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REVIEW

Rheumatology practice in Japan: challenges and opportunities

Kenji Oku[1] · **Tatsuya Atsumi**[1]

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Abstract
This article aims to and describes the characteristics of rheumatology practice in Japan, focusing on the medical environment for the treatment of rheumatoid arthritis (RA). In Japan, the introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs) has led to a significant paradigm shift in medical care; satisfactory safety outcomes have been demonstrated by periodic analysis, post-market surveillance and the development of guidelines via an industry–academia–government collaboration. Drug discontinuation is also considered an option, as well as medical economic analysis of any increase in the financial burden engendered by use of bDMARDs. Tocilizumab, a bDMARD established in Japan, was developed in an environment that facilitates translational research. The rheumatology community in Japan is expected to continue to develop novel therapies, while ensuring consistent quality of medical care despite limited healthcare resources.

Keywords Rheumatoid arthritis · Japan · CME · Japan College of Rheumatology (JCR)

Introduction

Systems for medical care and training of doctors in Japan

Before describing the characteristics of rheumatology practice in Japan, it is necessary to explain its unique medical system. In Japan, every resident is required to have healthcare insurance, which is provided by local public authorities or the owners of the companies/organisations for which they work; public funds are allocated to support this system. The average citizen is entitled to medical care co-payments amounting to 10–30% [1]. Further assistance is provided to those who cannot afford high-cost medical treatments, and to economically disadvantaged individuals. In addition, there is a system for combating intractable diseases managed by the Ministry of Health, Labour and Welfare (MHLW), to reduce long-term care expenses for diseases of unknown aetiology (intractable diseases), which include many connective tissue diseases [2].

Another feature of the Japanese healthcare system is "free access" to care, where every resident can visit any medical institution without restriction, and where the costs are essentially the same. Furthermore, the system allows doctors to practice their medical specialties with little restriction as long as they are acting according to the guidelines established by the MHLW [3]. These features of the healthcare system in Japan facilitate wide access to advanced medical care, but there are also problems such as increased burden on public funds allocated to healthcare, including maintenance costs, and the difficulty in achieving consistent quality of care. These problems have been addressed in communications between the government and healthcare professionals aimed at improving the quality of medical care.

After completing 6 years of undergraduate medical education, most doctors enrol in specialist training courses at the medical school from which they graduated [4]. This training enables them to acquire knowledge of advanced medical specialties as well as basic/applied medical sciences, and some trainees choose to pursue graduate education. Therefore, even physicians working in community hospitals and private practitioners can provide advanced medical care, given their advanced knowledge of medical science. Following the gradual transformation of medical training for doctors beginning in the early 2000s, doctors in the early

✉ Kenji Oku
kenoku@med.hokudai.ac.jp

Tatsuya Atsumi
at3tat@med.hokudai.ac.jp

[1] Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine, Graduate School of Medicine, Hokkaido University, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

stages of training are now required to complete rotations in various departments, instead of being associated with one particular department. Japanese clinicians are traditionally quite familiar with translational research approaches to bridge the bed–bench gap, and are also proactive in introducing advanced therapies in daily clinical practice. Against this background, the subsequent sections of this paper will describe the conditions surrounding rheumatology practice in Japan, particularly focusing on rheumatoid arthritis (RA), an archetypal rheumatoid disease with an estimated prevalence rate of 0.6–1.0% in Japan [5]. To this end, reimbursement data from health insurance societies, comparable to data from the USA [6] and Europe [7], will be used.

Aim

To introduce and describe clinical practice pertaining to RA in Japan.

Search strategy

We adhered to previously published guidelines for conducting a narrative literature review [8]. We searched PubMed from November 4, 2008 to November 4, 2018, using the following criteria: document type, journal article, review, or randomised controlled study, and country, Japan (restricted to articles written in English). Furthermore, we searched article titles, abstracts, and keywords using the term "rheumatoid arthritis". The search results are presented in Table 1. Various RA practice-related topics were identified based on the collected articles and the knowledge of the authors.

