyngeal lesion and aortic arch. Pharyngeal biopsy revealed granuloma with giant cells pathologically. We diagnosed GPA and had her treated with some immunosuppressants (IS) in turn with glucocorticoid, but IS could not be continued due to the adverse events. After starting mycophenolate mofetil (MMF) 1 year ago, OME no longer relapsed. PET evaluated 3 months ago showed multiple FDG-a only in the small intestine (SI). After EMR of the transverse colon polyp, she developed ileal perforation, but her medical condition improved by surgery. The pathology showed monoclonal proliferation of CD20 B cells with EBER. In her peripheral blood, EB virus (EBV) PCR was positive and the lymphocyte count (LC) decreased to 410 /μL. After cessation of MMF, the LC recovered. The old ulcers of SI, negative conversion of EBV-PCR, and the withdrawal of FDG-a were revealed. No chemotherapy was needed. [Clinical significance] SI perforation due to MMF-related LPD is rare. Discontinuation of MMF and recovery of LC may contribute to prognosis.

## P59-3

### Clinicopathological study of iatrogenic immunodeficiency-related lymphoproliferative disorders in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To clarify the clinicopathological features of iatrogenic immunodeficiency-related lymphoproliferative disorder (OIIA-LPD) in patients with rheumatoid arthritis (RA) at our hospital. [Methods] We retrospectively analyzed the clinical features of 15 cases of OIIA-LPD that developed in RA patients at our hospital from January 2010 to October 2021. [Results] MTX was administered in 13 cases (86.7%). Histological diagnosis in 13 cases, clinical diagnosis in 2 cases, the histological findings were DLBCL in 9 cases, AITL in 2 cases, MALT in 1 case, and MF in 1 case. The lesion sites were nodal lesions only in 3 cases, extranodal lesions only in 9 cases, and nodal + extranodal lesions in 3 cases. LPD treatment improved with MTX discontinuation alone in 4 cases and chemotherapy or radiation therapy in 10 cases. After chemotherapy, there were some cases in which the activity of RA itself had subsided, and there were cases in which low-disease activity was maintained with low doses of steroids or DMARDs. [Conclusions] Although MTX is an anchor drug for RA treatment, It was suggested that even if MTX is withdrawn after the onset of LPD, RA activity may be suppressed by the immunosuppressive effect of chemotherapy.

## P59-4

### A case of methotrexate-associated lymphoproliferative disorder: Extranodal NK/T-cell lymphoma nasal type regressing with cessation of methotrexate

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Conflict of interest: None

Sixty years old-Japanese female was diagnosed with rheumatoid arthritis (RA) 5 years ago. Methotrexate (MTX) had been prescribed with the dosage 12 mg/week for 3 years, brought good outcome as disease activity. Two weeks before admission, fever and cervical lymphadenopathy



appeared, and the patient was carried to our hospital with symptoms of vomiting and diarrhea. CT scan revealed multiple pulmonary nodules, abdominal free air, edema of ileum, and lymphadenopathy of mesenteric and para-aortic lesion. The operative findings showed ileum and enlarged lymph nodes were adherent to mesentery with partial ileum-perforation. Partial small bowel resection including lymph nodes was necessary and pathological examination elucidated extranodal NK/T-cell lymphoma (ENKL)-nasal type. The lymph nodes and multiple pulmonary nodules promptly disappeared after cessation of MTX based on MTX-LPD. Pathologically, ENKL-nasal type is very rare subtype in MTX-LPD, and only a few cases have been reported, moreover prognosis of non-MTX-LPD ENKL-nasal type without nasal involvement is extremely poor. Herein, we report a case of MTX-LPD ENKL-nasal type that resolved with MTX withdrawal alone, so we report the outline of MTX-LPD and the characteristics of MTX-LPD ENKL-nasal type.

## P59-5

### A case that required differentiation between MTX-LPD and disseminated cryptococcosis

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Conflict of interest: None

[Case] A 75-year-old woman was diagnosed as having rheumatoid arthritis due to bone erosion, rheumatoid factor positivity, anti-CCP antibody positivity, and polyarthritis 5 years ago, and started treatment with MTX 6 mg/week. The dosage of MTX was increased to 10 mg/kg from one year ago. One month ago, she became aware of a mass in her left inguinal region. Enlarged lymph nodes in the left inguinal region were observed, and MTX-LPD was suspected. Cryptococcus antigen in the blood was positive. Based on the imaging findings, positive blood cryptococcus antigen, and detection of cryptococcus in bronchial specimens, a diagnosis of pulmonary cryptococcosis was made, and oral administration of FLCZ 400 mg/day was started. Although bilateral inguinal lymph node biopsies and transbronchial lung biopsies did not show pathological diagnosis of MTX-LPD, the patient improved only with MTX withdrawal, and the course of the disease suggested MTX-LPD complications. Because of the appearance of pancytopenia, the FLCZ dose was reduced to 200 mg/day and the treatment was continued. [Clinical significance] In addition to MTX-LPD, fungal infection should also be considered in the differential diagnosis of pulmonary nodule shadows and enlarged lymph nodes during MTX medication.

## P59-6

### Rheumatoid arthritis suspected recurrence of other iatrogenic immunodeficiency-associated lymphoproliferative disorders: a case report

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Conflict of interest: None

An 85-year-old woman with a 27-year diagnosis of RA, which was treated with PSL and MTX, was referred to our hospital with cough and dyspnea. Ten years earlier, the patient presented with multiple lymphadenopathy and pleural effusion and was diagnosed with other iatrogenic immunodeficiency-associated lymphoproliferative disorder (OIA-LPD) based on lymph node biopsy findings; she improved following MTX discontinuation and continued treatment with biological or targeted synthetic DMARDs in a local clinic. CT revealed right pleural effusion and thickening. Cytological examination of pleural effusion suggested but could not confirm the presence of lymphoma cells. Bone marrow aspiration did not reveal tumor cells. A biopsy of bump lesion of right chest skin revealed positivity for histiocyte cell surface markers, leading to the diagnosis of myeloid sarcoma (MS). The patient declined treatment and was provided the best supportive care. She died on the 30th day of admission. MS is an extramedullary presentation of AML and is associated with AML in 2.5%-9.11% of patients. MS can be misdiagnosed as malignant lymphoma, es-

pecially before the onset of AML. Even in patients with a history of OIA-LPD, differential diagnosis should include MS in cases where malignant lymphoma is suspected.

## P59-7

### A case of rheumatoid arthritis complicated with ATTR amyloidosis

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Conflict of interest: None

[Background] ATTR-amyloidosis is a rare condition, in which mutated transthyretin protein causes several organ damages, is recently known as the first disease adapted to siRNA therapy in the world. We experienced a case of rheumatoid arthritis (RA) with numbness in lower limb, finally diagnosed as ATTR-amyloidosis. We report this case with some literature review. [Case] A 78-year-old male was diagnosed as RA in our hospital five years ago. He presented with numbness in lower limb two years ago. NCV study suggested the findings of axonal damage. Drug-induced neuropathy was suspected and MTX was discontinued, but lower distal muscle weakness and sensory damage progressed gradually. IVIg was not effective. As 99mTc-pyrophosphoric acid heart scintigraphy revealed abnormal uptake, he underwent biopsy from gastrointestinal tract and abdominal wall, which showed TTR-positive amyloid deposition. As a result, he was diagnosed as having familial ATTR amyloidosis (Val30Met) with polyneuropathy and heart amyloidosis. He is now continuing siRNA therapy. [Discussion] About 700-1000 patients with FAP-ATTR are estimated in Japan, but much more patients may exist potentially. Rheumatologist should take care of this rare condition. [Conclusion] We experienced a case of RA with ATTR amyloidosis.

## P59-8

### Are AA-amyloid deposits cleared-up under inflammation-stable state?

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Conflict of interest: None

**INTRODUCTION:** Amyloid A (AA) amyloidosis is a rare disease secondary to chronic inflammatory states, especially rheumatic diseases in Japan. Although the inflammatory state is under well-controlled, we encounter the presence of AA amyloid deposits by the specimen obtained from GI-endoscopic procedure. **CASE PRESENTATION:** Two cases with rheumatoid arthritis and familial Mediterranean fever, respectively, had a long disease duration and revealed to associate with AA amyloidosis. By the introduction of biologics, their disease activities were well-controlled and the values of SAA had reached to within normal limits. In spite of the improvement in both clinical and labo data, pathological findings revealed to deposit AA amyloid fibrils. **RESULTS:** AA amyloid fibrils are detected by the specimens from sequential GI tract examinations, despite the rheumatic disease activities are well-controlled. **DISCUSSION:** The deposited amyloid fibrils are believed to be cleared-up by the disruption of SAA supply in the management of rheumatic inflammation. During the disease activities are controlled, the deposited fibrils are not yet cleared-up. We must consider some degenerative mechanisms and further clarification on disappearance mechanisms of the deposited fibrils *in situ* will address the answer.

## P59-9

### Examination of effectiveness and safety of ipragliflozin for glucocorticoid-induced hyperglycemia in patients with autoimmune diseases

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Conflict of interest: None

[Objective] To investigate the efficacy and safety of ipragliflozin for glucocorticoid-induced hyperglycemia in patients with autoimmune diseases. [Methods] We retrospectively examined HbA1c and adverse events after initiation of ipragliflozin for glucocorticoid-induced hyperglycemia in patients with autoimmune diseases followed up for 24 weeks at our hospital between 2015 and 2021. [Results] Among 33 patients on ipragliflozin, 4 discontinued it within a month because of insufficient effect (2), liver disfunction (1), or dizziness (1). The remaining 29 patients (RA 21, SLE 4, MCTD 1, PMR 1, MRA 1, AOSD 1; 20 females and 9 males, average age 67.8±10.2 yr) were followed up for 24 weeks on ipragliflozin. At 24 weeks, HbA1c was significantly reduced (7.89±0.91 to 7.20±0.77,  $p=0.00159$ ), even though the PSL dose was significantly reduced (5.7±3.5 to 4.7±3.1,  $p=0.000521$ ). In 7 patients receiving a fixed or increased dose of PSL and fixed antidiabetic drugs, HbA1c was also significantly reduced (7.69±0.32 to 7.17±0.53,  $p=0.036$ ). No cases of urinary tract infection were observed. [Conclusions] Ipragliflozin is efficient and safe for glucocorticoid-induced hyperglycemia in patients with autoimmune diseases.

## P59-10

### Efficacy of metformin for high-dose glucocorticoid induced hyperglycemia in four patients with rheumatic disease

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Conflict of interest: None

Patient 1: A 67-year-old woman with adult-onset Still's disease received mPSL 1000 mg pulse therapy followed by PSL 45 mg per day. Glucose tolerance was impaired, and intensive insulin therapy was needed. Metformin (MTF) 750 mg per day was administered, and insulin was tapered off over two weeks without deterioration of blood glucose control. Patient 2: A 63-year-old woman with ANCA associated vasculitis received oral PSL 35 mg per day. Intensive insulin therapy was needed for glucocorticoid induced hyperglycemia (GIH). Metformin (MTF) 750 mg per day was administered, and insulin was tapered off over two weeks without deterioration of blood glucose control. Patient 3: A 51-year-old woman with dermatomyositis (DM) was admitted to our hospital due to exacerbation of DM and interstitial pneumonia, and received PSL 20 mg per day. MTF 500 mg per day was improved mean amplitude of glycemic excursion. Patient 4: A 62-year-old man was diagnosed with anti-synthetase syndrome, and PSL 50 mg per day was administered. Addition of MTF 500 mg per day to nateglinide improved hyperglycemia, despite nateglinide alone had insufficient effect. Among our patients, MTF was effective for GIH with no adverse events. MTF is inexpensive and may be promising therapeutic option for GIH.

## P59-11

### Azathioprine-induced severe pancytopenia potentiated by the concurrent use of febuxostat

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Conflict of interest: None

[Background] Azathioprine (AZA) is still a drug used in rheumatic diseases. The interaction between febuxostat (FEB) and AZA is significant and requires caution. [Case presentation] A 77-year-old woman presented to our department complaining of pancytopenia for 2 months. Eight years before presentation, she had been started on prednisolone (PSL) and AZA therapy for GCA. She was taking AZA 100 mg and PSL 7.5 mg once daily, and was prescribed FEB 3 months ago to treat hyperuricemia. So she admitted for further investigation and treatment. Her laboratory investigations showed that she had a hemoglobin of 4.7 g/dL. Her other blood test results were as follows: MCV 130.3 fL, white blood cell count 880 / $\mu$ L, and platelet count of 109 G/L. Our differential diagnosis included other rheumatic diseases, hemolysis, malignant disease and drug-induced pan-

cytopenia. On admission to hospital, FEB was stopped. Since no other causes could be identified and her pancytopenia showed improvement, we considered her pancytopenia to be drug-induced by AZA and FEB. Her 6-TGN titer, which was very high at the time of admission (1420 mol/8x10<sup>8</sup> RBC), decreased by one-half per week. [Conclusion] We reported a case of severe pancytopenia caused by FEB and AZA in which 6-TGN and 6-MMP were evaluated over time.

## P59-12

### A case of EBV-associated hemophagocytic lymphohistiocytosis in a patient with rheumatoid arthritis

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Conflict of interest: None

The patient is a 70-year-old female with rheumatoid arthritis was treated at our hospital with PSL 5 mg/day and SASP 1000 mg/day with good control. Since May, she had a fever and high CRP level (23.18 mg/dL), which spontaneously resolved in about a week, repeating once a month. She was admitted to our department in July, had no fever, but sIL-2 receptor was elevated at 2272 U/mL and ferritin at 3165.47 ng/mL, but CT scan showed no obvious lymph node enlargement. Seven days after admission, she had fever, hematopenia (WBC 2900 / $\mu$ L, PLT 54,000/L), LDH 863 U/L. EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) was diagnosed based on hemophagocytosis in bone marrow examination and EBV-DNA 5.51 Log IU/mL. HLH is a disease caused by an excessive immune response and is often fatal, resulting in multiple organ failure. HLH is the predominant disease in children, but it also occurs rarely in adults. The risk factors for HLH include old age, infections such as EBV, malignancies, and rheumatic diseases. HLH is often overlooked because of the nonspecific clinical and laboratory findings. The possibility of HLH should be considered in patients with systemic inflammatory response syndrome, sepsis, and multiple organ failure without an obvious source of infection.

