Perspective

International Journal of Clinical Rheumatology

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How can the treatment of rheumatoid arthritis be improved in Japan?

In Japan, orthopedists are largely responsible for the treatment of rheumatoid arthritis. Japanese rheumatologists therefore seem to prefer safer and milder regimens for rheumatoid arthritis. Although methotrexate is an anchor drug with a higher dose regimen of 15–30 mg/week elsewhere around the world, lower dosages of 8–12 mg/week have been popular in Japan. Since the advent of biologics, however, several valuable studies have been published from Japan, such as the limited effects of biologics on large joints, the concept of biologic concentration, stopping biologics, risk factors for adverse events and trends in orthopedic surgery. A lower dosage of methotrexate might not represent a drawback, but rather a clue to new insights for Japanese rheumatologists in the era of biologics.

Keywords: adverse events • biologic agents • domestic medicine • health insurance • IL-6 • methotrexate • orthopedic surgery • rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic, inflammatory disorder characterized mainly by joint inflammation, arthritic pain, progressive deformity of the extremities, disability in daily living and an overall negative influence on quality of life [1,2]. The etiology remains unclear, but is considered to have a partially genetic background [3] and to involve environmental risk factors such as smoking [4,5]. RA might be incurable, and although the prevalence has changed over the decades, RA affects 0.5–1.0% of adults in developed countries [6,7].

As with other incurable chronic diseases like hypertension and diabetes mellitus, RA should be tightly controlled to avoid irreversible outcomes such as joint deformity and subsequent disability. Treatment toward target levels of variables associated with negative disease outcomes is a concept that has long been applied to several chronic diseases other than RA. The concept of the treat-to-target (T2T) strategy has recently been developed in the field of RA therapy [8–10]. The primary reason for delaying the development of this strategy in RA was the lack of clear targets analogous to hemoglobin A1c in diabetes mellitus or blood pressure in hypertension. Biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have not proven useful as targets for disease control. Instead, disease activity score (DAS) has appeared as a new target [11–13]. Although some variations exist in methods to gauge DAS, this measure basically includes information on swollen joints, tender joints, a patient self-report of general health and acute-phase response (using CRP or ESR). According to this composite measure, disease activity of RA can be classified as in remission, low, moderate or severe. DAS shows some weaknesses [14], but has still allowed at least an initial estimation of overall RA disease activity.

In parallel with developments in estimating disease activity, several biologic disease-modifying antirheumatic drugs (bDMARDs, or 'biologics') have been developed and have induced a paradigm shift in the treatment of RA since the turn of the millennium. In clinical trials, some research has shown interesting results supporting the

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concept of T2T with bDMARDs or a combination of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [15–19]. With the advent of a new era in the methods of evaluation and medication, treatment of RA in Japan is undergoing major changes.

Differences in the medical insurance system

Japan has adopted a national health insurance system that insures the population against the costs of medical care. As a result, all residents receive the benefits of universal care in Japan. Furthermore, free access to a medical institution or doctor is guaranteed for all patients in Japan. Prescription of medicines is allowed equally by all physicians, rather than being limited to specialists. These conditions allow patients with RA to receive bDMARDs more easily than in other countries. In Japan, physicians can treat RA patients with bDMARDs based on the reliable results of several clinical trials from around the world, but might choose other options due to the high cost of bDMARDs. In this situation, some researchers in Japan have tried to clarify the effectiveness of low-cost combination therapy with csDMARDs for RA [20–22]. Unfortunately, no head-to-head randomized controlled trials (RCTs) between bDMARDs and combination therapy with csDMARDs for the treatment of RA comparable to the RACAT study [23] have been conducted in Japan. We hope that Japanese rheumatologists will be able to create new, cost–effective, safe and effective therapeutic options for the treatment of RA in the near future.

