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VIEWPOINT

What are the hot topics in Japanese rheumatology? Go above and beyond

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ABSTRACT

Japanese rheumatology and immunology have contributed to progress in the field and advancement of rheumatology, including postmarketing surveillance, development of IL-6-targeting therapy and concept of drug tapering, have accelerated in the 21st century. The 67th Annual Scientific Meeting of the Japan College of Rheumatology, held on Fukuoka on 24 April 2023–26 April 2023, will go ahead and beyond such an advancement. Profound discussion on future perspectives such as precision medicine, the elucidation of pathology and genome-based drug discovery by multilayered integration with various types of omics information, information on metabolome and proteome of blood metabolites, and database of target proteins and compounds for drug discovery will be discussed.

I am honoured to serve as the president of the 67th Annual Scientific Meeting of the Japan College of Rheumatology (JCR) to be held in Fukuoka for 3 days from 24 April 2023 to 26 April 2023. I review the hot topics in rheumatology in Japan and future rheumatological viewpoints. The JCR was established in 1957 and has an almost 70-year history. Its annual meetings attract approximately 8000 participants from Japan and overseas, which is the third largest number of participants after the European Alliance of Associations for Rheumatology and American College of Rheumatology.

The history of immunology in Japan has its roots in Kyushu, with Fukuoka being the major city. The oldest academic work was on variolation by Shunsaku Ogata from Fukuoka in 1790. He developed an immunisation method in which variolar crusts from patients with smallpox were ground, applied on a wooden spatula and inhaled. This method saved many lives in Japan. This occurred 6 years before the successful prevention of smallpox by vaccination developed by Edward Jenner in the UK. Shibasaburo Kitazato, from Kumamoto in Kyushu, discovered the antitoxin against tetanus in 1890 and developed an antibody serum therapy. In 1890, he along with Emil von Behring published an article entitled The Development of Immunity to Diphtheria and Tetanus in Animals. Mikito Takayasu, who reported Takayasu's arteritis, was from Saga in Kyushu, and Hakaru Hashimoto, who reported Hashimoto's disease, graduated from Kyushu University.

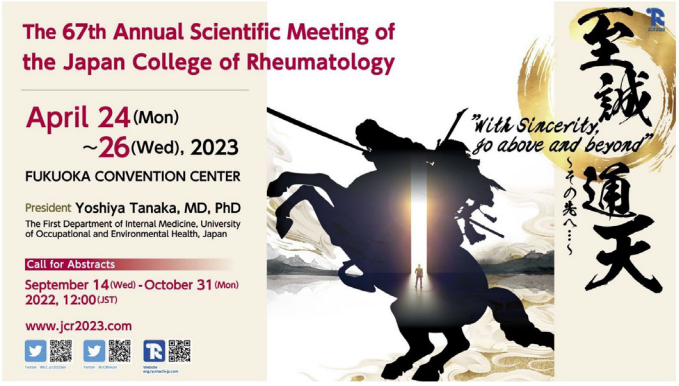
In the late 20th century, Japanese scientists made tremendous contributions to the advancement of immunology and rheumatology. In 1986, Tasuku Honjo, Kiyoshi Takatsu and Tadamitsu Kishimoto discovered IL-4, IL-5 and IL-6, respectively. In 1987, Kouji Matsushima reported IL-8 and monocyte chemoattractant protein 1, and Susumu Tonegawa received a Nobel Prize in Physiology or Medicine for elucidating the genetic mechanism of antibody production by V(D)J gene rearrangement. In 2018, Tasuku Honjo received a Nobel Prize in Physiology or Medicine for the discovery of immune checkpoint blockers and their application to cancer therapy. Thus, Japanese scientists have markedly contributed to the advancement of basic immunology that led to clinical application.

RECENT PROGRESS IN RHEUMATOLOGY AND HOT TOPICS

In Japan, the advancement of rheumatology accelerated in the 21st century. Infliximab was marketed as the first biological agent for rheumatoid arthritis (RA) in 2003. The first Janus kinase (JAK) inhibitor tofacitinib was approved in 2013. Belimumab was approved for managing systemic lupus erythematosus (SLE) in 2017. Thus, the year 2023 is the 20-year, 10-year and 5-year anniversary, respectively, for these drugs in Japan.