## P59-13

### A case of rheumatoid arthritis with drug hypersensitivity syndrome accompanied with marked serum bilirubin elevation

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Conflict of interest: None

A 65-year-old male admitted to the hospital for jaundice. He was diagnosed with rheumatoid arthritis, and was treated with methotrexate (MTX) 16 mg/week, infliximab (IFX), and salazosulfapyridine (SASP) 1 g/day 10 years before admission. MTX and IFX were discontinued due to MTX lymphoproliferative disorder 1 year before admission. He had been taking allopurinol for hyperuricemia. Blood test revealed elevated liver enzymes and direct bilirubin (17.94 mg/dL) without biliary obstruction in abdominal enhanced CT and ultrasonography. Fever, erythroderma, diarrhea, and renal failure appeared afterward. Under the diagnosis of drug induced hypersensitivity syndrome (DIHS), Methylprednisolone pulse therapy was performed followed by prednisolone (PSL) 80 mg/day. Eosinophilia and HHV-6 reactivation were not observed. Symptoms disappeared and renal function improved after initiation of PSL, but liver failure progressed. Initiation of intravenous gamma globulin therapy and plasma exchange ameliorated the liver failure but hyperbilirubinemia persisted. Cytomegalovirus reactivation was repeatedly observed during clinical course. If liver damage with markedly elevated bilirubin is observed while taking medicine such as SASP or allopurinol, the possibility of DIHS should be considered.

## P59-14

### Prevalence and Risk Factors of Avascular Necrosis of the Femoral Head in Patients with ANCA-Associated Vasculitis

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Conflict of interest: None

[Objective] The pathogenesis of avascular necrosis of the femoral head (ANF) is still unclear. At present, no effective prophylaxis is available for ANF. Systemic lupus erythematosus (SLE) is frequently associated with ANF due to its vascular pathogenicity. Like SLE, ANCA-associated vasculitis (AAV) affects small vessels, but the prevalence and risk factors of ANF in AAV remain unknown. Therefore, we sought to examine the prevalence and risk factors of ANF in AAV to explore its preventative measures. [Methods] 183 AAV patients who underwent hip MRI screening after 6 months from the initial induction therapy (IIT) were collected and retrospectively analyzed. [Results] The prevalence of ANF in AAV patients was 17%, and more than half of them were asymptomatic. Logistic regression analysis identified PSL dose (mg/day) (OR=1.08) on day 90 after IIT as a risk factor for ANF development. Other independent risk factors were LDL-cholesterol (LDL-C) level (mg/dL) at the start of treatment (OR=1.02) and the new onset of hip pain during the observation period (OR=16.0, positive predictive value 60%). [Conclusion] Managing LDL-C levels and rapid reduction of PSL doses within 3 months after IIT may reduce ANF accrual in AAV patients.

## P59-15

### Cross-sectional study on dysgeusia in patients with rheumatoid arthritis: do anti-rheumatic drugs cause dysgeusia?

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Conflict of interest: None

Objective: Most anti-rheumatic drugs (DMARDs), including methotrexate (MTX), have dysgeusia / abnormal taste in the package insert. However, the causal relationship is unknown. The aim of study is to study the relationship between DMARDs and dysgeusia. Methods: A questionnaire about taste to patients with rheumatoid arthritis (RA) was conducted. Taste was evaluated on a 4-point Likert scale, all responses except normal being defined as abnormal. Reported risk factors were also inquired. Results: Among 150 respondents, 125 were analyzed after excluding 20 with multiple checks on Likert scale and 5 with other diseases. The average age was 64±14 years and 84% were women. None had COVID-19 infection. Use of conventional synthetic DMARDs, biological DMARDs, and targeted synthetic DMARDs were 90% (i.e., MTX 66%, salazosulfapyridine 19%, tacrolimus 13%), 41% (i.e., abatacept 12%, tocilizumab 10%, etanercept 10%), and 4% (tofacitinib 4%), respectively. Dysgeusia was observed in 27 patients (22%). Univariate analysis identified only known factors (age, sickness, kidney disease, glossitis, chemotherapy, radiation therapy), but not DMARDs, as risks of dysgeusia. Conclusion: Anti-rheu-

matic drugs are unlikely to be a cause of dysgeusia in RA patients.

## P59-16

### Clinical characteristics of EBV-positive mucocutaneous ulcers (EBV-MCU) in patients with rheumatoid arthritis treated with methotrexate

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Conflict of interest: None

[Objective] The purpose of this study is to demonstrate the characteristics of EBV-positive mucocutaneous ulcers (EBV-MCU) among RA patients concurrently treated with MTX. [Methods] We retrospectively evaluated 7 RA patients with EBV-MCU from 2013 to 2021 regarding their clinical features. We also compared with 46 RA patients that developed LPD during MTX treatment other than EBV-MCU (other LPD). [Results] Seven EBV-MCU patients (3 males and 4 females) enrolled in this study. Their average age of EBV-MCU onset was 69.6 years, disease duration of RA was 233.3 months, and duration of MTX treatment was 127.7 months. The initial site was oral cavity in 5 cases and skin in 2 cases. After cessation of MTX, LPD spontaneously regressed in 6 patients, but 1 patient required chemotherapy. Compared to other LPD group, EBV-MCU group showed more long-term MTX administration, PSL combination, biologics combination and significant recovery of lymphocyte after 2 weeks cessation of MTX. [Conclusions] Our data indicated that EBV-MCU suggested that drug-induced immunosuppression may be involved in the onset of EBV-MCU. Furthermore, many oral lesions were found at the initial site of EBV-MCU, suggesting the importance of histological search in patients with refractory stomatitis during MTX treatment.

## P59-17

### A case of microscopic polyangiitis with thrombotic microangiopathy induced by trimethoprim-sulfamethoxazole

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Conflict of interest: Yes

[Case] A 82-year-old woman presented with fever, numbness in her hands, and an exacerbation of chronic cough. She was diagnosed with microscopic polyangiitis (MPA) on the basis of interstitial pneumonia on CT scan, kidney injury with hematuria and proteinuria, a positive MPO-ANCA titer and necrotizing vasculitis in the muscle biopsy of her right thigh. She was treated with prednisolone 60 mg/day and two doses of rituximab and then her fever and kidney injury improved. Two weeks after the commencement of the treatment, thrombocytopenia developed. Elevated indirect bilirubin, decreased haptoglobin, and schistocytosis indicated the presence of TMA. TMA induced by trimethoprim-sulfamethoxazole (TMP/SMX) was suspected. After the cessation of TMP/SMX, her TMA ameliorated. [Clinical significance] TMA is a syndrome characterized by organ damage by thrombotic microangiopathy and thrombocytopenia. In the spectrum of this condition, thrombotic thrombocytopenic purpura and autoimmune disease-associated TMA are treated with plasmapheresis or rituximab. However, drug-induced TMA can be managed with discontinuation of causative agents. In the management of patients with autoimmune diseases complicated by TMA, drug-induced TMA must be considered to avoid unnecessary treatment

## P59-19

### A Case of Palmoplantar Pustulosis-like Eruption Induced by Baricitinib for Treatment of Rheumatoid Arthritis

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Conflict of interest: None

[Introduction] Biologic DMARDs that suppress cytokines can be a treatment for psoriasis and palmoplantar pustulosis (PPP). However, it may cause a paradoxical reaction that induces psoriasis and PPP. It is rare for JAK inhibitors to cause such a reaction. We report a case of RA with PPP-like eruption after baricitinib (BAR) administration. [Case] A 70-year-old male was diagnosed with RA 2 years previously. Polyarthralgia and swelling of the finger joints appeared 1 month ago. Blood tests at the first visit showed CRP 2.2, RF 363, and anti-CCP antibody 697, and X-ray images showed bone erosion in the MP joint of the right thumb. He had been treated with MTX but discontinued it due to liver dysfunction. He was started on oral BAR 4 mg once daily. The pain was halved 2 weeks after administration. Cystic blisters appeared on both palms and soles after 7 weeks, and he was treated by a dermatologist. BAR was suspended and the eruption was alleviated. Since BAR was effective for joint symptoms, the dose was reduced to 2 mg and he is under follow-up. [Clinical significance] To the extent we searched, there is only one case report of PPP during RA treatment with BAR. Cytokine imbalances can occur not only with biologic DMARDs but also with JAK inhibitors, resulting in PPP-like eruption.

## P59-20

### A case of rheumatoid arthritis who developed ulcerative colitis during treatment with etanercept

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Conflict of interest: None

[Case] 65-year-old woman. [Present Illness] From year X-15, She has been treated for dermatomyositis, scleroderma, and interstitial pneumonia. She developed arthritic symptoms from year X-11 and was diagnosed with rheumatoid arthritis (RA). She has been treated with methotrexate (MTX), and started treating with etanercept in July, year X-3. She suffered from diarrhea since May, year X, and in August, year X she underwent colonoscopy, and no findings were found. She was suspected to have drug-induced diarrhea, and discontinued treatment with MTX and etanercept in August, year X, exacerbating her diarrhea. She was diagnosed with ulcerative colitis (UC) by colonoscopy in September, year X. She was treated with mesalazine and her symptoms improved, but she discontinued it, due to drug fever. She was treated with adalimumab and golimumab for UC, both of which were ineffective. UC improved after starting treatment with ustekinumab in July, year X+2. But her symptoms of RA worsened. She resumed treatment with MTX. [Clinical significance] A case of UC during treatment for RA with etanercept have been reported. The pathogenic mechanism has not yet been clarified. There are few reports of UC during treating with TNF $\alpha$  inhibitors, and we report this with a review of the literature.

## P60-1

### A Case of Rheumatoid Arthritis with Cushing's Syndrome

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Conflict of interest: None

A 65-year-old woman had suffered from arthralgia. 160.0 cm, 76.7 kg TJC 2 joints, SJC 2 joints, VAS 20 mm, CRP 0.29 mg/dL, ESR 4 mm/h, MMP-3 168.6 ng/mL, ACPA <0.5 U/mL, RF 6 IU/mL. MRI showed multiple bone erosions and synovitis at Carpal bones and PIP. She was diagnosed with rheumatoid arthritis and started to treatment by MTX. But CT showed a 29 mm large left adrenal tumor. Casual blood glucose 110 mg/dL, HbA1c 6.2%, ACTH <1.5 pg/mL, cortisol (F) 17.5  $\mu$ g/dL. ACTH and F in 1.0 mg DEX suppression test were <1.5 pg/mL, 15.9  $\mu$ g/dL respectively. MRI showed left adrenocortical adenoma. Adrenal cortex scintigraphy showed the accumulation of adosterol in the left adrenal gland, but in the right suppressed. She was diagnosed with Cushing's syndrome and underwent tumor resection. She received hydrocortisone after surgery, but joint pain worsened, TJC 20 joints, SJC 10 joints and VAS 70 mm. So she

was administered with Sarilumab 200 mg s.c. 8 weeks after, TJC, SJC and VAS improved to 11, 5 and 20 mm respectively. It is well known that the autoimmune response is suppressed by the autonomous production of cortisol by Cushing's syndrome. Even if steroids are properly supplemented after surgery, symptoms may worsen, so it is necessary to pay close attention to the changes in symptoms after surgery.

## P60-2

### A case of granulomatosis with polyangiitis associated with hypertrophic pachymeningitis and diabetes insipidus

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Department of Rheumatology, Saga University Hospital

Conflict of interest: None

A 73-year-old female patient, who had been diagnosed with hypersensitivity pneumonitis and treated with prednisolone (PSL) 2 years ago, developed otitis media with positive MPO-ANCA. She was diagnosed with granulomatosis with polyangiitis (GPA) and treated with PSL. Subsequently, right frontal and temporal pain and right oculomotor nerve palsy appeared. Contrast-enhanced MRI showed findings of hypertrophic pachymeningitis, then the patient was transferred to our hospital. She was treated with intravenous methylprednisolone 500 mg/day for 3 days followed by oral PSL 60 mg/day and intravenous bolus cyclophosphamide, which improved her symptoms. However, she showed dry mouth with polyuria and polydipsia 10 days after initiating these treatments. Urine osmolality increased with vasopressin injection, and a brain MRI showed loss of high signal intensity of the posterior pituitary gland. These results indicated that the patient developed diabetes insipidus. The symptoms improved with an administration of desmopressin. Two similar cases have been reported so far. Both cases were MPO-ANCA positive, and the diabetes insipidus appeared at the time of initial diagnosis in one case and at the time of relapse in the other.

## P60-3

### A case report of atypical hemolytic uremic syndrome during treatment of microscopic polyangiitis

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Conflict of interest: None

Atypical hemolytic uremic syndrome (aHUS) is a type of thrombotic microangiopathy (TMA) defined by thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. We report rare case presentation of aHUS. A 83-year-old Japanese woman presented with edema and numbness. Blood test showed nephropathy (Cre 1.6 mg/dL), anemia (Hb 7.2 g/dL), CRP 12.8 mg/dL, MPO-ANCA 153 U/mL. Liver function test was normal. She was diagnosed as microscopic polyangiitis and started prednisolone 1000 mg, intravenous immunoglobulin, rituximab. After treatment, blood test and symptoms got better. The day 20 of admission, She had seizure and loss of consciousness. MRI showed posterior reversible encephalopathy syndrome (PRES). Blood test thrombocytopenia, increase LDH, and schistocyte. Finally we diagnosed aHUS and started Eculizumab. Her consciousness got recovered after treatment. This case tells us that aHUS can cause organ damage during treatment for microscopic polyangiitis.

## P60-4

### Clinical study of cases of CTD-PAH

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Hitachinaka General Hospital

Conflict of interest: None

[Objective] Evaluate the characteristics of CTD-PAH treated in our hospital. [Methods] As of the end of December 2020, we will extract cases

of CTD-PAH that are still being treated at our hospital. Compare and examine background diseases, treatments for collagen diseases, and pulmonary hypertension. [Results] As of the end of December 2020, there were 6 cases of CTD-PAH that had been continued treatment at our hospital, and 4 of them had been diagnosed with CTD-PAH at our hospital. There were 3 cases of SLE as background diseases, and 1 case each of MCTD, scleroderma, and Sjogren's syndrome. At the time of diagnosis, the NIHA / WHO functional classification was 2 cases in group I, 1 case each in groups II, III, and IV. 2 patients in Group I were treated with initial oral monotherapy, and the other 4 patients were treated with initial oral combination therapy. In two of the cases with systemic lupus erythematosus as a background disease, the drug for treating pulmonary hypertension was reduced or discontinued. For cases with scleroderma as a background disease, the dose of a therapeutic drug for pulmonary hypertension was increased. [Conclusions] Controlling the background diseases of CTD-PAH may also make it possible to control pulmonary hypertension.