The role of orthopedic surgeons in the treatment of RA in Japan

About half of the members of the Japan College of Rheumatology (JCR) are orthopedic surgeons. Reasons include the fact that orthopedic surgeons in Japan are the main providers of treatment for patients with RA in terms of rehabilitation and surgical procedures, given the relative underdevelopment of pharmacotherapy for RA. This represents a unique situation compared with other countries around the world. In Japan, patients with arthralgia usually consult orthopedic surgeons first. Some of those orthopedic surgeons might prescribe csDMARDs including methotrexate (MTX) after they reach a diagnosis of RA. If the control of disease activity proves inadequate, a majority of orthopedists introduce such patients to a rheumatologist. However, other orthopedists who are familiar with the treatment of RA start to strengthen the treatment regimen by themselves, such as by using bDMARDs. Dealing with complications during the treatment of patients with RA such as pulmonary infection might represent an area of relative weakness for orthopedic surgeons, but these clinicians are able to monitor evaluations of the joints, including the fingers and toes, and are less likely to make errors in operation timing. The Japanese specialist system is not mature compared with western countries. At present, two systems are available to certify specialists in the treatment of RA in Japan: by the JCR, and by the Japanese Orthopaedic Association (JOA). As we describe later, up to 16 mg/week of MTX has been available for clinical use in the treatment of active RA since 23 February 2011 in Japan. More than 1 year after that, we performed a questionnaire survey of MTX doses in usual clinical use with 500 JCR board-certified rheumatologists and 500 JOA board-certified orthopedists. The response rate was 52.8% from JCR members and 58.4% from JOA members. Limitations to the questionnaire survey existed and some overlap was seen among participant groups. Orthopedic surgeons showed a tendency toward using relatively lower doses of MTX for clinical practice. However, no significant difference in dose of MTX prescribed was seen among subspecialities (data not shown). In the future, board-certification of rheumatologists might be unified to ensure consistent medical quality in Japan.

However, orthopedic rheumatologists in Japan have reported clinical evidence from a unique perspective. Kanbe *et al.* completed a series of studies comprising an immunohistochemical investigation of synovial tissues collected at operation for RA patients receiving bDMARDs [24–26]. They collected samples from groups treated with MTX or a combination of MTX and etanercept, a decoy receptor for TNF-α, by arthroscopic synovectomy and revealed that expressions of cytokines such as TNF-α and IL-6 were similar in both groups, but expressions of matrix metalloproteinase-3 and CD68 were significantly inhibited in the MTX + etanercept group compared with the MTX-alone group [26]. We orthopedists often observe contracted synovial tissues during joint replacement surgeries for patients receiving bDMARDs, and this study provided scientific confirmation.

Other notable studies that Japanese orthopedists have conducted relate to the progressive destruction of weight-bearing joints [27]. Seki *et al.* investigated radiological changes in the hip, knee and ankle joints of 42 consecutive patients receiving anti-TNF bDMARDs for 1 year. They used the Larsen scoring method to assess structural damage to weight-bearing joints and found that radiographic progression was inhibited in most grade 0-II joints (low grade), but hip/knee joints with pre-existing grade III/IV (high grade) damage showed apparent progression even in patients with good clinical response to bDMARDs [27]. This means that delayed application of bDMARDs for advanced destruction of weight-bearing joint might not keep

destructive changes at bay and declines in the activities of daily living of the patient may not be halted. Early intervention before the onset of destruction of the weight-bearing joints by not only bDMARDs, but also effective use of csDMARDs is thus recommended.

Conventional synthetic disease-modifying antirheumatic drugs

Domestic brands of csDMARDs

Numerous csDMARDs are available around the world. Not all drugs are authorized in all countries. Hydroxychloroquine (HCQ) has been used for the treatment of RA for the last 50 years all over the world, especially in combination therapy for RA [28]. However, this agent has not been approved for the treatment of RA in Japan because of lawsuits in the 1970s as a result of chloroquine retinal toxicity [29]. Japanese physicians thus cannot prescribe the gold-standard combination therapy of MTX, sulfasalazine and HCQ for the treatment of RA [30]. On the other hand, an original Japanese immunosuppressant (tacrolimus) and csDMARDs such as bucillamine and iguratimod have been developed. Tacrolimus is an oral calcineurin inhibitor that has been proven to have suppressing effects on disease activity and joint destruction in patients with early RA [31]. Although tacrolimus is widely recognized and used in the field of transplantation [32], countries that have approved tacrolimus for RA treatment are largely limited to Asia and Canada. Effects of tacrolimus as additional therapy when the effects of bDMARDs start to attenuate should be examined in future. Fortunately, HCQ seems likely to be approved before long in Japan. Japanese physicians should compare gold-standard combination therapies with original combination therapies to provide alternative therapeutic options for the treatment of RA.