Medical environment of RA practice

As in the other countries, the introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs) into clinical practice in the early 2000s caused a major paradigm shift in RA practice in Japan. Historically, management of RA was supervised by orthopaedic surgeons or other physicians not specialising in rheumatology, but specialised care is now provided mainly by specialist rheumatologists. The following sections will describe the characteristics of RA practice in Japan, including: (1) the use of conventional synthetic DMARDs (csDMARDs) and targeted synthetic DMARDs; (2) a big data platform established by an industry–academia–government collaboration (post-marketing surveillance of biologics); (3) transitional medicine bridging the gap between basic research (e.g. studies on interleukin [IL]-6) and clinical research; (4) the development of guidelines promoting consistent quality of medical care; and (5) collection of "drug holiday" data for medical cost analysis.

Conventional and targeted synthetic DMARDs

The most widely used csDMARD, methotrexate (MTX), was approved for the treatment of refractory RA in Japan in 1999, which was approximately 10 years after its approval in the USA and Europe. At that time, the maximum dose of MTX was restricted to 8 mg/week. In 2011, MTX was approved by the MHLW as first-line therapy for RA, with the maximum dose set at 16 mg/week, partly based on actual treatment practices [9]. However, the tolerable dose of MTX is often lower in Japanese patients, as shown by the high rate of adverse events (AEs) at relatively high doses, such as gastrointestinal symptoms [10]. The C-OPERA (Certolizumab-Optimal Prevention of joint damage for Early RA) trial [11] in Japan involved rapid dose escalation of MTX up to 16 mg/week (unless there were safety concerns). The average MTX dose throughout the 52 weeks was approximately 12 mg/week (11.6 mg/week in both the MTX + certolizumab pegol group and the MTX + placebo group). The relatively low tolerable MTX dose in the Japanese population may be partly due to the lower average body weight (57 kg in C-OPERA) compared to the USA and Europe. Moreover, it has been reported that the concentrations of MTX polyglutamate, a potential marker for MTX, is higher in red blood cells in the Japanese versus American population, suggesting that a lower dose of MTX may be efficient in Japanese patients [12].

As target synthetic DMARDs (tsDMARDs), two Janus kinase (JAK) inhibitors, tofacitinib and baricitinib, have been used for the treatment of RA patients in Japan. There are accumulating data that these agents are effective and safe in Japanese patients at doses similar to those used in Americans and Europeans [13–15]. The risk of herpes zoster was suggested to be higher in Japanese patients treated with tsDMARDs [16], but further studies in larger populations are required to confirm this.

Table 1 Publication from Japan related to rheumatoid arthritis (2009–2018)

Year	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	Total
Article	523	513	509	489	444	409	501	483	373	357	4601
Review	51	57	49	59	47	58	72	72	44	32	541
RCT	10	20	23	25	20	18	14	9	6	5	150

Article: original article, *RCT* randomised controlled study

Big data platform established by an industry–academia–government collaboration

In Japan, a post-marketing survey (PMS) was conducted covering many bDMARDs after they were first introduced, at the request of the MHLW. This was prompted by the increased incidence of tuberculosis (TB) following the clinical introduction of tumour necrosis factor (TNF)-α inhibitors in the USA: the MHLW decided to conduct safety surveillance before their introduction in Japan, which has a moderate TB burden. In parallel with the PMS, activities to promote awareness and provide information about bDMARDs were regularly implemented, under the oversight of the Japan College of Rheumatology (JCR) and various university hospitals. For example, the JCR recommended a mandatory screening program consisting of history taking, tuberculin testing, and chest X-ray, where prophylaxis with isoniazid is recommended for patients with positive results on any of these tests. This industry–academia–government collaboration has been a great success: the PMS of infliximab ($n = 5000$) showed a TB incidence of only 0.3% [17]. In subsequent PMS of various bDMARDs, the incidence rates of AEs were low for all agents, and the occurrence of any AE was followed by thorough follow-up. These PMS provided big data on real-world RA patients, and these data then used for post hoc surveillance and other activities to understand the pathophysiology of RA in Japanese patients. These activities led to the preparation of guidelines on the use of bDMARDs [18], and thus contributed to the safe and effective use of these agents in Japan. Furthermore, several databases comprising thousands to tens of thousands of RA patients have been developed [19, 20], and are expected to serve as big data platforms for integration of all PMS data, and to contribute to a better understanding of the pathophysiology of rheumatic diseases.