## P60-5

### A case of mixed connective tissue disease with lower limb paralysis due to piriformis syndrome associated with gluteal hematoma

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Conflict of interest: None

A 74-year-old woman had a history of pulmonary thromboembolism and was taking edoxaban. She had previously been pointed out of Raynaud's phenomenon and anti-RNP antibody positivity, but she was not particularly followed. She visited our emergency outpatient department with fever and vomiting and was hospitalized. She was initially suspected of sepsis and DIC from pancytopenia and marked increases in D-dimer and procalcitonin. She received antibiotic treatment and anticoagulant therapy, but did not improve. She was diagnosed with exacerbation of mixed connective tissue disease because of pancytopenia, myositis, and arthritis and took PSL 50 mg/day (1 mg/kg/day). On day 6 of admission, she had right lower limb pain and lower limb paralysis. Blood pressure decreased and anemia progressed. CT showed hematomas in the right gluteal and piriformis muscles, and she was diagnosed with lower limb paralysis due to piriformis syndrome associated with gluteal hematoma. After blood transfusion and discontinuation of anticoagulant therapy, the general condition improved, and her hematoma shrank. Her lower limb paralysis improved after rehabilitation. Differentiation of skeletal muscle hematoma was considered important in anemia of patients on anticoagulant therapy.

## P61-1

### The relationship between the behavioral restriction of COVID-19 pandemic and the frailty of patients with rheumatoid arthritis

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Conflict of interest: None

[Object] We reported the prevalence of frailty and relation of disease activity at RA. The behavioral restriction (BR) of COVID-19 pandemic influenced for the lifestyle. The relationship between the BR and frailty was investigated. [Methods] We used the date from prospective observational study (CHIKARA study). 70 from 100 RA were followed-up and evaluated frailty and subcategories (social, physical, mental, nutritional, and cognitive) by checklist. The prevalence of frailty and the change of exercise (EX) and daily life activity (DLA) were investigated at pre- and post-BR. The correlation of frailty examined by univariate analysis. [Results] Mean age was 69.7 years. The prevalence of frailty at post-BR increased compared that at pre (35.8 vs 30.0%). The cognitive and total score at post-BR increased significantly. The rate of decrease of EX and DLA was mean 20% and 44%. The change of EX was significantly negatively correlated with the change of nutrition ( $R=-0.245$ ,  $P=0.041$ ). There was no correlation between the change of DLA and subcategories. [Conclusions] The EX and DLA decreased by the BR of COVID-19 pandemic.

The prevalence of frailty increase 5.8% and, the cognitive and total score were significantly high at post-BR. The decrease of EX correlated with the worse of nutrition.

## P61-2

### Seronegative Rheumatoid arthritis accompanied by Parkinson's disease: 3 case reports

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Conflict of interest: None

[Case 1] 77 y.o. man. Due to muscle rigidity of both upper limbs and wiggle walking, he got treatment as Parkinson's disease. Multi-joint swelling and high CRP and MMP-3 levels were observed. RA Treatment was started as seronegative RA. Remission was obtained with methotrexate and golimumab. [Case 2] 71 y.o. man. He was treated with methotrexate as RA, right hand tremor appeared, and treatment was started as Parkinson's disease and dyskinesia. Total knee arthroplasty was performed for knee contracture. Fourteen years after surgery, a surgical site infection occurred and thigh amputation was needed. [Case 3] 51 y.o. man. Right lower limb dyskinesia appeared during treatment with methotrexate and golimumab as RA. According to the diagnosis of Parkinson's disease, treatment was started. He became difficult to move and diagnosed as a worsening of Parkinson's disease, but it turned out that RA treatment was self-interrupted. Immediately after resuming RA treatment, he improved walking ability. [Discussion] Parkinson's disease may cause finger deformity similar to swan-neck deformity such as dystonia. Decreased mobility may be diagnosed as exacerbation of Parkinson's disease. It should be noted that there are cases in which RA is actually accompanied.

## P61-3

### Single-cell RNA sequencing of bronchoalveolar lavage fluid and clinical characteristics of progressive fibrosing interstitial lung diseases

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Conflict of interest: Yes

[Objective] Progressive fibrosing interstitial lung diseases (PF-ILD) is progressive phenotype of fibrosing ILDs. Clinical characteristics and appropriate prognostic biomarker of PF-ILD is unclear. The aim of this study is to investigate the characteristics of PF-ILD with single-cell RNA sequencing (scRNA-seq). [Methods] We collected bronchoalveolar lavage fluid (BALF) through bronchoscopy from 22 patients including 7 idiopathic interstitial pneumonia (IIP), 5 rheumatoid arthritis, 4 dermatomyositis, 4 Sjogren's syndrome, 2 systemic sclerosis. We analyzed immune cells in BALF by using scRNA-seq with Seq-Well. We measured cytokine and chemokine levels in BALF and serum from each patient with multiple ELISA and analyzed the clinical characteristics of PF-ILD. [Results] Seven out of the 22 patients who required bronchoscopy met the criteria for PF-ILD. PF-ILD patients had higher CRP (median 2.19 vs 0.43 mg/dL) and KL-6 (1320 vs 1007 U/mL) than non-PF-ILD patients. The concentrations CXCL10, and IL-6 were increased in BALF of PF-ILD patients. By using scRNA-seq, we found 19 different phenotypes of immune cells, and increased neutrophils in BALF of PF-ILD patients. [Conclusion] Neutrophils increased in BALF of PF-ILD patients, which may be involved in the pathophysiology of PF-ILD.

## P61-4

### A Clinical Study of Hypertrophic Pachymeningitis (HP) in Our Hospital

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Conflict of interest: None

[Objective] HP is caused by connective tissue diseases, infections, malignancies, and more, so it is often difficult to diagnose. The aim of this study is to elucidate the clinical characteristics of HP. [Methods] We retrospectively reviewed medical records of HP patients in our hospital from October 2015 to September 2021. [Results] We experienced 6 HP cases. The causes of HP were ANCA associated vasculitis (AAV: 4 cases), giant cell arteritis (GCA: 1 case), and idiopathic HP (iHP: 1 case). The mean age of the patients was 67.8 years old. All 4 cases of AAV were positive for MPO-ANCA. In 2 cases of AAV, HP developed while other organ lesions were in remission. In the case of GCA, HP developed while the vasculitis was in remission. In the case of iHP, the aortic vessel wall had partially thickened, but ANCA was negative and IgG4 was normal. Two of 6 patients were resistant to treatment and required a biopsy of the dura mater. The mean initial dose of prednisolone was 48 mg/day, and 2 patients were treated with steroid pulse therapy, 2 with cyclophosphamide, and 1 with rituximab. [Conclusions] There are several cases in which HP appeared during the treatment of AAV. In such cases, it is necessary to exclude infections and malignancies, and a biopsy of the dura mater is important.

## P62-1

### Two cases of macrophage activation syndrome complicating adult-onset Still's disease successfully treated by evaluating IL-18/CXCL9/sTNFR2 profile

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Conflict of interest: None

Macrophage activation syndrome (MAS) is a fatal complication of adult-onset Still's disease (AOSD), where aberrant activation of macrophages and T cells, and hypercytokinemia are involved. Although biomarkers such as ferritin are in use, more reliable biomarkers are required. Here we report two cases of AOSD/MAS successfully treated by using the serum profile of IL-18, a macrophage activation marker, IFN- $\gamma$ -inducible CXCL9, a T cell activation marker, and sTNFR2, a surrogate TNF- $\alpha$  marker. Two patients who developed fever, erythema, arthritis, leukocytosis, liver dysfunction, and elevated serum ferritin, were diagnosed as AOSD. Initial treatment with corticosteroid improved the symptoms, but AOSD flared with fever, leukopenia and thrombocytopenia. A diagnosis of MAS was made. At this point, serum IL-18/CXCL9/sTNFR2 levels were highly elevated despite comparable serum ferritin levels. Although steroid pulse therapy failed, the symptoms improved with liposteroid, continuous intravenous cyclosporin A, and plasmapheresis (PE). Because MAS flared up again upon PE discontinuation and liposteroid reduction, we continued PE until serum IL-18/CXCL9/sTNFR2 levels improved. We propose that serum IL-18/CXCL9/sTNFR2 profiling is useful to monitor the disease activity of AOSD/MAS.

## P62-2

### A case of recurrent pericarditis with resistance to steroids and immunosuppressive drugs

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Conflict of interest: None

Case: A 38-year-old woman. At the age of 36, she became aware of fever, anterior chest pain, neck pain and dyspnea. Blood samples showed elevated WBC and CRP. Chest CT showed pericardial effusion, and she was diagnosed as acute pericarditis. NSAIDs and colchicine were ineffective, she was started on PSL, improved temporarily. However, relapses

repeated when the dose of PSL was reduced, even with azathioprine (AZP), she was admitted. After mPSL pulse therapy, palpitations and chest pain improved. We decided to gradually decrease the PSL dose while using tocilizumab (TCZ). Discussion: Recurrent endocarditis (RP) is diagnosed when pericarditis flares up after a symptom-free period of 4 to 6 weeks. The European Society of Cardiology (ESC) guidelines recommend NSAIDs, colchicine, PSL, AZP, IVIg and IL-1 inhibitors for the treatment of RP. Familial Mediterranean fever and TNF receptor-associated periodic syndromes can present with pericarditis, suggesting that some RPs are related to autoinflammatory syndromes (AIS). Clinical significance: In refractory RP, the use of biologics and genetic search should be considered because of the possibility of AIS.

## P62-3

### A case of SAPHO syndrome complicated by sternoclavicular arthritis and subcutaneous abscess

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Conflict of interest: None

The patient is a 76-year-old male with tattoos, a smoking history, and a tonsillectomy. At the age of 41, shoulder pain spread to the peri-clavicular area. Skin ulcers on the sternocostal, sternoclavicular joint, and clavicle occurred in X-1. Scaling and vesicular eruptions appeared on the palms and plantar. MRI showed thickening of the clavicles, and we started MTX and bisphosphonates with the diagnosis of SAPHO syndrome. Since the pain and ulceration didn't improve, he'd transferred to our hospital in April X. The ulcer was draining with high CRP and negative antinuclear antibodies. A contrast-enhanced CT exhibited the right sternum area showed an abscessed lesion with a contrast effect of septal walls without traffic with the skin or bone. Stab culture showed *MRCNS* and *S. epidermidis*. We discontinued MTX, administered VCM and RFP. On the 20th day, we switched to oral LVFX, and GLM was introduced, judging the infection was improving. Arthralgia disappeared on the 17th day. In August X, He was re-admitted because of worsening of subcutaneous cysts and joint pain. We changed GLM to CZP, and it disappeared. SAPHO syndrome can be associated with aseptic cysts, but the infection can also lead to subcutaneous abscesses, and we need to pay attention to pyogenic arthritis and abscess.

## P62-4

### Systematic review of E148Q variants in patients with familial Mediterranean fever

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Conflict of interest: Yes

[Objective] There are more cases of familial Mediterranean fever (FMF) patients in Japan with *MEFV* gene polymorphisms such as exon 2 compared to Europe and the United States. In particular, the significance of the E148Q (Glu148Gln) variant remains unclear. We reported that the compound heterozygotes group containing the E148Q variant had a significantly higher FMF diagnosis rate than the E148Q variant heterozygotes group at this conference last year. This time, we investigated the contents of the papers on E148Q variants published so far. [Methods] In the E148Q search on PubMed, 333 papers were extracted and their contents were examined. [Results] Of the 333 papers extracted, 21 papers discussing E148Q variant and FMF onset and diagnosis (12 positive papers, 6 negative papers). Among the positive papers, there were 4 papers suggesting the possibility of progressing to FMF by adding other variants to the E148Q variant. [Conclusions] From a systematic review of the E148Q variant, the E148Q variant alone has no effect, but the addition of other *MEFV* variants to the E148Q variant acts as a modifier for other risk alleles, as a result, it was suggested that the threshold for disease susceptibility could be lowered and contribute to the onset of FMF.



## P62-5

### Real-world data showing maldistribution in intractable familial Mediterranean fever in Japan

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Conflict of interest: Yes

[Objectives] Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by serositis and periodic fever. It develops with many atypical presentations, which makes the diagnosis challenging. This study aims to clarify the regional differences in the number of the patient in Japan to verify the presence of underdiagnosed patients. [Methods] Based on hygiene administration reports from 2015 to 2019, we compared the ratio of patients certified for intractable FMF fever modified with populations in each region in each fiscal year. [Results] The number of certified patients per 1 million people was 6.9 in Hokkaido and 5.3 in the Kyushu and Okinawa region in 2019, both being significantly larger than 2.8 in Japan. In the Kyushu region in 2015, Nagasaki Prefecture had 9.5, which was significantly larger than the other prefectures in Kyushu. The above differences had been consistently increasing since 2015. [Conclusion] There were significant regional differences in the ratio of certified patients with FMF. In particular, the maldistribution within the Kyushu region suggests that the patients may not be adequately diagnosed even in areas where similar prevalence is expected.

## P62-6

### Hyper-inflammatory syndrome after mRNA COVID-19 vaccination in the elderly

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Conflict of interest: None

[Objective] We describe clinical manifestations of hyper-inflammatory syndrome among persons who admitted to the hospital because of fever of unknown origin (FUO) after mRNA COVID-19 vaccination. [Methods] Medical charts were retrospectively reviewed for the cases of FUO who admitted to our hospital since April, 2021. Included were patients who developed sustained fever within 6 weeks after the mRNA COVID-19 vaccination. Infection including COVID-19, malignancy, autoimmune and auto-inflammatory diseases were excluded. [Results] There were 4 cases, with 2 male and mean age 81. Organ involvement was liver dysfunction (3), rash (2), arrhythmia, headache, mononeuritis, diarrhea, and arthritis (1 each). Mean number of organ involved was 2.75. All the patients showed hyper-inflammatory states. The mean value included CRP (21.5 mg/dl), ferritin (3112 ng/ml), D-dimer (13.6 µg/ml). One developed DIC. Treatment included methylprednisolone pulse (4), oral prednisolone (3), tocilizumab (3), thrombomodulin alfa (1), high-dose immunoglobulin G (1). All recovered and discharged after the mean of 35 days. [Conclusions] COVID-19 sometimes leads to severe hyper inflammation and coagulopathy. The present cases suggest the need of careful follow-up in elderly persons after mRNA COVID-19 vaccination.