Methotrexate

MTX is a folic acid antagonist widely used for the treatment of RA as an anchor drug in csDMARDs for long-term use, mainly in western countries. The effects of MTX on clinical outcomes were obviously superior to placebo in many clinical RCTs for RA patients [33]. Furthermore, MTX is well known to reinforce the actions of other drugs in combination with csDMARDs or bDMARDs [16,17,19,20,23,28,33]. From a systematic review, starting with 15 mg/week of oral MTX and rapidly escalating to 25–30 mg/week at +5 mg/month seems optimal for achieving sufficient clinical response in RA [34]. Treatment with csDMARDs for RA in Japan is characterized by lower doses of MTX compared with other countries. Indeed, the average MTX dosage in clinical trials to show the effectiveness of bDMARDs in western countries [19,28] was absolutely higher than the dose shown in postmarketing surveillance (PMS) programs to confirm the safety of bDMARDs in Japan [35–37].

Prior to 2011, 8 mg/week of MTX was the upper dosage limit, and a limit of 16 mg/week has been used since 2011. However, Japanese physicians still tend to hesitate to apply high-dose MTX for RA patients, mainly due to the risk of several adverse events such as nausea, mouth sores, liver function abnormalities, interstitial pneumonia and myelosuppression, perhaps due to memories of the era when MTX was administered without concomitant use of folic acid. In such situations, clinical results from research conducted in Japan to investigate the effects of combination therapy with bDMARDs and MTX did not show marked differences from studies conducted in western countries [35–37]. One reason for the sufficient effects in combination therapy using lower-dose MTX and bDMARDs in Japan might be the difference of the required dose of MTX between Japanese and western people.

Recently, high-dose MTX use has been reconsidered based on the results of the CONCERTO study [38], a randomized, double-blinded study dividing early active MTX-naive RA patients into weekly blinded 2.5-, 5-, 10- and 20-mg MTX groups receiving combination therapy with open-label adalimumab (humanized anti-TNF-α monoclonal antibody, 40 mg every other week) for 26 weeks to assess whether efficacy tended to increase with increasing MTX dose. The results showed comparable effects for adalimumab with 10 and 20 mg of MTX. This result was supported by another study including etanercept and infliximab as bDMARDs in a daily clinical practice setting [11]. Such results suggest that patients receiving 10 mg of MTX do not need a higher MTX dose at the start with anti-TNF inhibitors such as infliximab, etanercept or adalimumab. A lower dose of MTX might also be sufficient for concomitant use with anti-TNF inhibitors due to the lower body weight of Japanese patients. We worry that Japanese rheumatologists might misunderstand the message from the CONCERTO study, in that those results only apply to combination therapy comprising MTX and bDMARDs. The efficacy of low-dose MTX still has not been established in the case of monotherapy or in combination with other csDMARDs. Japanese rheumatologists should not assume from the results of the CONCERTO study that low-dosage MTX is sufficient for the usual treatment for RA patients in daily clinical practice.

Furthermore, other reports have suggested that not MTX dose, but rather the concentration of MTX polyglutamates (MTX-PG) as active forms of MTX are associated with the clinical effects of MTX or inflix-

imab pharmacokinetics [39,40]. The influence of MTX-PG concentration according to situations of ethnic difference, disease activity or concomitant medicines is currently under investigation. The concentration of MTX-PG in Japanese or other ethnic groups should be clarified in terms of the relationship with the clinical efficacy of MTX mono- or combination therapy. At least in terms of clinical efficacy, a higher dose of MTX might be required to achieve effective MTX monotherapy, while a lower dose might suffice for combination with anti-TNF bDMARDs.

Glucocorticoids

Glucocorticoids (GCs) could show the disease-modifying effects in patients with early RA by a low dose (5–10 mg/day prednisolone). In several randomized clinical trials, GCs significantly retarded radiological progression of erosions compared with control group over 1 year [41]. For example, in recent double-blind randomized controlled CAMERA II study [42], 236 MTX and GC-naive RA patients with a disease duration of less than 1 year randomly assigned to 10 mg prednisone or placebo group under the strategy of tight control with escalation of MTX dosage (up to 30 mg/week). The primary end point of this study was the Sharp-van der Heijde erosion score during 2 years. Under the tight-control strategy, erosive joint destruction after 2 years was limited in both groups and much less in the group receiving MTX and prednisone (n = 117) than MTX and placebo group (n = 119). Of course, the group receiving MTX and prednisone showed significant reduction of disease activity. Judging from those results, GCs should have a DMARD effect beyond their anti-inflammatory effects. However, Japanese rheumatologists, especially orthopedic surgeons, have hesitated to use GCs for the treatment of RA due to their side effects such as infection or osteoporosis. It is important for us to notice that such adverse events should occur under the condition of usage of higher dose of GCs for a longer term. Clinical evidences only indicated that GCs have a clear DMARD effect in early RA with lower dosage for a shorter period.