IL-6 research and clinical applications

IL-6 was initially discovered by Kishimoto et al. [21] as a B cell differentiation-inducing factor. Its receptors were later identified, along with its association with the JAK/STAT signalling pathway and numerous physiological functions [22–25]. IL-6 is produced by various cell types, including B cells, T cells, monocytes/macrophages, fibroblasts, and vascular endothelial cells, and contributes to the onset and maintenance of RA by inducing B cell differentiation, producing pro-inflammatory factors, and activating osteoclasts [26–28]. Following TNF-α, this cytokine has become a new target of anti-cytokine therapy in RA. Through a co-development project with Chugai Pharmaceutical in Japan, Kishimoto et al. developed the anti-IL-6 receptor antibody, tocilizumab [29]. After phase I/II trials conducted in 1999, a phase III trial of tocilizumab also demonstrated significantly higher efficacy and safety of the agent compared to placebo; approval for its use in Japan followed in 2008, ahead of other countries [30, 31]. Tocilizumab is superior to other bDMARDs in terms of its single-agent efficacy in treating RA without co-administration of csDMARDs, such as MTX [32]. This led to the development of various similar drugs, among which sarilumab, a fully humanised anti-IL-6 receptor antibody, showed particularly strong performance. Accordingly, it has been applied clinically in Japan, as well as in other countries [33, 34]. These bench-to-bed research activities are ongoing and expected to lead to the development of innovative treatments in the field of rheumatology in Japan.

Guideline development and consistency of medical care quality

Japan is a single-nation state, such that it is relatively easy to achieve homogeneous treatment outcomes. In addition, the Japanese healthcare system is characterised by free access of patients to medical institutions, and physicians have a high degree of freedom in practicing their specialty. Other characteristic features of the Japanese population include a very low frequency of use of the anti-IL-1 inhibitor, anakinra, due to the high risk of pulmonary fibrosis, and a relatively high incidence of pneumocystis pneumonia. These characteristics underlie the importance of ensuring consistency in the quality of specialised medical care in Japan, and have led to the development of domestic guidelines in the field of rheumatology.

Comprehensive treatment guidelines were developed in 2014 encompassing the diagnosis, treatment, and monitoring of RA patients [35]. In parallel, a modified version of the guidelines was developed specifically for internal medicine physicians and other clinicians not specialising in rheumatology who may encounter patients with RA. Subsequently, usage guidelines were developed for several new drugs included in the national health insurance (NHI) list, such as tofacitinib and denosumab. MTX treatment guidelines were also developed after dose escalation was permitted, i.e. a dose above that applied to Japanese patients until 2016 due to their smaller physique compared to Western patients [36]. Moreover, amendments were made to the usage guidelines for TNF and IL-6 inhibitors based on routinely collected data. Some of the criteria in these guidelines are also used as quality indicators for the purpose of clinical evaluation. Through these activities, the Japanese rheumatology research community is committed to meeting patients' expectations by promoting consistency in the quality of the medical care provided by specialists at regional core hospitals, as well as by internal medicine physicians and private practitioners.

The guidelines for the management of RA of the JCR (Fig. 1) [37] were based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method and the concept of treat-to-target, in accordance with the European League Against Rheumatism (EULAR) recommendations [38] and American College of Rheumatology (ACR) guidelines [39] for the treatment of RA. Briefly, the guidelines recommend starting RA treatment with MTX unless the drug is otherwise contradicted. Short-term low-dose steroid use has been approved. If the patient has not reached the treatment goal (clinical remission or low disease activity) within 6 months after commencement of treatment, bDMARDs or additional csDMARDs should be considered. Tocilizumab, the TNF inhibitor, and abatacept are both considered as first-line therapies. If the treatment goal is not achieved after an additional 6 months, another bDMARD or tofacitinib is recommended. Baricitinib, which was not available when the guidelines were published, now has the same status as tofacitinib.