## P62-7

### Three new cases of adult-onset Still's disease (AOSD) following SARS-CoV-2 vaccination

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Conflict of interest: None

We experienced three cases of AOSD after SARS-CoV-2 vaccination (V). [Case 1] A 59-year-old woman was diagnosed with AOSD based on spiking fever, sore throat, polyarthralgia, rash, lymphadenopathy, splenomegaly, leukocyte 13,320/µL, liver dysfunction, CRP 13.5 mg/dL, serum ferritin (Fr) 1,776 ng/dL after the first V. The disease improved with prednisolone (PSL) 50 mg and tocilizumab. [Case 2] A 77-year-old woman had spiking fever, polyarthralgia, rash, leukocyte 10,090/µL, liver dysfunction, CRP 14.5 mg/dL, serum Fr 18,002 ng/mL after the second V. She was diagnosed as AOSD with hemophagocytic syndrome, because anemia and thrombocytopenia progressed, and hemophagocytosis was observed on bone marrow examination. The disease improved with steroid pulse therapy, followed by PSL 60 mg in combination with cyclosporine. [Case 3] A 35-year-old man had spiking fever, sore throat, polyarthralgia, rash, leukocyte 15,350/µL, liver dysfunction, CRP 10.5 mg/dL, serum Fr 1,263 ng/mL after the first V. The disease was improved with PSL 40 mg. The onset and relapse of rheumatic disease after vaccination have been reported. Our cases that developed AOSD after vaccination included moderate to severe patients who required steroid pulse therapy, immunosuppressive drugs or biologic agent.

## P62-8

### A case with A20 haploinsufficiency suffered from repeated diplopia mimicking neurological Behçet's disease

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Conflict of interest: None

[Case] A 38-year-old man with a history of incomplete Behçet's disease (BD), he visited our hospital with the chief complaint of acute onset diplopia and persistent singultus. He was suspected neurological BD based on his medical history, but did not reach a definitive diagnosis. There was an episode of recurrent aphtous ulcer that persisted from the late teens. A genetic test related to hereditary autoinflammatory disease was performed. As a result, c.259C>T (p. Arg87\*) mutation was found in the *TNFAIP3* gene in a heterozygous manner. The mutation has been reported in two families of A20 haploinsufficiency (HA20). Functional analysis revealed that the suppression of NF-κB activity was significantly disrupted compared to the wild-type. Being considered to be a pathogenic variant, HA20 was diagnosed. In 2016, Zhou Q et al. was reported HA20 as a novel auto-inflammatory disease that presents with symptoms similar to BD due to a mutation of the *TNFAIP3* gene. Dysfunction of A20 protein encoded by *TNFAIP3* gene impairs control of TNF-α and other cytokine. Although BD-like symptoms have been reported for HA20, there are few reports of central nervous system symptoms. We report a rare case of HA20 in a Japanese adult male with central nervous system symptoms.

## P63-1

### Utility and Problem of AI interview system Ubie in first visit at outpatient clinic in Rheumatology department

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Conflict of interest: Yes

[Objective] Evaluation of usefulness of AI interview system in outpatient clinic [Methods] Patients at the outpatient clinic for the first visit, were randomly assigned to two groups: interviewed with a paper or an AI tablet. The attending doctors confirmed the results of the interview. Patients evaluated the satisfaction level of the interview system (0-10) and the medical care (0-10). The doctors also described the degree of satisfaction with the interview (0-10) and measured the time of consultation (min). [Results] 405 patients (209 in AI, 196 in paper) participated the study. Patient satisfaction in the interview system was significantly higher in AI than that of paper (7.3 ± 2.1 vs 6.6 ± 2.3, p < 0.01), and the satisfaction to the medical care was as good as 8.8 ± 1.4 vs 8.5 ± 1.8 in both group (p = 0.14). The doctor's interview satisfaction level was significantly lower in AI than that of paper (4.0 ± 1.9 vs 5.0 ± 1.7, p < 0.01), and the consultation

time was comparable in both group ( $22.1 \pm 9.1$  vs  $20.6 \pm 8.7$  min,  $p = 0.11$ ). [Conclusions] Since the AI interview was easier to answer than the paper, the patient satisfaction was improved. Although there was no significant effect on the consultation time, the doctor's satisfaction was low due to the inadequacy of the contents.

### P63-2

#### The current status of tracing reports for patients with rheumatoid collagen disease

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Conflict of interest: None

[Objective] A tracing report (TR) is a medication information that provides prescribers with information about a patient's medication status and side effect. The current study aimed to extract information about the present status and issues of TR for patients with rheumatoid collagen disease. [Methods] We included patients with rheumatoid collagen disease treated at Showa University Koto Toyosu Hospital, for whom a TR was produced. We surveyed the insurance pharmacies that reported a TR for the target patients. The following three items were included in the questionnaire: (1) Do you feel that TRs are less commonly used for rheumatoid collagen diseases? (2) Do you feel that it is more difficult to use TRs for rheumatoid collagen diseases? (3) If so, why? [Results] There was a total of 704 TRs used during the study period; of them, 16 (2.3%) were for patients with rheumatoid collagen diseases, including seven for side effect, three for prescription suggestions and adjusting remaining medication. The results of the questionnaire were: (1) TRs were not less commonly used; (2) Yes, the hurdles were high; (3) It was difficult to intervene because the reasons for drug changes were unknown. [Conclusions] It is important strengthen cooperation between medical institutions and insurance pharmacies.

### P63-3

#### Hoffmann's syndrome simulating as inflammatory myopathies: a case report

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Department of Rheumatology, Japanese Red Cross Kochi Hospital

Conflict of interest: None

The patient is a 65-year-old man has treated rheumatoid arthritis with prednisolone and sulfasalazine for ten years. He had suffered from dysphagia and dysarthria for 5 months and proximal muscle weakness for one month. Because his serum creatine kinase (CK) level was elevation, he initially visited our rheumatic department that he was suspected of having inflammatory myopathies (IM). He had erythema on posterior cervical, right auricle and periungual. Laboratory test revealed that CK, serum aldolase and CRP levels were elevated. Thyroid function was low. Antinuclear antibody and myositis-specific autoantibodies were negative. Imaging studies showed bilateral interstitial lung shadows by chest CT, and hyperintense at femoral muscles by fat-suppressed T2-weighted MRI. Muscle biopsy, from his left semimembranosus muscle specimen demonstrated inflammatory cell invasion and muscle degeneration. He was started on levothyroxine treatment and, subsequently, clinical symptoms and biochemical parameters completely resolved with replacement therapy. Lung shadows also eliminated by some antibiotics. Finally, we diagnosed Hoffmann's syndrome associated with hypothyroidism. The present case highlights that Hoffmann's syndrome should be considered in the differential diagnosis of IM.

### P63-4

#### A case of primary malignant lymphoma of the central nervous system presenting with Froin's syndrome and resembling ventriculitis

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Internal Medicine, Sanuki Municipal Hospital

Conflict of interest: None

The elderly man with PMR was diagnosed with B-cell malignant lymphoma of the ENT region in November 2014, which went into remission after chemotherapy and has never relapsed after treatment. However he was impaired consciousness and deteriorated suddenly in March 2021. Bilateral Babinski reflexes were positive. Head MRI showed strong contrast in all ventricular walls and severe edema around the ventricles. There was no SOL in the brain parenchyma. Whole body CT showed no recurrence of lymphoma. The spinal fluid was xanthochromic and hypercoagulated with markedly elevated protein levels. The PCR test for Mycobacterium tuberculosis in the CSF was negative, but the ADA level was markedly high. We initially thought that the patient had tuberculous ventriculitis and administered anti-tuberculosis drugs and steroids, but these were ineffective. Later, based on the results of IL-10 level in CSF, cytology, and immunoglobulin H-chain gene rearrangement, we made a final diagnosis of Primary Central Nervous System Lymphoma (PCNSL) confined to the ventricles of the brain. PCNSL localized in the ventricles is very rare and its diagnosis is very difficult. We will discuss about the mechanism of Froin's syndrome, differentiated diagnosis of ventriculitis, and diagnostic approaches for PCNSL.

### P63-5

#### Cytomegalovirus gastric ulcer in patient with systemic lupus erythematosus: case report

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Conflict of interest: None

[Case] A 69-year-old woman, with a 32-year history of systemic lupus erythematosus (SLE), was admitted to our hospital because of anemia, hyponatremia, and renal dysfunction. She had been consecutively treated with prednisolone (PSL) and cyclosporine (CsA), allowing for maintaining remission; meanwhile, tacrolimus and mycophenolate mofetil were previously administered because of repeating relapse. She showed positivity for cytomegalovirus (CMV) antigenemia. Additionally, upper endoscopy demonstrated gastric ulcer, whose biopsy specimen indicated CMV inclusion bodies and some CMV immunostaining positive cells, leading to the diagnosis of CMV gastric ulcer. She was treated with ganciclovir and proton pump inhibitor after discontinuing CsA, resulting in achieving remission. [Conclusion] CMV gastritis, which may be causal of gastrointestinal bleeding or perforation, sometimes develops in patients with connective tissue disease during immunosuppressive therapy. Therefore, it is necessary to initiate appropriate treatment immediately after making diagnosis definitely determined by endoscopic and significant histological findings.

### P63-6

#### Elevated rheumatoid factor and anti-galactose-deficient immunoglobulin G in syphilis were decreased by treatment

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Conflict of interest: None

(Introduction) Rheumatoid factor (RF) positivity and elevated anti-galactose-deficient immunoglobulin G (IgG) levels may be observed in chronic infections, such as tuberculosis; however, these findings are uncommon in patients with syphilis. (Case Presentation) A 32-year-old woman developed generalized skin rash and swollen cervical lymph nodes since March 10, 2021 and arthralgia and joint swelling of both hands and feet on March 20. She was admitted to our hospital on March 23. Laboratory test results on admission revealed serum RF level of 225.7 IU/mL, anti-galactose-deficient IgG level of 178 AU/mL, anti-*Treponema pallidum* antibody cutoff index of 17.4, and a positive result on rapid plasma reagin testing. The patient was diagnosed with second-stage syphilis and received amoxicillin (1500 mg/day) for 8 weeks, which led to improvement in arthritis and reduction in serum RF and anti-galactose-deficient IgG levels. (Discussion) The prevalence of syphilis is increasing in Japan

in recent years. In this case, treatment of syphilis led to reduction in serum RF and anti-galactose-deficient IgG levels; elevated serum RF and anti-galactose-deficient IgG levels appeared to be secondary to chronic infection.

## P64-1

### Influences of patients' characteristics on femoral rotation angle after total hip arthroplasty for Rheumatoid Arthritis

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Conflict of interest: Yes

[Introduction] The purpose of this study was to measure femoral rotation (FR) after total hip arthroplasty (THA) for rheumatoid arthritis and to investigate patients' factors that affect FR. [Methods and Subjects] Thirty-four joints that underwent THA were included in the study. FR, the anatomical anteversion angle (ASA) and the functional femoral anteversion angle (FSA) were measured on CT preoperatively and 1 week after THA. To investigate patients' factors that affect FR, Correlation coefficients between the postoperative FR and preoperative FR on affected side. Coefficients between FR and the contralateral FR, ASA and FSA were also calculated. [Results] FR was  $1.3 \pm 10^\circ$  preoperatively and  $1.4 \pm 14^\circ$  postoperatively with no significance; ASA increased significantly from  $18 \pm 10^\circ$  to  $32 \pm 12^\circ$  and FSA increased significantly from  $19 \pm 8^\circ$  to  $34 \pm 12^\circ$ ; Pearson's correlation coefficient results showed that postoperative ASA on the affected side ( $r = -0.55$ ,  $p < 0.01$ ), preoperative ASA ( $r = -0.39$ ,  $p = 0.02$ ), preoperative FR ( $r = 0.49$ ,  $p < 0.01$ ), and healthy FR ( $r = 0.38$ ,  $p = 0.03$ ) on the affected side were significantly correlated with FR. [Conclusion] In RA patients, there was no significant change in femoral rotation angle after THA surgery, but it was affected by the anteversion of femoral components.

## P64-2

### The influence of low muscle mass estimated by cystatin C and creatinine in patients with osteoarthritis undergoing total hip and knee arthroplasty

Toki Takemoto, Takeshi Oguchi, Sakurako Yoshio, Shiro Urata  
Department of Orthopedic Surgery, Anjo Kosei Hospital

Conflict of interest: None

[Objective] Arthroplasty generally give good results for osteoarthritis (OA) but there are some differences in individual cases. It has been reported that low muscle mass may be screened by creatinine (Cre), cystatin C (CysC) and body weight. This study investigates the relationship between patient background and postoperative results was examined in OA patients undergoing TKA (49 cases) and THA (37 cases). [Methods] The cut-off points for low muscle mass of  $\text{Cre} / (\text{CysC} \times \text{body weight})$  were 0.0145 for men and 0.009 for women. We compared the low muscle mass group (L group) and the normal group (N group). [Results] For both TKA and THA, the differences between the L and N groups were gender (male had a higher proportion of N group), preoperative Hb (high in N group), and BMI (high in N group). Only TKA was different in age (73.5 years in L group, 65.5 years in N group). Postoperative wound complications occurred only in 2 patients in L group of TKA. There was no difference in the JOA score 6 months after the operation and the number of days required to obtain 10 m of walking with a cane after the operation. [Conclusions] In the TKA case, group L was older and had postoperative wound complications, so it may be a worse case, but there was no significant difference in postoperative results.

## P64-3

### Short-term clinical results of triple arthrodesis for rheumatoid hindfoot deformity

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Keita Koyama, Shiho Nakano, Koichi Nakagawa  
Toho University Sakura Medical Center

Conflict of interest: None

[Objective] To investigate short-term clinical results of triple arthrodesis for rheumatoid hindfoot deformity. [Methods] Four feet of 3 patients, of which surgery was performed at our hospital between 2016 and 2020, were included in this study. The triple arthrodesis was performed for hindfoot rheumatoid arthritis. Their mean follow-up period was 37 months (range, 12-61 months). Postoperatively, the calcaneal pitch, Mearys angle were measured on the standing lateral radiographs for the hindfoot. RA foot ankle scale of the JSSF-RA scale, SAFE-Q were also recorded. [Results] Postoperatively, the calcaneal pitch, Mearys angle significantly improved compared to those preoperatively (mean: calcaneal pitch  $13.3 \rightarrow 18.3$ , Mearys angle  $10.8 \rightarrow 6.3$ ). The postoperative mean JSSF-RA scale showed pain: 30, deformity: 25, ROM: 11.7, walking ability: 20, ADL: 7.3, and total: 94 points. The postoperative mean SAFE-Q showed pain: 90.3, physical functioning: 88.7, social living: 91.7, shoe-related: 86, general health: 91.7 points. No complications such as nonunion, infection, or adjacent joint symptoms were observed. [Conclusions] Short-term results of triple arthrodesis for rheumatoid hindfoot were good. long-term follow-up will be necessary to evaluate this surgical method for the rheumatoid hindfoot deformity.