Biologic disease-modifying antirheumatic drugs

A paradigm shift has been brought about with the entry of bDMARDs, adding new options for the treatment of RA. Most bDMARDs directly block the activities of inflammatory cytokines such as TNF and IL-6. Compared with csDMARDs, Japanese physicians and patients can prescribe almost all bDMARDs for the treatment of RA. With the exception of the IL-1 antagonist anakinra and rituximab, an anti-CD20 monoclonal antibody targeting B cells, all bDMARDs and targeted synthetic DMARDs (tsDMARDs, tofacitinib) have been approved in Japan. However, Japanese physicians seem hesitant to use tofacitinib due to reported adverse events including infections, malignancies, low neutrophil and lymphocyte counts, reduced hemoglobin, liver enzyme elevations and lipid elevations.

As of 2015, eight preparations of bDMARDs have been approved for the treatment of RA in Japan: infliximab (approved for RA in 2003), etanercept (2005), adalimumab (2008), tocilizumab (2008), abatacept (2010), golimumab (2011), certolizumab pegol (2012) and infliximab biosimilar (2014). After the introduction of bDMARDs to Japan, strict PMS of infliximab was performed and a higher incidence of pneumocystis pneumonia in Japanese RA patients was identified [37]. In clarifying the results of that report, Harigai *et al.* identified advanced age, coexisting pulmonary disease and use of a higher dose of prednisolone as risk factors for pneumocystis pneumonia in Japanese RA patients receiving infliximab [43]. The profile of adverse events during the aggressive treatment for RA might differ between countries and ethnic groups. Pneumonia, tuberculosis, *Pneumocystis jirovecii* pneumonia, interstitial pneumonitis and viral infections such as hepatitis B, C and herpes zoster are severe adverse events observed during treatment with molecular-targeted agents. Patients on TNF-α inhibitors have a higher risk of such serious infections compared with patients on csDMARDs. Early in the introduction of infliximab, outbreaks of tuberculosis were a serious concern for Japanese physicians. PMS of 5000 RA patients receiving infliximab revealed that prophylactic antituberculosis was partially performed for patients with positive results in a tuberculosis screening test at the beginning due to underestimation of tuberculosis screening test results under the condition of widespread BCG vaccination in Japan. After the evaluation of the first 2000 cases, prophylactic antituberculosis treatment for suspected patients was strongly recommended again. The number of cases of tuberculosis then decreased from 11 cases in the first 2000 patients to only three cases in the last 3000 patients [37]. In terms of adverse events with tsDMARDs, increased herpes zoster rates were observed among patients treated with tofacitinib, especially in an Asian population [44]. Japanese rheumatologists could provide useful insights into the pathogenesis of adverse events in the treatment of RA.

Infliximab

Infliximab, a monoclonal antibody against TNF-α, was the first bDMARD approved in Japan. Information on predictors of the effectiveness of infliximab

treatment [45–47] and results of a trial for discontinuing infliximab after achieving low disease activity [48] have since been published from Japan. The 'dose equilibrium theory' coming out of the RISING study seems particularly attractive [45]. The RISING study included 327 patients with active RA under previous treatment with MTX. Those patients were administered a standard dose of infliximab (3 mg/kg body weight) in an initial standard clinical protocol (0, 2 or 6 weeks) and were then randomly assigned to three groups, receiving 3, 6 or 10 mg/kg of infliximab every 8 weeks from 14 to 54 weeks. Takeuchi *et al.* reanalyzed data from the RISING study using circulating concentrations of both TNF and infliximab, the target molecule and antibody. Results showed that higher doses of infliximab might be required in patients with a high baseline TNF and lower doses of infliximab might prove sufficient for patients with low baseline TNF to achieve good clinical response [49]. In the near future, if we could more easily measure circulating concentrations of infliximab or TNF in clinical practice settings, cost–effective, personalized treatment for RA patients with infliximab would finally be achievable.