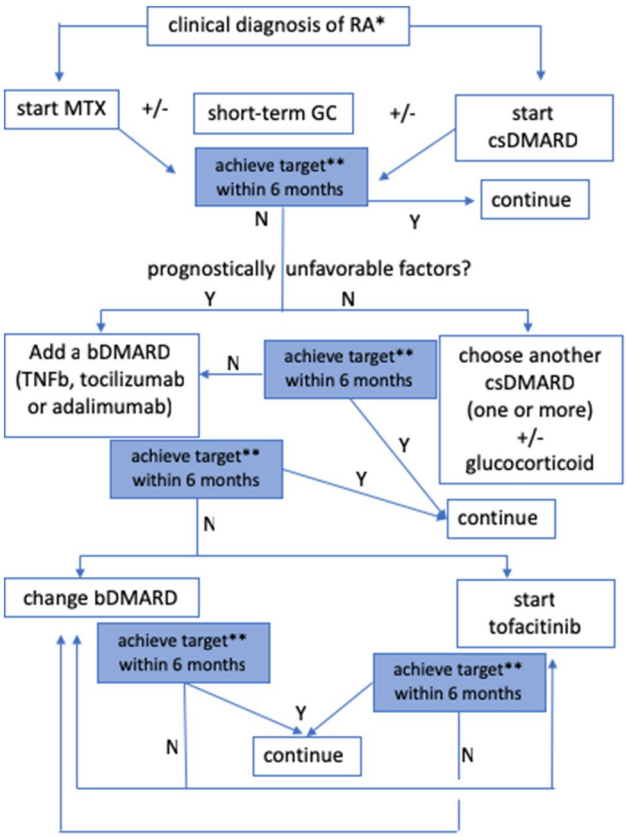

Fig. 1 Algorithm based on the 2014 Japan College of Rheumatology guideline on rheumatoid arthritis management. (Asterisk) 2010 ACR-EULAR classification criteria can support early diagnosis. (Double asterisk) The treatment target is the clinical remission according to the ACR-EULAR definition, or if it is not achievable, the low disease activity. *Y* yes, *N* no, *RA* rheumatoid arthritis, *MTX* methotrexate, *csDMARD* conventional synthetic disease-modifying anti-rheumatic drug, *bDMARD* biologic DMARD, *GC* glucocorticoid

Drug holidays, early therapeutic interventions, and medical economics

After the paradigm shift in the 1990s and 2000s, RA has become a condition for which the target of management is remission; the goals of treatment are becoming increasingly challenging to achieve. Current treatment goals include not only clinical remission, but also structural/functional remission. Moreover, an increasing number of specialists consider improvement in patient-reported outcomes (PRO), including malaise, fatigue, and other physical subjective symptoms experienced by patients, as a realistic treatment goal. Achievement of such challenging treatment goals inevitably requires the long-term use of expensive drugs, such as bDMARDs and JAK inhibitors. However, long-term use of these drugs is associated with unresolved safety issues and represents a major medical micro- and macroeconomics issue.

In Japan, there are no restrictions regarding the use of bDMARDs, as long as the patient's disease and economic status render them appropriate for such treatment. Therefore, as mentioned above, it is possible to prescribe biologics in relatively large numbers of patients on request. At the same time, there is still controversy regarding the amount of money that should be allocated to medical expenses, which have already exceeded 10% of Japan's GDP. As a possible solution to this, the concept of "drug holidays" was developed in Japan. In this treatment strategy, administration of biologics is discontinued after confirmation of a reduction in disease activity. This strategy has been applied in several large-scale studies in Japan, including the Remission induction by Remicade in RA (RRR) study [40] and the HONOR (Humira discontinuation without functional and radiographic damage progressiON follOwing sustained Remission) study [41]. The RRR study was designed to evaluate disease activity after 1 year of treatment withdrawal in patients who had been treated with infliximab and showed low disease activity for 24 weeks. The study was conducted in 26 major medical institutions in Japan. A major finding was that 43% of patients met the remission criteria; furthermore, a low disease activity score-erythrocyte sedimentation rate (DAS28-ESR) was identified as a prognostic factor in patients with sustained remission (cutoff score of 2.2 for deep remission). It was initially difficult to conduct withdrawal studies due to resistance from pharmaceutical companies. With gradual accumulation of positive data, drug holidays and discontinuation have become widely recognised as important concepts. With regard to drug holidays, the use of bDMARDs for treating early-stage RA should also be considered. It is established that early-stage RA has