## P64-4

### Cup-in-cup technique to manage recurrent anterior dislocation after total hip arthroplasty: a report of two cases

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Department of Orthopedic Surgery, Sagami National Hospital

Conflict of interest: None

[Introduction] Dislocation is a major complication after total hip arthroplasty (THA). In cup-in-cup technique, a new acetabular shell is cemented in an existing shell. We present two cases of repetitive anterior dislocation after THA which is managed using cup-in-cup technique. [Case 1] A 68-year-old male with a history of rheumatoid arthritis (RA) underwent posterior approach (PA) right THA. 2 years after the surgery, recurrent anterior partial dislocation occurred. Revision surgery was performed using cup-in-cup technique and Dual mobility system. Postoperative course was uneventful. [Case 2] A 70-year-old male with a history of RA underwent PA left THA. 8 years after the surgery, recurrent postoperative anterior dislocation occurred. The patient underwent revision surgery using cup-in-cup technique and dual mobility system. Postoperative course was uneventful. [Discussion] In these two cases, a standard cup revision surgery may result in insufficient offset and hip instability due to soft tissue laxity and bone fragility. Cup-in-cup technique, which can extend offset, and dual mobility system are useful option for repetitive THA dislocation in RA patients. [Conclusion] Cup-in-cup technique is a useful THA revision technique which is less invasive and extend offset.

## P64-5

### Revision total knee arthroplasty for a case of loosening with extensive defect of the distal femur

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Conflict of interest: None

[Introduction] The treatment result of total knee arthroplasty (TKA) is good. But revision TKA has recently increased with increases in the number of operative cases and the aging of the patients. We report our experience with one case of revision TKA in extensive defect of the distal femur. [Case] Patient was 88-year-old woman with a history of TKA for osteoarthritis. She consulted our hospital because of knee pain. On radiography, loosening with extensive defect of the distal femur was recognized. Because she complained of severe pain and gait disturbance, we chose to perform revision TKA with distal femur replacement. There were no post-operative complications, and she had successfully returned to her pre-operative daily living. [Clinical significance] Distal femur replacement is a viable option for a case of loosening with extensive defect of the



distal femur after TKA.

## P65-1

### Evaluation of usefulness of pharmaceutical outpatient clinic for RA patients in our hospital

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Conflict of interest: None

[Objective] We conducted a questionnaire about patient understanding before and after pharmaceutical outpatient clinic, and evaluated the effectiveness of that. [Methods] The subjects were 20 analyzable patients at our hospital from April 2019 to October 2019. We evaluated the difference of understanding of RA drugs before outpatient practice between the biological DMARDs use group (BIO) and non-use group (nonBIO) by Fisher's test. We evaluated the difference of questionnaire results before and after outpatient practice by McNemar test. [Results] Study patients: 20, questionnaire collection rate before practice: 95%, after: 80%, disease duration: median 5 years. There was no difference in the patient understanding before practice with or without BIO. Many patients understood what to do if they forgot to take medicine after outpatient guidance ( $p=0.03$ ). In the questions about what to do with RA drugs when you have a illness, especially an infection, the correct answer rate tended to increase in BIO ( $p=0.13$ ), on the other hand it didn't change in nonBIO. [Conclusions] Pharmaceutical outpatient clinic was helpful in understanding proper medication. However, there was a difference in effect between the two groups, and so we may be necessary to change contents of teaching with or without BIO

## P65-2

### Interventions of nursing for leukocytapheresis (LCAP) at rheumatoid arthritis

Miyuki Takemoto<sup>1</sup>, Takako Kaneda<sup>3</sup>, Atsushi Sunami<sup>2</sup>, Masamitsu Natsumeda<sup>3</sup>, Yosuke Asano<sup>3</sup>

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Conflict of interest: None

[Objective] Leukocytapheresis (LCAP) for rheumatoid arthritis is now one of the safe treatments for drug resistant RA. And granulocytapheresis (GCAP) has been also one of the treatments for psoriatic arthritis since 2019. The purpose of this study was to define whether apheresis therapy assisted by nurse can help the patients get better on the result of treatment and PROs or not. [Methods] We studied 58 patients who had LCAP at our hospital from February 2019 to February 2021. At the end of LCAP, the patients filled out the questionnaire about their psychological state which was originally made in our hospital. And we measured the disease activity state using it. [Results] We found out the strong negative correlation between at the first time of LCAP and the post 8 weeks of it on  $\Delta$ DAS28-CRP ( $p=-0.632$ ) and  $\Delta$ DAS28-ESR ( $p=-0.645$ ). We also found out the strong negative correlation on  $\Delta$ HAQ-DI ( $p=-0.524$ ),  $\Delta$ physician VAS ( $p=-0.711$ ) and  $\Delta$ patients total VAS ( $p=-0.533$ ). This was a highly useful result of LCAP for rheumatoid arthritis with high disease activity. [Conclusions] During apheresis therapy, many staffs such as the nurses and engineering technicians manage the patients. So, the patients can feel relieved to take the therapy, and they can accept the necessary number of the therapy.

## P65-3

### An attempt to improve foot care in patients with rheumatoid arthritis

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Yu Family Clinic

Conflict of interest: None

[Objective] Toe deformities can adversely affect the quality of life of

patients with rheumatoid arthritis (RA). Here, we report our attempts to improve foot care for RA patients. [Cases] The common foot problems observed in these 55 patients were nail troubles (23), callus/clavus (23), and both (9). The most common nail troubles were pincer nails and ingrown nails, which were considered to have grown due to toe deformity and the lack of movement of the toe owing to aging and/or pain. Some patients experienced an increase in pain and difficulty with self-care with the growth of pincer nail and later, ingrown nail. We recommended correction of repeated growths of ingrown nail. The callus was shaved using a special tool, and a pad was applied for decompression, when necessary. We also considered the use of insoles and provided guidance regarding walking appropriately to facilitate adequate movement and stretching of toes. [Conclusions] Despite advances in the treatment of RA, toe deformities due to long-standing RA are not uncommon. Nurses play an important role in foot care because patients often share their foot related concerns with nurses. Therefore, nurses should pay attention to these issues shared by patients and provide appropriate foot care in collaboration with physicians.

## P65-4

### Development of Rheumatoid Arthritis Recovery Experience Questionnaire (RAREQ) -Item Selection Process-

Hatsumi Kanzaki

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Conflict of interest: None

[Objective] We define RA patients' abilities and processes to adapt well to difficulties as "recovery". In order to develop a scale to measure the processes and degree of recovery, we selected the items to be measured. [Methods] 1) We selectively read the papers on recovery of patients with RA published in and after 2000 to identify qualitative content for scale items; 2) we evaluated the items; and 3) RA patients who experienced recovery evaluated the items (content validity). [Results] We searched "adaptation" within MeSH in the MEDLINE/CHINHL database, and found 422 studies. We also searched ICHUSHI, using its thesaurus search browser, and found 29 studies. Out of the 451 qualitative studies, 437 studies were excluded by the exclusion criteria, leaving 14 studies to be analyzed, all of which were in English. We then selected 82 items as candidates for scaling. Five RA patients then evaluated and reduced the 82 items to 62. In the future, we will conduct a Web survey on RA patients, asking them to rate the 62 items by a five-point Likert scale. After that, the process and degree-of-recovery scale will be finalized through a test of reliability and validation. [Conclusion] Eighty-two items were identified, and based on an evaluation by RA patients, 62 final items were selected.

## P65-5

### Foot care might give the chance of opportunity for surgical treatment, A case report

Rumi Inoue<sup>1</sup>, Ryoza Harada<sup>2</sup>, Koji Takasugi<sup>3</sup>, Kazuhiko Ezawa<sup>3</sup>, Kie Inoue<sup>4</sup>, Shinichiro Fujita<sup>4</sup>, Sakiko Shinmyo<sup>5</sup>, Wataru Yamamoto<sup>6</sup>, Ryuichi Nakahara<sup>7</sup>, Yoshihisa Nasu<sup>7</sup>, Keiichi Nishida<sup>7</sup>

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Conflict of interest: None

[Objective] we describe a case in which an elderly patient with RA cleared up the patient's misconceptions about treatment through outpatient foot care, and ADLs improved markedly after surgical treatment. [Case] The patient was a woman in her 90s. She had been suffering from painful calluses associated with severe deformity of both forefeet for more than ten years, and An acquaintance referred her by an acquaintance to our outpatient foot care clinic. As the nurse in charge of the patient's care continued to talk, we revealed a misunderstanding about surgical treatment. The patient underwent excisional arthroplasty of both forefeet. At one year after surgery, there was no recurrence of painful calluses, and the

SAFE-Q showed improvement in pain and pain relatedness from 57 to 85 before surgery, overall health from 0 to 90 before surgery, and shoe-relatedness from 50 to 92. [Conclusions] Many patients with RA who use foot care are not eligible for surgical treatment due to complications. In this case, the patient missed the opportunity for surgery due to a misunderstanding caused by the loss of opportunity. We had a chance to feel outpatient foot care's role, responsibility, and satisfaction through this case in RA team medicine.

### P66-1

#### **Clinical courses and pregnancy outcomes of eleven cases complicated with Behcet's disease in our institution**

Kanako Chujo, Hiromi Shimada, Risa Wakiya, Shusaku Nakashima, Mikiya Kato, Taichi Miyagi, Yusuke Ushio, Koichi Sugihara, Rina Mino, Mao Mizusaki, Tomohiro Kameda, Hiroaki Dobashi  
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Conflict of interest: None

[Objective] We clarify the disease activity and pregnancy outcomes in Behcet's disease (BD). [Methods] We used the data of BD patients who were registered and became pregnant. We analyzed disease activity and therapeutic agents, and pregnancy outcomes. [Results] The subjects were 11 pregnancies of 8 cases. The age at conception was  $32.6 \pm 3.7$  years, and the disease duration was  $4.5 \pm 3.1$  years. Before conception, there were 4 cases of oral ulcer and 2 cases of genital ulcer. 5 cases received glucocorticoid (GC), and one case received adalimumab, and the other received colchicine. There were two cases of exacerbation during pregnancy, one with arthritis after discontinuation of adalimumab and the other with oral ulcer and erythema nodosum due to withdrawal of colchicine. These two cases needed to increase GC dose. Mean dose was  $5.7 \pm 2.2$  mg per day. All cases were live births and 2 cases ended in cesarean section. Gestational weeks was  $39.3 \pm 1.6$  weeks, and birth weight was  $2739.4 \pm 231.9$  g. One case had a preterm birth and 2 cases had low birth weight. [Conclusions] In the pregnancies with BD, the disease activity was relatively stable, and it was possible to control only with low-dose GCs. It is necessary to consider the usefulness of biologics and colchicine for maintaining disease activity.

### P66-2

#### **A case of anti-MDA5 antibody-positive amyopathic dermatomyositis with onset and re-exacerbation in the course of two pregnancies**

Shotaro Suzuki, Mitsuru Imamura, Yoshiki Ishizaki, Takayasu Ando, Harunobu Iida, Yutaka Goto, Kanako Suzuki, Tatsuya Kawasaki, Keiichi Sakurai, Tomofumi Kiyokawa, Machiko Mizushima, Kazuko Yamazaki, Hiroko Nagafuchi, Seido Ooka, Kimito Kawahata  
Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine

Conflict of interest: Yes

At 16 weeks gestation with her second child, a 31-year-old woman experienced erythematous skin rash on extensor surfaces of the fingers and knee joints. At 28 weeks gestation, intrauterine fetal growth retardation developed and she had a caesarian section. The levels of anti-melanoma differentiation-associated gene 5 (MDA5) antibody were elevated at 1250 (index value), and chest CT showed a nodular shadow along the left dorsal pleura, leading to the diagnosis of anti-MDA5 antibody-positive amyopathic dermatomyositis. Prednisolone (PSL) 60 mg/day and tacrolimus (Tac) 6 mg/day were started, resulting in rapid improvement of the skin rash and abnormal chest CT findings. One and a half years after her second pregnancy, she became pregnant with her third child. From the 20 weeks' gestation, her anti-MDA5 antibody and KL-6 titer increased rapidly and her elbow and knee rashes worsened. After increasing the dose of Tac only from 2 to 3 mg/day, the anti-MDA5 antibody titer gradually decreased and the skin rash improved. She gave birth to her third child at full term safely. We report a case of anti-MDA5 antibody-positive amyopathic dermatomyositis that developed and re-exacerbated over the course of two pregnancies, with some literature review.

### P66-3

#### **A case of anti-MDA-5 antibody-positive amyopathic dermatomyositis (CADM) with interstitial pneumonia had a healthy child 17 months after the start of triple therapy**

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Center for Rheumatic Diseases, Mie University Hospital

Conflict of interest: None

[Case presentation] A 24-year-old woman developed induration and erythema on her hips and legs. Prednisolone (PSL) 20 mg/day was started. Eighteen months later, she was referred to our department and hospitalized. She had Gottron papules and heliotrope rash, infiltrative shadow in the right lung field on chest X-ray, and positive anti-MDA5 ab without muscle symptoms. CADM was diagnosed. Considering the progression of rapidly progressive interstitial pneumonia (RP-IP), PSL 55 mg/day and tacrolimus (TAC) 2 mg/day and intravenous cyclophosphamide (IVCY) biweekly were started. The triple therapy suppressed RA-IP progression and PSL was gradually reduced to 5 mg/day. A total of 2.5 g of IVCY was performed. Seven months after the last IVCY, she turned out to be 5 weeks pregnant. TAC and PSL were continued during her pregnancy. No abnormalities were seen in the course of pregnancy and CADM didn't relapse. She delivered a 3372 g healthy girl at 40 weeks. [Clinical significance] Pregnancy and childbirth in patients with CADM has not apparent yet and effect of pregnancy on CADM is obscure. We report this case as a valuable case in the point that triple therapy resulted in early remission and patient obtained a healthy baby.