Etanercept

Etanercept, a unique bDMARD, is not a monoclonal antibody against cytokines, but rather a decoy receptor for TNF-α and -β. The approved dosage for etanercept in Japan is 25–50 mg/week subcutaneously. Etanercept has been demonstrated to effectively reduce clinical symptoms and slow joint damage in patients with RA as a monotherapy compared with MTX monotherapy [50]. Such characteristics of etanercept are very convenient for Japanese physicians in private clinics who hesitate to use higher dosages of MTX. In real-world clinical practice, such physicians are willing to use a lower dose of etanercept for their patients with RA from the perspectives of safety (short half life of the agent) and economy. We therefore conducted a randomized PRECEPT study [51] in Japan to compare the abilities of standard-dose (50 mg/week) and low-dose (25 mg/week) etanercept with MTX for reducing disease activity and radiographic progression. Disease activity as assessed by the DAS28 improved quickly and ended up comparably low in both groups during the 52 weeks. However, the non-progression rate defined as a change in modified total Sharp score [52] ≤0.5 from baseline was significantly lower in the low-dose group (36.7%) than in the standard-dose group (67.7%). We recommend Japanese rheumatologists use a sufficient dose of etanercept to achieve the restraint of joint destruction, rather than palliation of symptoms in RA patients.

Adalimumab

Adalimumab, a humanized monoclonal antibody against TNF-α, is the most popular bDMARDs in the world, but not in Japan. The percentage of patients who achieved the American College of Rheumatology criteria for 20% improvement (ACR20) at week 24 in the early clinical trial to estimate the effects of adalimumab on active RA patients in Japan was relatively lower (44.0% in the adalimumab 40 mg every other week group [53] compared with other early clinical trials conducted in Japan to test the effects of infliximab [% of ACR20: 61.2% at week 14] [54] or etanercept [90.4% at week 24]) [55]. One of the most well-established mechanisms impairing the pharmacokinetic and clinical efficacy of bDMARDs is the emergence of immunogenicity and the formation of neutralizing anti-bDMARD antibodies. The percentage of patients showing anti-adalimumab antibody in serum was 44.0% in the adalimumab 40 mg group in the above-mentioned clinical trial in Japan [53]. The most notable point in that clinical study was that adalimumab was administered for patients as a monotherapy without concomitant use of MTX. Although sources of information comparable to the CONCERTO study [38] regarding the necessary dose of MTX required to induce clinical effectiveness of adalimumab in Japanese RA patients are not available, adalimumab in Japan might become more popular if a clinical study of combination therapy with MTX were to be undertaken.

Tocilizumab

Tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, was created and developed in Japan. IL-6 and its receptor have been cloned in Japan [56,57] and several clinical reports have been published from our country [35,58–62]. Concomitant use of MTX also provides additive effects to therapy with tocilizumab [63,64]. However, compared with anti-TNF bDMARDs, tocilizumab might not necessarily require combination with MTX. Many RA patients appear intolerant of MTX administration due to side effects in Japan. Tocilizumab should offer an effective modality for such patients or in cases of failed anti-TNF bDMARD therapy. On the other hand, tocilizumab absolutely decreases the CRP level and ESR by blocking IL-6 signaling, so infections may develop undetected during tocilizumab therapy. Tocilizumab can be usefully considered as a weapon that allows the user to cope with various situations, but close attention is necessary given that inflammatory reactions due to infection are masked. Experience with using tocilizumab led us into a train of thought about re-evaluating assessments of disease activity. DAS28 using CRP or

ESR might not offer a useful tool for assessing disease activity in patients receiving tocilizumab due to strong inhibition of acute-phase reactants by tocilizumab [14]. Four components in the DAS as a composite measure are subjective, unlike CRP or ESR. Now is the chance for Japanese rheumatologists to create new and objective assessment methods to evaluate disease activity in patients with RA in place of the old DAS.

Golimumab

Golimumab, a fully human monoclonal antibody against TNF-α, is one of the newest bDMARDs that has become available for the treatment of RA. The regular dose of golimumab is 50 mg/body sc., increasing to 100 mg in patients over 100 kg in body weight and showing insufficient response to 50 mg of golimumab in Europe [65]. However, both 50 and 100 mg of subcutaneous golimumab are approved in Japan for the treatment of RA. Japan is the only country in the world to have approved the use of 100 mg of golimumab for treating RA. A prospective observational cohort study was undertaken to investigate the relationship between trough level of golimumab and clinical response at 1 year [66]. Clinical responders at 1 year were defined as DAS28-ESR <3.2. As a result, responders showed a significantly higher golimumab trough level. CRP and ESR displayed a significant inverse association with the trough level of golimumab.