Postmarketing surveillance

It is highly regarded worldwide that manufacturers, governments and academia work together to complete postmarketing



■ Meeting details:

- Name: The 67th Annual Scientific Meeting of the Japan College of Rheumatology
- Meeting Theme: "With Sincerity, go above and beyond"
- Dates: April 24 (Mon.) - 26 (Wed.), 2023
- Venue: FUKUOKA CONVENTION CENTER: https://www.marinemesse.or.jp/eng/
- 8000 participants from Japan and overseas
- Currently, 24 academic symposia including 9 English sessions, 25 education lectures, 26 international concurrent workshops, 29 meet-the-experts, 131 workshops including poster session and about 72 sponsored education sessions are schedules.
- 1561 abstracts (on December 1)
- Call for Abstracts: https://www.jcr2023.com/en/abs/index.html
- Deadline for Abstract Submission: October 31 (Mon.), 2022, noon (Japan time)
- Submission of Late-breaking abstracts: February 1 to March 15, 2023.
- Official website: https://www.jcr2023.com/en/index.html

Figure 1 Meeting details.

surveillance (PMS) of biological agents and provide invaluable evidence. Infliximab, a tumour necrosis factor (TNF) inhibitor, was introduced in Japan in 2003. Since the relative risk of TNF inhibitors causing tuberculosis in patients with RA was reportedly approximately 4–7 in the USA, special attention was required in Japan, where the incidence of tuberculosis was higher in Japan than in the USA. The Japanese Ministry of Health, Labour and Welfare ordered the manufacturer to conduct PMS mainly to investigate safety, requested the JCR to cooperate and established a special investigative committee on PMS. The results of a 28-week safety survey of all 5000 patients who used infliximab were submitted. This study showed all adverse events observed in the 5000 patients enrolled in the 6-month study, which were reported from generous and inclusive of huge number of centres from all over Japan. To ensure complete registration and quality data, the registration and reporting were all centrally performed to maximise completeness in capturing information by the JCR committee. Only institutions willing to comply with the protocol had access to infliximab during this investigation. The serious adverse drug reactions were bacterial pneumonia (108 patients), Pneumocystis pneumonia (22, and tuberculosis (14). The JCR recommended screening for preventing tuberculosis and isoniazid administration to patients with any risk factor. While 11 patients with tuberculosis were reported between the 1st and 2000th patients, the incidence of tuberculosis reduced to 3 cases after an alert calling for attention was issued again for the 2001st and subsequent patients.[1]

The PMS of 13 894 patients treated with etanercept also showed that bacterial pneumonia was the most common serious adverse event (174 patients). The risk factors included advanced age, a history of respiratory diseases and concomitant use of glucocorticoids.[2] These studies are examples of much more work ongoing around Japan, namely, such surveillance has been conducted for all subsequently marketed biological agents, JAK inhibitors and others as well, accumulating thousands of 6-month Japanese safety data for each drug in actual clinical practice and becoming a pillar of the medical safety culture.

Since 2003, at our department, patients who are started on or switched to treatment with biological agents have been registered in the FIRST registry and admitted for screening for contraindications, risk factors (eg, serious infections and malignancies). Of a total of approximately 4700 patients, 15 and 36 developed lung cancer and atypical mycobacterial infection, respectively. Based on the results of PMS, patients with risk factors receive a pneumococcal vaccine and interventions to prevent Pneumocystis pneumonia and herpes zoster, while thoroughly managing patients for serious adverse drug reactions such as infections.[3]