### P66-4

#### **Outcomes of pregnancies complicated by systemic lupus erythematosus (SLE) in our maternity outpatient**

Mika Hatano, Sakiko Isojima, Ryo Takahashi, Takahiro Tokunaga, Yoko Miura, Ryo Inoue, Eriko Ishidaka, Nobuyuki Yajima  
Division of Rheumatology, Department of Medicine, Showa University School of Medicine

Conflict of interest: None

[Objective] Pregnancies complicated by SLE require well planned and strict management. This study was conducted to evaluate the pregnancy outcome with SLE who attended the our maternity outpatient. [Methods] We conducted a retrospective study of pregnancy outcome, child prognosis, and maternal disease activity in 20 SLE patients and 23 pregnancies managed at our department of obstetrics and gynecology among 22 patients who attended our maternity outpatient clinic with a desire to have a baby between October 2014 and October 2021. Descriptive statistics were used for analysis. [Results] The 20 patients had established pregnancies (23 pregnancies), 4 of which were current pregnancies. Pregnancy outcomes for the 19 pregnancies, excluding interpregnancy, were 4 spontaneous abortions, 1 artificial abortion, 1 mid-term stillbirth, 5 preterm births, and 8 full-term births. In 13 pregnancies with live births, intrauterine fetal growth retardation was 2, gestational hypertension 4 and neonatal death 0. Relapse during pregnancy was 1. [Conclusions] The planned pregnancies of SLE patients in our maternity outpatient had fewer cases of SLE relapse during pregnancy. On the other hand, the probability of obstetric complications in pregnancies complicated by SLE is high even when the activity is stable.

### P66-5

#### **A case of systemic lupus erythematosus that took a long time to the permission of pregnancy, but resulted in delivery**

Takahiro Tokunaga, Yoko Miura, Mika Hatano, Sakiko Isojima, Norihisa Tada, Ryutaro Gunji, Kunika Shimizu, Noriko Konishi, Shinichiro Nishimi, Airi Nishimi, Sho Ishii, Yuzo Ikari, Kuninobu Wakabayashi, Takeo Isozaki, Tsuyoshi Kasama  
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Conflict of interest: None

The case is a 31-year-old patient who presented with lupus nephritis

type IV at the age of 17. She was treated with PSL and TAC, and developed lupus enteritis at the age of 25. She was treated with PSL 8 mg+TAC 2 mg+HCQ 200 mg at the time of introduction. eGFR: 92 ml/min/1.73 m<sup>2</sup>, urine protein/creatinine ratio: 1.2, anti-ds-DNA antibody: 30.4 IU/ml, C3: 76.0 mg/dl, C4: 13.9 mg/dl, IC-C 1q: 3.8 µg/ml. 2018 guidelines state that urine protein less than 0.5 g/day is criteria for permission of pregnancy, and 2017 EULAR guidelines state that high serological activity is risk for relapse. In this case, the dose of PSL was increased, and AZP was introduced, HCQ and TAC was increased. I got her to quit smoking. Although the treatment was effective, it took 1 year and 6 months, because the 2017 EULAR was to reduce the risk of miscarriage by maintaining stable disease for more than 6 months. After that, she conceived spontaneously and passed without relapse. The baby has grown to 1 month of age in good health. Treatment guidelines have been improved, including perinatal management methods and expansion of the range of permissible drugs. However, there have been no recommendations for treatment aimed at the perinatal period, and we look back at this case.

## P66-6

### A case of systemic lupus erythematosus (SLE) with severe proteinuria due to Hypertensive disorders of pregnancy (HDP)

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Conflict of interest: None

[Background] In pregnancy with SLE, the rate of SLE flare is 15-30%. However, the rate of HDP is also 16-30%, and it is important to differentiate the two. we report a case of HDP in which severe proteinuria was observed in late pregnancy. [Case] A 29-year-old woman was diagnosed with SLE and lupus nephritis IVb from a facial skin rash in X-18 years. X years, she became pregnant. her disease activity was stable, although she was taking medication that could not be used during pregnancy. Those medication were adjusted and She continued pregnancy. At 35 weeks, her proteinuria increased to 6.1 g/gCr, and her blood pressure was 152/96 mmHg, and she was admitted to the hospital as an emergency. Because of the lack of abnormalities in urinary sediment and changes in SLE activity markers, the possibility of flare was considered low, and the pregnancy was continued without strengthening treatment for SLE. She underwent a cesarean section at 36 weeks, and after deliver, a relatively rapid decrease in blood pressure and proteinuria was observed, and she passed without SLE flare. [Conclusion] Severe proteinuria in pregnancies with SLE should raise suspicion of flare, but since HDP can also present with the same symptoms, evaluation of SLE activity is important.

## P67-1

### Analysis of pseudo-PMR and pseudo-RA cases responding to colchicine

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Conflict of interest: None

Polymyalgia rheumatica (PMR), elderly onset rheumatoid arthritis (EORA), and RS3PE syndrome are major diseases in the elderly which cause arthralgia and myalgia with severe inflammation and ADL impairment. While most patients respond to corticosteroids and anti-rheumatic drugs, we sometimes experience refractory or relapsing cases. It is known that crystal-induced arthritis including calcium pyrophosphate dehydrate deposition (CPPD) disease can be found which conditions called pseudo-PMR and pseudo-RA. It is hard to confirm the diagnosis in many cases because detection and evaluation of crystal deposition is often difficult. In the present study, we found that some patients with treatment-resistant PMR, EORA, and RS3PE, who had a course suggestive of CPPD, responded to colchicine. In these cases, corticosteroids and antirheumatic drugs could be reduced. Crystal-induced arthritis is widely recognized as acute monoarthritis of the knee and the cervical spine (e.g. crowned dens syndrome), but polyarticular articular manifestations are not rare. The possibility of chronic crystal-induced arthritis, such as CPPD, in our practice of rheumatic diseases will be discussed, along with literature review.

## P67-2

### An case of crowned dens syndrome seen in the acute phase of stroke

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Conflict of interest: None

50 year old male On March 28, X, right hemiplegia and impaired consciousness appeared, and he visited a nearby doctor and was diagnosed with cerebral infarction of the left middle cerebral artery. After admission, he began to have a fever of 39 degrees but the cause was unknown. Suspected vasculitis, PSL 15 mg / day was started, and he was transferred to our department. Head CT showed calcification around the axial dens, and the diagnosis was crowned dens syndrome. Parathyroid cinch (99mTC-MIBI) showed a small mass on the dorsal side of the right lobe and a tumor derived from the parathyroid gland, and the patient was diagnosed with primary hyperparathyroidism. The disease was judged to be a risk of pseudogout, and Evocalcet 2 mg / day was started, the condition became stable, and steroids gradually decreased. [Discussion] In this case, consciousness disorder was observed at the onset of cerebral infarction, and then there was motor aphasia, which made it difficult to communicate with medical staff. Among them, fever and CRP increased, and vasculitis was suspected and introduced, but it was a pseudogout attack. It should be recognized that patients with acute stroke may have pseudogout attacks.

## P67-3

### A case of refractory crystalline arthritis leading to the diagnosis of myelodysplastic syndrome

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Conflict of interest: None

Refractory crystalline arthritis has been reported as one of the arthropathies caused by myelodysplastic syndrome (MDS). We herein report a patient who could be diagnosed MDS with refractory crystalline arthritis. A 55-year-old woman was hospitalized for examinations of developing onset of neck pain, fever and positive inflammatory reaction one month ago. One week after hospitalization, she developed left elbow arthritis. Bacterial cultures of the left elbow joint fluid showed negative, and she received a clinical diagnosis of crystalline arthritis. She received taking NSAIDs under a diagnosis of crystalline arthritis. Once her symptoms improved, she soon developed polyarthritis. CT showed calcification around the tooth process, and musculoskeletal ultrasonography showed synovitis with crystals. She had crystalline arthritis onset while using NSAIDs. Pancytopenia was observed, and bone marrow examination revealed MDS. MDS is reported to be associated with immunity disorder, and Refractory crystalline arthritis is reported as one type of arthritis caused by MDS. Refractory crystalline arthritis and pancytopenia led to the diagnosis of arthritis associated with MDS. By paying attention to symptoms other than arthritis, we may be able to diagnose other diseases.

## P67-4

### A Case of Chronic Gouty Arthritis Presenting Severe Enthesophytes Successfully Diagnosed by Ultrasonography

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Conflict of interest: None

A 69-years-old male was referred to our institution complaining of remitting polyarthritis in MCP, wrist, knee, and ankle joints. His symptom had started 7 years before and was exacerbated during the last half year. Physical examination revealed painless swelling in some MCP, wrist, and knee joints and painful swelling around right forefoot and ankle joints. Laboratory testing showed high levels of CRP (9.1 mg/dL) and MMP-3



(191 ng/mL) but no significant findings in the levels of urate, electrolyte, thyroid hormone, and autoantibodies. Radiographs demonstrated significant spurs and ankylosis in axial joints and enthesophytes in calcaneum, patellae, and tibiae but no bone erosion. While ultrasonography showed hypoechogenicity in some extensor and flexor tendons of the ankle joints and conspicuous aggregates in Achilles tendons, there was a subcutaneous nodule around the lateral malleolus. The ultrasonographic images revealed the characteristic feature of tophus and led to the diagnosis of gouty arthritis. NSAIDs and colchicine markedly alleviated his symptoms and hyperuricemia was detected several months later. Ultrasonography helped diagnose the case of chronic gouty arthritis with some spondyloarthritis-like features including tenosynovitis, enthesitis, and enthesophytes.

## P67-5

### A case of Streptococcal bacteremia caused by tophus

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Department of Rheumatology Kochi Red Cross Hospital

Conflict of interest: None

An introverted 49-year-old male had been taking NSAIDs many times to release foot pain for about two years. He was urgently admitted to our hospital because of oliguria and disturbance of consciousness. Laboratory test revealed renal dysfunction and significant elevation of inflammatory markers. There were many tophi in his foot. One of them was self-destructed and ulcerating. Urate crystals were found in the smear of the wound and *Streptococci* were detected in the culture of the wound. Same bacteria were detected in blood culture, so we guessed tophus caused bacteremia. He underwent hemodialysis and debridement of wound and administration of antimicrobial agent, his clinical course ameliorated rapidly. However, shortly after completing the antimicrobial treatment, he developed lumbar pyogenic discitis. Secondary spillover from bacteremia was considered as a possible form of pathogenesis, we gave him another round of antimicrobial therapy. He was transferred to the hospital with a good recovery. [Discussion] Our experience with this case has made us realize that it is essential to treat gout patients with caution, suspecting not only gouty arthritis but also infectious complications. We believe this case has clinical significance and report it here.

## English Poster Session

### EP1-1

#### The analysis of new bone erosion at hands in rheumatoid arthritis with ultrasonographic remission

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Conflict of interest: None

[Objective] Ultrasonography of joints is a useful test, however is it enough to evaluate of bone joint damage progression? [Methods] 65 cases in which the no synovial signs of ultrasonography at the wrist at least 1 year were checked by X ray (in comparison with X ray at base line). [Results] Four cases clearly have new erosions. One case of them the erosions were huge. [Discussions] In RA patients, progression of bone erosions may occur even if there is no synovial signs by ultrasonography. In RA patients, there is a possibility that there is a synovium that cannot be detected by ultrasonography, or the erosions formation might be an inside out deformation of the bone.

### EP1-2

#### The role of methotrexate monotherapy along with vitamin D in newly diagnosed rheumatoid arthritis

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Conflict of interest: None

Introduction: Rheumatoid arthritis is a very common chronic inflammatory and autoimmune disease affecting approximately 1% of world population. The subsequent inflammatory changes lead to cartilage and bone destruction and the corresponding systemic inflammation may result in disorders of multiple organ systems. AIM: To study the role of methotrexate monotherapy along with vitamin D in newly diagnosed cases of rheumatoid arthritis. Materials and Methods: This is a prospective randomized controlled study. It comprised of two groups each having 50 patients of RA each. One group only methotrexate subcutaneously was given and in another group along with methotrexate vitamin D in a high loading dose was given. The dosage of Methotrexate was 25 mg/week and 0.6 million IU Vitamin D was given. The maximum follow up was of about 2 years which was done by clinical evaluation, ACR and DAS scoring. RESULTS: On the basis of this study it was found that patients who were given vitamin D along with subcutaneous methotrexate, the relief to the symptoms was early, significant ( $P < 0.05$ ) and more dramatic as compared to patients receiving only subcutaneous methotrexate. A significant association between vitamin D levels and ACR scores, CRP levels and ESR was observed. Lower vitamin D levels were associated with higher ACR scores, CRP levels and ESR. Conclusion: The findings of the present study thus showed that vitamin D deficiency was quite common in patients with rheumatoid arthritis and vitamin D deficiency was significantly associated with disease activity. Vitamin D supplementation helped to improve the outcome of methotrexate therapy among early cases of rheumatoid arthritis and also helped to eradicate the vitamin D deficiency in the targeted group. These findings suggest subcutaneous Injection Methotrexate monotherapy along with high dose Vitamin D is an excellent treatment regime for adult patients diagnosed with early RA.

### EP1-3

#### Usability and Acceptability of a New Autoinjector Device and its Associated App in Japanese Patients with Rheumatoid Arthritis

Hideto Kameda<sup>1</sup>, Lisa Gunther-lavergne<sup>2</sup>, David Gruben<sup>3</sup>, Tomohiro Hirose<sup>4</sup>, Simon Moss<sup>5</sup>, Mark Latymer<sup>6</sup>, Rieke Alten<sup>7</sup>

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Conflict of interest: Yes

Objective: ClicWise/Smartclic is a new reusable autoinjector with a dose dispensing cartridge for subcutaneous self-administration of biopharmaceuticals in development for patients with rheumatoid arthritis (RA) and

other diseases. The device can connect to a mobile phone app (ClicNote in Japan) to aid in tracking injections and other treatment or symptom data. The study objective was to collect ease of use and usability data on the ClicWise/Smartclic injector/app. Methods: After completing a patient profiling questionnaire, adult patients ( $\geq 18$  yrs) from Japan with RA, prescribed an injectable biologic, each received training on the use of the device/cartridge, and performed simulated injections. Participants completed a questionnaire with evaluations of the device categories (number of questions): 'ease of use' (14), 'usability effectiveness' (11), 'benefit of features' (8), and 'form factor' (7). Participants also received a storyboard presentation summarizing the key features of the app and completed 14 questions on connectivity and usability. Responses were recorded as Likert scale ratings from 1 (extremely negative) to 7 (extremely positive), and an estimate of patient training time for the device. Mean values are reported. The percentage of negative (Likert scale rating 1-2), neutral (3-5), and positive (6-7) responses for each category were determined. Results: Fifty patients (mean age [range], 55 [24-84] yrs; 86% female) participated in the study. Mean scores (percentage of positive responses) were: ease of device use 6.28 (81.7%), usability effectiveness 6.29 (82.7%), benefit of features 6.36 (84.1%), form factor 5.85 (69.4%), and connectivity & app 5.96 (70.6%). Mean estimated time for training a patient to effectively use the device/cartridge was 11 min (range, 0-30 min). Conclusions: Japanese patients with RA responded positively on the new autoinjector device/app across all categories, indicating its suitability for self-administration of biotherapeutics.