a good prognosis. In Japan, based on the high efficacy of bDMARDs in treating early-stage RA, as demonstrated in the HOPEFUL (Humira Outcome Study for the Persistent Efficacy under Allocation to Treatment Strategy in Rheumatoid Arthritis) study [42] and other investigations, guidelines were also developed stating that "for patients with high disease activity and poor prognostic factors, treatment may begin with a TNF-α inhibitor in addition to MTX". It is necessary to determine the micro- and macroeconomic costs of identifying suitable patients at an early stage of treatment, inducing deep remission and then discontinuing treatment. Early treatment and discontinuation (or dose delay) after remission are important factors to consider when introducing biologics and JAK inhibitors [43].

The MHLW also announced in 2017 that active measures would be instituted, such as setting incremental cost-effectiveness ratios for relatively rare diseases, such as rheumatic diseases, at slightly higher levels than those used for more frequently occurring diseases [44]. It is expected that medical cost analyses will be performed for various rheumatic diseases, including RA.

Continuing medical education on rheumatology in Japan

The lifelong education of doctors in Japan is at a crossroads. There is no system in Japan mandating that the professional qualifications of medical specialists be updated; that is, the doctor's license is valid throughout their professional life and requires no renewal, with the pursuance of any additional medical education being left to the discretion of the individual doctor.

One reason for this is that education for Japanese doctors has long been focused on practical, on-site experience. In addition, a system of lifelong education has been implemented in all universities and regions, wherein the doctors belong to a particular department of the medical school and rotate between the university hospital and other hospitals in the region.

In recent years, however, uniform and sustained education of doctors has become a requirement, and the trend is especially pronounced in the context of specialist education. There has been a massive overhaul of the specialist certification system, including that of rheumatologists, in Japan. With support from the Japanese Medical Specialty Board, the JCR supervised the curriculum for a rheumatology training program, which has been implemented by teaching hospitals. The training program is standardised, and it takes a minimum of 3 years to become a board-certified rheumatologist after first becoming a member of the JCR. The JCR then follows up the rheumatologists to ensure maintenance of skills and knowledge. The JCR has branches in six districts of Japan; annual conferences take place in each region, as well as the annual general JCR meeting. In addition, the JCR organises regular basic research conferences and educational training sessions aimed at developing skills and knowledge.

Modern Rheumatology, the official journal of the JCR, publishes original papers on research pertinent to rheumatology. The journal covers a very wide range of clinical and basic sciences, including pathology, physiology, clinical immunology, microbiology, biochemistry, use of experimental animal models, pharmacology, and orthopaedic surgery.

The editorial board of *Modern Rheumatology* consists of JCR faculty members, along with an international advisory board. In 2017, *Modern Rheumatology Case Reports*, a sister journal, focused on case reports of high quality. These two journals successfully disseminate modern scientific information from Asia, including Japan, and other countries all over the world.

Conclusion

This report discussed the current medical environment of rheumatology in Japan, with a special focus on RA. RA treatment in Japan is characterised by the involvement of a wide variety of medical institutions, ranging from university/regional core hospitals to smaller scale hospitals and clinics, and of physicians with varying backgrounds, including rheumatologists, internal medicine physicians, and orthopaedic surgeons, as well as other specialists in dermatomyositis and lupus nephritis, such as dermatologists, neurologists, and nephrologists. While this environment facilitates multidisciplinary understanding of diseases, it is also important to maintain consistent quality of medical care. Furthermore, the unique healthcare insurance system in Japan has contributed to wide access to advanced medical care, but at the same time has placed a strain on the nation's finances. Thus, judicious allocation of healthcare resources to reduce costs without affecting patient benefits remains a major challenge. Even with these restrictions, Japan's healthcare system has made a substantial contribution to the rheumatology community, along with biotechnological developments, and will continue to contribute to the global rheumatology community based on a proper industry–academia–government balance.

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Compliance with ethical standards

Conflict of interest Kenji Oku and Tatsuya Atsumi declare that they have no conflict of interest.

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