For example, herpes zoster was reported in 3.63% (25/6866) in tofacitinib PMS in Japan. Since most of the serious opportunistic infections observed were severe herpes zoster, and disseminated herpes zoster has also been observed, the Japan Pharmaceutical Reference and JCR guidelines recommend that patients be alert for signs and symptoms of reactivation of herpes viruses and that if signs or symptoms are observed, patients should seek medical attention and promptly receive appropriate treatment. Although no guidelines have been established for vaccines, the FIRST registry actively recommends recombinant vaccination, and about half of the patients have been vaccinated. Although JAK inhibitors are orally administered drugs, patients are also hospitalised and screened before the use of the inhibitors. In response to the results of the ORAL surveillance study, a warning on the use of JAK inhibitors has been issued. The revised Japan Pharmaceutical Reference regarding each JAK inhibitor warns that malignancies after treatment with JAK inhibitor are reported and that this drug should be administered only when the therapeutic benefit is judged to outweigh the risk, and only after the patient has been fully informed. The reference also caution that there is a risk of cardiovascular events such as myocardial infarction, venous thromboembolism, etc, and other treatment should be considered when this drug is administered to patients with risk factors for cardiovascular events.

It should be necessary to reiterate the importance of screening before their use.

IL-6 targeting

Biological agents targeting IL-6, which was discovered in Japan, were developed as therapeutic agents and proven to be highly effective and safe. In 1986, Professor Kishimoto *et al* discovered a differentiation-inducing factor for B cells and named it IL-6. This group also discovered IL-6 receptors, JAK/signal transducer and activator of transcription signalling pathways. Professor Kishimoto *et al* in collaboration with Chugai Pharmaceutical developed the anti-IL-6 receptor antibody tocilizumab, which was approved for the management of RA in addition to Castleman's disease and juvenile idiopathic arthritis in Japan in 2008, ahead of that in other countries.[4] Tocilizumab monotherapy was also recommended for cases in which methotrexate, an option for patients with an inadequate response to TNF inhibitors, cannot be used.[5] This confirmed the significance of IL-6-targeted therapy. Tocilizumab is also used for managing diseases in which IL-6 plays a major role, such as Takayasu's disease, scleroderma, adult-onset Still's disease, cytokine release syndrome associated with tumor-specific T-cell infusion therapy and pneumonia caused by SARS-CoV-2. Expansion of the indications of tocilizumab to cover relatively rare and diverse autoimmune diseases and others is an important issue. The development of this antibody preparation may serve as a model for developing other drugs in the future.

Drug tapering

In Japan, almost all patients bear 30% of healthcare costs and the healthcare costs as well as medical economic problems due to the long-term use of expensive drugs need to be addressed urgently. There are also safety concerns regarding long-term drug use. Patients always ask, 'How long will I use this drug?' or 'Will I use this drug for the rest of my life?' The principle of RA treatment was continuation, and there were no guidelines for drug tapering or discontinuation. Thus, we conducted the RRR and HONOR studies, which demonstrated that remission could be maintained in about half of the patients even if TNF inhibitors were withdrawn after remission was induced by them. After a relapse, remission could be induced again in most patients.[6 7] The predictive factors for treatment withdrawal that were identified in these studies included maintenance of deep remission and non-use of glucocorticoids. Although there is a concern that tapering partially relieves immune regulation and is more likely to lead to an increase in neutralising antibodies, tapering, which is more reliable than discontinuation, can be recommended. Maintenance of bio-free remission suggests the possibility of drug-free remission in the subsequent stage. If the pathological process is controlled, immune abnormalities may be reset, and cure may be achieved without the resolution of causes. If driver molecules that inhibit the transition from remission to cure can be identified, cure is achievable.[8]