## EP1-4

### Correlation of cortical thickness ratio with bone mineral density and osteoporotic fracture during treating patient with rheumatoid arthritis: A longitudinal cohort study

Ichiro Yoshii

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Conflict of interest: None

Objective: Patients with rheumatoid arthritis (RA) are threatened by a substantial risk of osteoporotic fractures. We developed an index called the third metacarpal cortex thickness ratio (CTR), which reflects bone mineral density (BMD) in RA patients. A longitudinal study was conducted to verify the utility of CTR during follow-up. Methods: Subjects were RA patients who underwent dual-energy X-ray absorptiometry and hand radiography on the same day, monitored disease activity and activities of daily living at intervals of 3 months or shorter, and measured BMD and CTR at intervals of 1 year or shorter. The mean CTR during follow-up was tested for correlation with mean BMD at both the lumbar spine (LS) and femoral neck (FN) during follow-up. The correlation was examined including other variants that may be correlated with BMD. The risk ratio of incident osteoporotic fractures in variance including CTR and BMD was evaluated. Results: CTR was significantly correlated with BMD in the FN using multivariate model of linear regression analysis ( $p < 0.0001$ ), but was significantly correlated with BMD in the LS using only the univariate model ( $p < 0.01$ ). The only variant with a significantly higher risk ratio of prevalent osteoporotic fracture was the presence of prevalent osteoporotic fractures. CTR and BMD using Cox regression analysis with multivariate models did not show a significantly higher risk ratio. Conclusions: CTR was significantly correlated with BMD even during follow-up, especially in the FN. However, CTR and BMD were not risk factors for osteoporotic fractures.

## EP1-5

### The impact of sustaining SDAI remission for preventing incident of bone fragility fracture in patient with rheumatoid arthritis

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Conflict of interest: None

Objective: Impact of simplified disease activity index (SDAI) remission on avoiding incident bone fragility fracture (BFF) in rheumatoid arthritis (RA) patient was analyzed using retrospective cohort study. Methods: RA patients and patients without RA who measured bone mineral density and followed up were selected (RA and non-RA). Baseline charac-

teristics and candidate risk factors of these patient groups were matched. In the RA group, disease specific and general candidate risk factors were evaluated with respect to incident of BFF. The RA group was divided according to mean SDAI score  $\leq 3.3$  or  $> 3.3$  (G-rem and G-nonrem), and candidate risk factors in these two groups were evaluated. Results: Higher anti-cyclic citrullinated polypeptide antibodies (ACPA) titer, lower SDAI remission rate, and prevalent BFF were the significant risk factors in the RA group. No significant difference of incident BFF was shown between the RA and the non-RA group. Incident of BFF in the G-rem was significantly lower than in the G-nonrem, whereas no significant difference was shown between the G-rem and the non-RA and between the G-nonrem and the non-RA group. Conclusions: Disease activity in RA patient contributes actual incident BFF. Persistent SDAI remission is most desirable for preventing the incident of BFF.

## EP1-6

### The effect of anti-citrullinated polypeptide antibodies on bone mineral density decrease in patient with rheumatoid arthritis: A retrospective cohort study

Ichiro Yoshii

Musculoskeletal Medicine, Yoshii Hospital, Japan

Conflict of interest: None

Objective: Effects of anti-citrullinated polypeptide antibodies (ACPA) on bone mineral density (BMD) decrease using dual-energy X-ray absorptiometry (DXA) in patient with rheumatoid arthritis (RA) was evaluated with retrospective longitudinal cohort study. Methods: Patients who were examined DXA at first consultation (baseline) and were treated for more than five years were recruited. BMD were measured every six months and disease activity, activities in daily living, joint deformation score were also measured at every consultations. Relationship between BMD and candidate risk factors including ACPA positivity and serum titer were evaluated statistically using linear regression analysis. Evaluations were performed for the BMD and Z-score at baseline, mean value of these during follow-up, and change from baseline. Change of Z-score during follow-up was compared between groups what classified according to ACPA positivity (ACPA positive/negative group). Results: A total of 222 patients were included. Higher ACPA titer correlated significantly low BMD and Z-score in total hip (TH) ( $p < 0.05$ ), whereas ACPA positivity significantly correlated with low Z-score in lumbar spine (LS) and total hip (TH) during follow-up using univariate models ( $p < 0.05$ ). The ACPA positivity correlated with decrease of Z-score in both LS and TH using univariate models ( $p < 0.05$ ), whereas no significant correlation demonstrated using multivariate model. Change of Z-score in the ACPA positive group was significantly lower than in the ACPA negative group ( $p < 0.05$ ). Conclusions: Presence of ACPA contributes BMD loss after gender and age were adjusted.

## EP1-7

### Clinical experience of Sarilumab for rheumatoid arthritis

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Conflict of interest: None

[Objective] To report the clinical experience of 9 patients treated with Sarilumab for rheumatoid arthritis. [Methods] Nine cases (3 males and 6 females) of rheumatoid arthritis who introduced Sarilumab between June 2018 and August 2020 were included in this study. The examination items consist of transition of values (CRP, MMP-3, DAS28, SDAI, CDAI), cumulative survival rate of Kaplan-Meier method, prior drug in switch cases, adverse events. This study is part of the NOSRAD registry. [Results] CRP (mg / dl) (5.2 before administration, 0.08 in 1 month after the start of administration, 0.03 after 3 months, 0.19 after 6 months, 0.06 after 12 months), MMP-3 (ng / ml) (414 before administration, 245 in 1 month after the start of administration, 203 after 3 months, 173 after 6 months, and 177 after 12 months), DAS28 (5.4 before administration, 2.3 after 1

month after the start of administration, 2.2 after 3 months, 2.6 after 6 months, 2.4 after 12 months), SDAI (30.5 before administration, 9.0 1 month after the start of administration, 10.5 after 3 months, 11.9 after 6 months, 10.3 after 12 months), CDAI (25.2 before administration, 8.9 1 month after the start of administration, 10.4 after 3 months, 11.7 after 6 months, 10.3 after 12 months), all values improved significantly 1 month after the start of administration and continued for up to 12 months. The cumulative survival rate of the Kaplan-Meier method was 89% for 1 year and 76% for 2 years. There were 8 cases of switching from the prior biologics / molecular target drug, and the pre-administration products were Etanercept 2 cases, Adalimumab 1 case, Tocilizumab 3 cases, Golimumab 3 cases, Abatacept 2 cases, and Baricitinib 2 cases. Adverse events, as a case of pneumonia in 1 case, in the other case for the leukopenic case. [Conclusion] In particular, the improvement in laboratory values and disease activity was observed early after the start of administration, which was considered to be characteristic of Sarilumab.

## EP1-8

### Importance of CT scan for detecting lung cancer before the introduction of b/tsDMARDs: From FIRST registry

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Conflict of interest: None

[Objective] We have been performing CT scans for screening malignancies before introducing b/tsDMARDs since 2005. We aim to investigate the role of CT scan in the prognosis of lung cancer and the outcome of rheumatoid arthritis (RA) after treatment. [Methods] The prevalence and diagnosis of lung cancer, and the course of treatment for RA were investigated in b/tsDMARD's first-initiated RA patients from the FIRST registry (4378 patients) from April 2005 to September 2020, when CT scan was performed in all patients. [Results] Of 2440 cases, 15 (0.6%) were diagnosed with lung cancer, which was significantly higher than that in Japanese controls (0.4%) (SIR 3.59 [2.01-6.47]). Twelve patients, accounting for 75% of the cases, had early-stage lesions that could not be detected on an x-ray (Xp). All of the 12 early-stage lesions underwent curative resection with no recurrence during the observation period (mean: 54.5 months). Further, all of the three advanced lesions that were detectable on Xp received best supported care and regressed after a mean duration of 6 months (log rank  $p < 0.01$ ). These results indicate the usefulness of CT scans. Significantly greater number of patients with lung cancer had a history of smoking ( $p < 0.01$ ); however, non-smokers were also diagnosed with lung cancer (7 out of 1868, 0.4%), making it difficult to narrow down the target of CT screening. After early-stage lung cancer resection, RA treatment could be resumed in collaboration with the surgeons, and treatment including bDMARDs (IFX, ETN, TCZ, ABT, GLM) was performed. In population in which lung cancer was not detected by CT screening, the rate of diagnosis of lung cancer within 1 year was 0.12/100 person-years, which was similar to that in Japanese controls (SIR 0.99). [Conclusions] Chest CT scan of RA patients prior to the introduction of b/tsDMARDs may enable early detection of lung cancer, which improves the prognosis of patients and allows for a better treatment of RA.

## EP2-1

### Risk weight calculation of bone fragility fracture in patients with high risks of osteoporosis

Ichiro Yoshii  
Musculoskeletal Medicine, Yoshii Hospital, Japan

Conflict of interest: None

Background: Risk factors for incident bone fragility fracture (incident-BFF) were evaluated retrospectively in patient who has high risk of major osteoporotic fracture tested with fracture assessment tool. Methods: Patients who were tested X-ray picture of spine and dual-energy X-ray absorptiometry simultaneously, were recruited. Variants in the patients such as sex, age, presence of chronic kidney dysfunction (CKD), prevalent fragility fracture (pr-BFF), T-score in the lumbar spine and in the femoral

neck (Tscore-LS and Tscore-FN), presence of lifestyle-related diseases such as type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), insomnia, hypertension, hyperlipidemia, cognitive impairment (CI), and musculoskeletal ambulation disability symptom complex (MADS), abdominal aortic calcification (AAC), and glucocorticoid steroid administration were set as independent factors. They were eligibly followed up continuously for more than eight years. Development of incident-BFF during follow up was set as primary endpoint. Odds ratios of each factor were evaluated using Kaplan-Meier curve. Final risk weight of each variant was evaluated using linear regression analysis. Results: A total of 931 patients with 123 male and 808 female were included with a mean age of 78.6 years old ranged from 54 to 93-year-old. Factors that correlated significantly were pr-BFF, MADS, CI, hypertension, CKD, female gender, hyperlipidemia, insomnia, COPD, Tscore-FN, GCS, and AAC, in order of greatness of the hazard ratio, respectively. Conclusions: These results suggested past fragility fracture history and gait disability were most weighted for the incident-BFF. T-score was not a high risk factor, but there are many other factors of stronger evidence.

## EP2-2

### Clinical significance of serum creatinine-to-cystatin C ratio as a surrogate marker for incident osteoporotic fracture

Ichiro Yoshii  
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Conflict of interest: None

Objective: The authors hypothesized that Cr/CysC might function as a surrogate marker of incident fragility fractures and tested this hypothesis in a retrospective cohort study. Methods: Eligible patients who were tested bone mineral density in femoral neck (BMD) and serum creatinine-to-cystatin C ratio (Cr/CysC) simultaneously, were recruited. They were followed up for more than 12 months or developed major osteoporotic fracture (MOF), as a development of first MOF was set as a primary endpoint. Various patient's variants were set as candidate risk factors and risk ratios for the variants were evaluated using Cox regression analysis. The statistical procedures were repeated with crude dataset and narrowed dataset without patient who has a prevalent MOF. Results: A total of 659 patients, 183 men and 476 women, were included in the crude dataset. Variants with a significantly higher risk ratio for incident MOF using multivariate model were prevalent MOF and presence of rheumatoid arthritis. When the crude dataset was narrowed, a higher Cr/CysC at follow-up was the only variant with a significantly lower risk ratio using univariate models, meaning exactly the same using multivariate model. Conclusions: These results suggest that Cr/CysC may function as a predictor of MOF development.

## EP2-3

### Insufficient efficacy of immunosuppressants on skin sclerosis in patients with systemic sclerosis without interstitial lung disease

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Conflict of interest: None

[Objective] It has been reported that several immunosuppressants (ISs) including cyclophosphamide or methotrexate (MTX) improved skin sclerosis in patients with systemic sclerosis (SSc), mainly in case with interstitial lung disease (ILD). Therefore, we investigated efficacy of these ISs on skin sclerosis in SSc patients without ILD. [Methods] We underwent nailfold video-capillaroscopy from April 2018 to September 2021 in 132 patients who fulfilled the 2013 ACR / EULAR classification criteria of SSc. Among them, 102 patients without a history of using ISs were included. Changes in modified Rodnan's total skin thickness score (mRSS) before and after using ISs, as well concomitant ILDs were evaluated. [Results] ISs were initiated in 16 patients during observation; intravenous cyclophosphamide (IVCY) was used in 11 patients, mycophenolate mofetil in 2, MTX in 2, and tacrolimus in 1. Prednisolone was also used in 4 of the patients who underwent IVCY. None of the patients used rituximab. In 10 cases with ILD, no cases of exacerbation of mRSS after treatment were observed. In 5 cases, improvement of 5 points or more was



observed. On the other hand, in the cases without ILD, the exacerbation occurred in 3 cases, and no case improved by 5 points or more. There was a significant difference between the two groups. (Wilcoxon rank sum test,  $p = 0.014$ ) [Conclusions] In patients with SSc without ILD, ISs did not sufficiently improve skin sclerosis.

## EP2-4

### Relationship between relapse and poor oral condition that required tooth extraction in patients with vasculitis

Shoichi Nawachi<sup>1</sup>, Takayuki Katsuyama<sup>1</sup>, Kazuya Matsumoto<sup>1</sup>, Kei Hirose<sup>1</sup>, Kenta Shidahara<sup>1</sup>, Takato Nakadoi<sup>1</sup>, Yosuke Asano<sup>1</sup>, Yu Katayama<sup>1</sup>, Keiji Ohashi<sup>1</sup>, Yoshia Miyawaki<sup>1</sup>, Eri Katsuyama<sup>1</sup>, Mariko Narazaki<sup>1</sup>, Yoshinori Matsumoto<sup>1</sup>, Ken-ei Sada<sup>1,2</sup>, Jun Wada<sup>1</sup>

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Conflict of interest: None

[Objective] Infection is one of the inducers of vasculitis. This study is aimed to identify the relationship between severe dental infections equivalent to tooth extraction and the prognosis of patients with vasculitis. [Methods] This retrospective study included 63 patients admitted to Okayama University hospital for remission induction of ANCA-associated vasculitis (AAV) and polyarteritis nodosa (PAN) between January 2010 and July 2021. All of them were referred to the dental department for screening purposes at the start of remission treatment. The patients were divided into two groups. Tooth Extraction (TE) group was defined as patients who presented tooth decay/oral cavity or periodontitis or etc. that needs tooth extraction. The TE group also include the cases in which the tooth extraction was postponed due to the patients' condition. Non-TE groups did not have dental infections equivalent to extractions. The relapse in AAV/PAN within 1 year was compared between the groups. [Results] 32 patients (50.8%) were in the TE group. There was no significant difference in age or CRP levels between the two groups at the time of tooth extraction. 31.3% (10 patients) vs. 12.9% (4 patients) of patients relapsed and the relapse rate was higher in TE group ( $p=0.12$  by Fisher's test). The multivariate analysis (covariates: age, PSL dose, and serum levels of CRP) showed same tendency (OR=3.14 95%CI: 0.88-13.1,  $p=0.08$ ). It is possible that poor oral condition that required tooth extraction is associated with make vasculitis relapse. [Conclusion] This study shows the tendency that dental infection is associated with the recurrence of vasculitis. Also, We found that more than half of AAV/PAN patients have dental infections equivalent to tooth extraction at the start of remission treatment. This study shows also the tendency that dental infection is associated with the recurrence of vasculitis. We should pay attention to dental infection in the treatment of vasculitis.