The Go-Forth study was a trial to assess the effects of subcutaneous golimumab (50 or 100 mg) in combination with MTX in Japan [67], while the Go-Further study examined intravenous golimumab at 2 mg/kg every 8 weeks in the USA [68] in a randomized, double-blinded, placebo-controlled manner. In both trials, golimumab plus MTX yielded significant inhibition of radiographic destruction and sustained clinical improvement in patients with active RA despite MTX. However, in the Go-Before trial using subcutaneous golimumab with MTX out of Japan, inhibition of structural damage was not clearly identified [69]. A sufficient dosage of golimumab might be important considering of the differing body weights of Japanese and western individuals. Monthly subcutaneous administration might be very convenient for patients with RA. As Japanese rheumatologists who can use 100 mg of golimumab subcutaneously, we should clarify for the world whether subcutaneous 100 mg of golimumab is useful or not. To clarify how we should use 50 and 100 mg of golimumab in T2T strategies, we are initiating a Go-Go trial in Japan (clinical trial registration, UMIN000009425).

Rheumatoid arthritis-related surgery

The total number of surgeries for RA patients might gradually decrease due to developments in the treatment of RA. Several reports on trends in orthopedic surgery have been published from different countries [70–73]. A Japanese report showed decreases in the number of major surgeries such as total knee replacement, and slight increases in the number of small surgeries such as foot and hand surgery [72]. This is quite a different tendency compared with reports from western countries [70,71,73]. Several reasons might underpin the declining number of surgical interventions for patients with RA. Over the last 2 decades, better pharmacotherapies have been applied for patients with early-stage RA, including bDMARDs with earlier and more aggressive intervention. Such a situation is presumably the same around the globe. The reason for the different tendency in Japan may be related to the fact that orthopedists themselves are taking on the bulk of Japanese rheumatic treatment in clinical practice. These clinicians are going to intervene in the slight obstacle in small joints to improve the quality of life of their RA patients.

Under the development of the intensive treatment strategy, surgical intervention remains prevalent for patients with RA. The most important decision-making step by physicians might be perioperative medication management for the treatment of RA, and whether to stop or continue anti-RA medication perioperatively. In general, it is recommended that csDMARDs such as MTX should be continued and anti-TNF blockers should be stopped in the perioperative period, in consideration of recurrent inflammation of RA and the increase in infection rate [74]. However, no clear evidence suggests that ceasing biologics for a fixed period is at all effective for perioperative infection control. There were two kinds of reports to search the effects of stopping bDMARD on the risk of developing surgical site infections (SSIs) perioperatively. One recommended discontinuation of bDMARDs for the reduction of SSIs [75] and the other concluded that perioperative continuation of anti-TNF did not seem to be an important risk factor for SSIs [76]. However, those studies were retrospective observational studies and there has been never a randomized controlled trial to reveal the answer for this issue. Provision of new data in this field from Japanese orthopedic rheumatologists is expected.

Conclusion

With recent advances in pharmacological and clinical research, we have most likely established a reliable treatment strategy for RA: T2T. Under an environment of low-dose MTX, clinical reports from Japan have shown results equivalent to those from western countries. We should therefore re-evaluate old DMARDs such as MTX in the new era of biologics using strict RCTs and/or observational studies. Japa-

nese orthopedic rheumatologists are well placed to offer new insights into the progression of large-joint destruction or immunohistological changes in synovial tissue in patients receiving bDMARDs, providing findings that would have remained obscured in the different treatment environments of other countries.

Future perspective

In the future, the T2T strategy is likely to become the mainstream treatment for RA all over the world. Sufficient doses of MTX will be identified and dose tapering might be considered during treatment with bDMARDs. However, we remain uncertain regarding the optimal method or choice of agents for the management of our patients in different stages of disease progression. It is the proposition that should be settled in the future. Orthopedic elective operations for patients with RA should decrease in number, but will never disappear. More delicate operations will be established for RA patients with milder deformities under safe, effective regimens for bDMARDs. Protocols for stopping bDMARDs after achieving targets will be provided.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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