FUTURE PERSPECTIVES SUCH AS GENETICS AND PRECISION MEDICINE

Precision medicine

As the types of molecular targeted drugs increase, it is necessary to establish a treatment system including differential use of drugs. Although it is an important issue with regard to highly diverse autoimmune diseases, tailor-made medicine, in which optimal drugs are selected for each patient, is not realistic considering the actual operations and costs. We, therefore, have tried to apply precision medicine using immune phenotype analysis to patients with psoriatic arthritis. In this disease, various cytokines are involved in the pathogenesis of conditions such as psoriasis, enthesitis and synovitis. Although biological agents targeting TNF, IL-17 and IL-12/IL-23 (p40 and p19) have been approved for treatment, how to differentiate their use is unknown. When flow cytometry was performed to analyse peripheral blood samples of patients, the expressions of chemokine receptors were classified into four types: Th1-dominant type, Th17-dominant type, hybrid type and normal type. We selected anti-IL-17 antibodies for the Th17-dominant type, anti-p40 antibodies for the Th1-dominant type, and TNF-targeted drugs for the hybrid and normal types. The patients were treated accordingly. After 24 weeks of treatment, joint and skin findings were evaluated with the Clinical Disease Activity Index and the Psoriasis Area and Severity Index, respectively. The results showed that treatment responses were significantly better in patients treated with biological agents selected according to flow cytometry than in patients conventionally treated with biological agents.[9 10] This may help develop work models of precision medicine.

From genetics to clinicals

Although stratification by immune phenotype has also been attempted in patients with RA, satisfactory results have not been obtained. It is necessary to classify patients into subpopulations based on multiomics analysis that combines information on elements including the genome and transcriptome and analysis of complex biomolecular information. Such analyses require precise evaluation of genetic predispositions and immunocompetent cells that are affected by genetic predispositions. Professor Fujio *et al* at the University of Tokyo constructed ImmuNexUT, a functional genomic database comprising information on the transcriptomes of 28 types of immunocompetent cells and genetic polymorphisms that were collected from 416 Japanese patients with rheumatic diseases. By using ImmuNexUT data, the genetic polymorphisms

that affect expression levels of approximately 13 000 genes were detected, and the genes and immunocompetent cells that are targeted by susceptibility polymorphisms for SLE in Japanese patients were accurately identified.[11] Furthermore, transcriptome analysis of patients with SLE revealed that the pathways associated with SLE onset were different from those associated with SLE exacerbation.[12] Although the pathways associated with SLE exacerbation were targeted by immunosuppressants and considered to be clinically important, they were found to be undetectable by conventional genome-wide association studies (GWAS).[13] As described above, functional genomic analysis of patients with rheumatic diseases may reveal detailed genetic risks important for stratification and clinically important immune pathways. Such analysis identified metal regulatory transcription factor 1, which is a new potential therapeutic target for RA.[14] Furthermore, disease risk scores can be calculated from genomic and gene expression information.

In addition to human leucocyte antigen genotypes that confer a high risk of autoimmune-related diseases, large-scale disease genomic analyses, represented by GWAS, have been performed to identify new susceptibility genes recently. Professor Okada *et al* performed a meta-analysis of a multiracial population from international collaborative studies on RA and identified more than 150 mutations in susceptibility genes in a large-scale analysis of 250 000 patients.[15 16] The use of the Polygenic Risk Score, which integrates the risk of genetic mutations in the entire human genome, has raised expectations for the social implementation of personalised genomic medicine. Integration of the results obtained by disease genomic analysis with information on cell-specific and tissue-specific gene expressions and epigenome has allowed elucidation of immune cell fractions and biological pathways that are key to disease onset.[17 18] Since the development of single-cell sequencing has allowed a better understanding of the dynamics of gene expression at single-cell resolution, integration with information on disease genomes is in progress. Furthermore, the major objectives of future studies may be the elucidation of pathology and genome-based drug discovery by multilayered integration with various types of omics information, such as metagenomic information on bacteria and viruses derived from microbiota, information on metabolome and proteome of blood metabolites, and database of target proteins and compounds for drug discovery.[19 20]

As described above, the development of molecular-targeted therapies based on pathology should increase the motivation of young researchers. The theme of the 67th Annual Scientific Meeting of the JCR is ‘with sincerity, go ahead and beyond’. This theme represents the expectation that researchers dedicate their hearts and minds completely, including education, clinical practice, and research, and look ahead to the future. I hope that new pathological studies and treatment developments will start at this meeting. While the uniqueness and characteristics of Japan will be applied, this meeting with a focus on the promotion of internationalisation will bring many leaders from the world and result in a wide range of joint sessions. It is necessary to congregate young researchers in Japan and overseas.

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