## EP2-5

### A case of familial Mediterranean fever complicated with Covid-19

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Conflict of interest: None

<Case> A 33-year-old woman was referred to our hospital for intermittent fever that repeats once a month for a few days, since half a year before. She experienced joints and back pain, while she was febrile. Serum CRP was elevated at the time of fever to 2 mg/dl, while not elevated in nonfebrile period. She had SARS-CoV2 PCR tests whenever she was febrile and they were always negative. Diagnosis of familial Mediterranean fever was made based on the characteristic medical history according to Tel-Hashomer diagnostic criteria, and 1.5 mg of colchicine was prescribed with good response. Since then, she never had fever taking colchicine until September next year, when she had high fever and cough. The PCR test for SARS-CoV2 was positive at that time, but fortunately she fully recovered in a week with continued colchicine and the combination of casirivimab and imdevimab without interstitial pneumonia. <Discussion> As recently reported, neither FMF nor colchicine therapy, appear to affect the disease course of COVID-19. So, treatment with colchicine for FMF

patients should be continued during the coronavirus infection.

## EP3-1

### Comparative study of serum biomarker levels in anti-CCP antibodies positive and negative untreated rheumatoid arthritis

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Conflict of interest: None

[Objective] Anti-CCP antibodies (ACPA) are involved in the pathogenesis of rheumatoid arthritis, but there are also seropositive and negative cases, and the mechanisms of the pathogenesis of both are thought to be different. [Method] Cytokine levels in the serum of 78 early onset untreated rheumatoid arthritis patients and 10 healthy subjects were measured by multiplex assay. In addition, rheumatoid synovocytes from rheumatoid arthritis patients and peripheral blood monocytes (PBM) from healthy subjects were stimulated with various cytokines, and the expression of IL-23 gene was analyzed by RT-PCR. [Results] The results showed that serum IL-23 was significantly higher in the ACPA-positive group ( $1.33 \pm 0.98$  pg/ml) than in the healthy group ( $0.64 \pm 0.27$  pg/ml) and the ACPA-negative group ( $0.78 \pm 0.41$  pg/ml). Examination of ROC curve of serum IL-23 in positive and negative serum reaction showed a high value of AUC=0.7397 (95%CI; 0.6243-0.8552). In addition, serum IL-23 correlated with serum IL-6 ( $p<0.0001$ ,  $r=0.6497$ ). To clarify the regulatory mechanism of IL-23 expression, we confirmed that *IL-1 $\beta$*  strongly induced the production of IL-23 when rheumatoid synovocytes/PBM were stimulated with inflammatory cytokines. [Conclusion] IL-23 was significantly higher in the ACPA positive cases compared to the negatives. IL-23 has effects related to antibody production and may play a certain role in the production of ACPA.

## EP3-2

### Bone histomorphometric findings of fracture sites of atypical femoral fractures

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Conflict of interest: None

[Objective] To evaluate the histological analysis of the fracture site in atypical femoral fractures (AFF). [Methods] We registered 30 cases (36 femora) of bisphosphonates (BPs)-related AFFs. Age was 71 years old on average (49-93 years old), The duration of BPs was 7.6 years on average (0.5 to 16 years). The site of AFFs were subtrochanteric in 22 and diaphyseal in 14 femora. The fracture sites (cortex) were curetted and primary iliac bone graft were applied. The fracture sites were subjected to histological assessment. Microcracks and the density of empty lacuna were measured by using bone histomorphometry. Crack density (Cr. Dn), crack surface density (Cr.S. Dn), osteocyte density, empty lacuna density, and rate of empty lacuna density were calculated. [Results] Cr. Dn was  $1.77$  N/mm<sup>2</sup> on average. Cr.S. Dn was  $186$   $\mu$ m/mm<sup>2</sup> on average. The percentage of "increased" microdamage accumulation (defined as  $\geq 0.21$  for Cr. Dn based on the previous report) was 95%. Rate of empty lacuna 56.9% on average and the percentage of more than 50% for rate of empty lacuna was 60%. The significant association between rate of empty lacuna and Cr. Dn or Cr.S. Dn was not detected. [Conclusions] Microdamage accumulation was detected in almost all cases, suggesting main causative factor of AFFs.

## EP3-4

### High Type I Interferon Activity is Associated with the Pathogenesis of SLE and the Accrual of Organ Damage in Japanese SLE Patients

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Conflict of interest: None

[Objective] Serum type I interferon (IFN) activity is elevated in patients with systemic lupus erythematosus (SLE) compared with healthy subjects, suggesting the involvement of IFN in the pathogenesis of SLE. In particular, the incidence of lupus nephritis has been reported to be higher in SLE patients with high IFN activity than those with low IFN activity. However, the levels of IFN activity, disease severity, and affected organ profiles vary widely among ancestral backgrounds in SLE, and the role of IFN in the pathogenesis of Japanese SLE patients remains largely unknown. Therefore, this study aimed to examine the relationship between serum IFN activity levels and disease activity indices, clinical phenotypes, and organ damage accrual in Japanese SLE patients. [Methods] We measured IFN activity of pre-treatment and post-treatment sera of 40 Japanese SLE patients and examined the association between the IFN activity levels and disease activity indices, organ involvements, and SLICC Damage Index (SDI). [Results] IFN activities of pre-treatment sera of SLE patients were significantly elevated compared to those in patients with other collagen diseases or healthy subjects. Improvement in SLEDAI score was positively correlated with the decrement of IFN activity ( $r = 0.39$ ,  $p = 0.012$  Spearman's rank correlation). In addition, high serum IFN activity was significantly correlated with mucocutaneous manifestations, hematologic manifestations, and decreased complement titers, but there was no significant association between the IFN activity levels and the incidence of lupus nephritis. Furthermore, patients who developed organ damage ( $SDI > 1$ ) during the observation period had significantly higher serum IFN activity in the pre-treatment sera than those who did not ( $p = 0.039$  Mann-Whitney U test). [Conclusion] Our results suggest that elevated serum IFN activity is involved in the pathogenesis of Japanese SLE patients and may predict future organ damage accrual.

### EP3-5

#### **Incidence and clinical features of immune checkpoint inhibitor-induced joint symptoms: a single center experience and systematic review of the literature**

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Conflict of interest: None

Immune-related adverse events (irAEs), caused by immune checkpoint inhibitors (ICIs), can sometimes be severe and affect cancer treatment and prognosis, thus appropriate management is necessary. Major irAEs are thyroiditis, pneumonitis, and skin rash, but less frequently. Arthralgia has been reported to be the most frequent, with an incidence of nearly 10%. Here, we performed a meta-analysis on arthralgia by analyzing phase III randomized controlled trials (RCTs) that compared the use of ICIs, either anti-programmed death-1/ligand-1 (PD-1/PD-L1) and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4), or without ICIs for cancer treatment. A total of 2343 events of arthralgia were observed in 14,377 participants from 24 RCTs. We found that arthralgia was significantly increased by ICI treatment compared to non-ICI treatment, with OR of (odds ratio 1.37; 95% confidence interval: 1.20-1.56,  $I^2=35\%$ ). The overall incidence of ICI-related arthralgia was 17.6%. To optimize its diagnosis and management, we also analyzed our single-institutional cohort consisting of a total of 382 patients (median age 73 years) treated with ICIs. Forty-eight patients (12.6%) developed arthralgia while receiving ICI, mostly in large joints such as shoulders and knees. Most of the patients were negative for autoantibodies. Median duration to symptom onset was eight weeks (1-120). 31 (64.5%) patients also had other irAEs. Glucocorticoids or immunosuppressants drugs were administered in six patients (12.5%), resulting in improvement of joint symptoms. Patients with joint symptoms had a longer observation period than patients without joint symptoms (19.6 months vs 16.2 months), suggesting that their prognosis may be improved. ICI-induced joint symptoms are distinguished from other irAEs because they can persist for longer time periods even after ICIs are discontinued.

tinued, information on the management is highly relevant.

### EP3-6

#### **Interleukin-6 Induces Osteoblastic Differentiation in Human Peripheral Blood Mononuclear Cells**

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Conflict of interest: None

[Objective] Rheumatoid arthritis (RA) is a well-known chronic inflammatory disease with an increased risk of developing cardiovascular diseases. One of the major risk factors for cardiovascular diseases is vascular wall calcification. However, its underlying molecular mechanisms remain unclear. Some studies have shown that circulating osteoblast-lineage cells in peripheral blood mononuclear cells (PBMCs) are associated with marked induction of vascular wall calcification. We investigated the effect of IL-6 as a proinflammatory cytokine on vascular wall calcification mechanism induced by osteoblast-lineage cells in human PBMCs. [Methods] PBMCs were collected from healthy volunteers following a standard protocol and cultured on dentine slices or Aclar plastic films in the presence of IL-6 (50 ng/ml) for 21 days. After removal of the cells, the mineralized nodules on the dentin slices and Aclar plastic films were examined under a scanning electron microscope. The structures formed in the mineralized nodules were evaluated by energy-dispersive X-ray spectroscopy (EDX) and stained with Alizarin Red. Expression levels of osteoblast marker mRNA were measured by quantitative reverse-transcription PCR (qRT-PCR). [Results] The mineralized nodules were formed upon stimulation with IL-6. EDX analysis confirmed that the mineralized nodules were calcified matrixes composed of calcium and phosphate. Alizarin Red staining identified calcium on the mineralized nodule. qRT-PCR analysis revealed that the mRNA expressions of *ALP*, *osteoprotegerin*, *osteocalcin*, *RUNX2*, *SP7*, and *WNT-10B* were significantly up-regulated in cultured PBMCs upon stimulation with IL-6 than that under non-stimulation condition. [Conclusions] IL-6 induces calcified nodule formations with osteoblastic differentiation in PBMCs on dentin slices or Aclar plastic film. This implies that anti-IL-6 therapy in patients with RA might improve not only the disease activity but also vascular wall calcification.

### EP3-7

#### **FoxO regulates CD11c expression on macrophages**

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Conflict of interest: None

[Objective] So far, we showed that spleen tyrosine kinase (Syk) promoted atherosclerosis by controlling CD11c expression positively and was associated with approximately 1000 bp upstream from the CD11c gene transcription start site. Then, we explored what downstream molecules of Syk regulated CD11c transcription. [Methods] First, we listed candidate transcription factors that bound the Syk related region in the CD11c promoter and the regions corresponding to each transcription factor using *in silico* analysis. Then, we identified a transcription factor by measuring the CD11c expression of BMDM added the inhibitor using a flow cytometer. The subcellular localization on GM-CSF primed BMDM was evaluated by Western blot. Next, we confirmed the transcription factor bound the corresponding region of CD11c promoter using reporter assay and EMSA. Finally, we measured the CD11c expression of peripheral monocytes from mice fed with a high-fat diet and administrated with 20 mg/kg of the inhibitor. [Results] Of candidate molecules, FoxO inhibitor suppressed the CD11c expression on GM-CSF primed BMDM. Intracellular FoxO was decreased in Syk deficient BMDM. A reporter assay with mutant sequences related to FoxO binding region did not show a significant difference between Syk wt and deletion, contrary to the result with original sequences. EMSA showed the interaction between FoxO binding region and

FoxO. The cell surface expression of CD11c in peripheral monocyte from atherosclerosis-prone mice was decreased by the FoxO inhibitor. [Conclusions] This present study showed that FoxO1 regulates CD11c expression downstream of Syk.

### EP3-8

#### **PARP inhibitor regulates production of inflammatory cytokine and osteoclastogenesis**

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Conflict of interest: None

[Objective] PARP, poly ADP-ribose polymerase, is an enzyme that regulates downstream signaling through poly ADP-ribosylation of its substrates. Some PARP family protein inhibitors have been developed as anticancer drugs and regulate its substrates “3BP2” and “AXIN” through ADP-ribosylation and subsequent ubiquitination. Previous studies showed that 3BP2 is an adapter protein that is required for signal transduction of tyrosine kinase, and AXIN, which inhibits the Wnt/ $\beta$ -catenin pathway, suppresses osteoclast differentiation. In this study, we investigate the role of PARP inhibitors for inflammatory cytokine production and osteoclastogenesis through these two substrates. [Methods and Results] We show that one PARP inhibition enhances inflammatory cytokine production and osteoclast differentiation in mouse primary macrophages, and nuclear translocation of NF $\kappa$ B, whereas these effects are rescued in 3BP2 knockout macrophages. Cell proliferation, which is enhanced by Wnt/ $\beta$ -catenin signaling, is attenuated by PARP inhibition. Additionally, lipopolysaccharide stimulation also enhanced 3BP2 and AXIN protein levels, and NF $\kappa$ B enhancement and cell proliferation in primary macrophages. [Conclusions] Our studies provide genetic evidence that PARPs play inhibitory roles in the innate immune system and osteoclastogenesis and that pharmacologic inhibition of PARP for the treatment of cancers could lead to adverse auto-inflammatory side effects.



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## **Modern Rheumatology Abstract Supplement**

The 66th Annual Scientific Meeting of the  
Japan College of Rheumatology

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**Publishing date: March 28, 2022**

**Publishers: Japan College of Rheumatology (JCR)  
Modern Rheumatology Editorial Board**

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URL: <http://eng.ryumachi-jp.com>  
E-mail: [MR@ryumachi-jp.com](mailto:MR@ryumachi-jp.com)

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Hidejima Inc.  
Toshin Nishi-Shinjuku Bldg. 2F  
7-18-16 Nishi-Shinjuku, Shinjuku-Ku, Tokyo, 160-0023, Japan  
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