Summary of evidence linked to recommendation
Overall, there is a lack of data on the safety of vaccination during treatment with most bDMARDs. Furthermore, there are not many studies on the efficacy of vaccines during treatment with bDMARDs; a study on pneumococcal vaccination suggested that patients on TNF inhibitors may not respond adequately to vaccination.[99] Thus, the recommendation of the Steering Committee in this regard aligns with that of most guidelines and is predominantly based on expert opinion.

Special comment/recommendation for the AP region
No region-specific comments.

Section 6 – Role of tofacitinib

Recommendation 40: **Tofacitinib may be considered if a bDMARD has failed. (Level II; Strength B).**
Supporting evidence
This recommendation is made not based on a review of the treatment recommendations/guidelines that the Steering Committee had initially identified. However, the role of tofacitinib was included in the EULAR RA treatment recommendations 2013 update.[17]

Summary of evidence linked to recommendation statement
Tofacitinib, a JAK inhibitor, has been under investigation as a therapy for RA. It is not a bDMARD or a cDMARD. In a number of placebo-controlled studies, tofacitinib, used either as a monotherapy or in combination with a cDMARD, primarily methotrexate, was associated with reductions in signs and symptoms of RA and improvement in physical function in patients with active disease despite previous treatment with cDMARDs.[100–102] In another study of active disease-patients receiving background methotrexate, tofacitinib was found to be significantly superior to placebo and was numerically similar to adalimumab in efficacy.[103] Furthermore, in a 6-month, double-blind, parallel-group phase 3 study involving 266 patients who were TNF inhibitor refractory, tofacitinib use was associated with meaningful improvements in signs and symptoms of RA and physical function.[104] However, the efficacy of this agent in other bDMARD refractory RA patients has not been reported.

Special comment/recommendation for the AP region
While there is evidence that tofacitinib is useful in active RA disease patients who have failed cDMARDs, and probably those who are refractory to TNF inhibitors, more data is needed to support its use as a first-line DMARD or after a patient has failed a bDMARD, specifically the non-TNF inhibitors. While we await long-term data on the efficacy and side-effect profiles, particularly infectious disease complications, of tofacitinib, the Steering Committee felt it is not yet ready to recommend its use in DMARD-naïve patients. The other consideration is to do with the possible high financial cost of tofacitinib which is significantly higher than that of all cDMARDs. This is an important consideration for many AP countries where there are financial constraints in obtaining access to expensive medications. Our decision to recommend its use in patients who have failed a bDMARD is based on an extrapolation of the data reported by Burmester *et al.*[104] The Steering Committee encourages national societies to include tofacitinib in their national drug formulary.

DISCUSSION

These are the first RA treatment recommendations developed by APLAR. The AP region is unique in many ways. It accounts for 61% of the world population with diverse ethnic, cultural and socioeconomic variations.[105] The prevalence, clinical manifestations, response to treatment and outcome of RA patients in many Asian countries have been suggested to differ from those reported in the West. Importantly, rheumatology is still a developing medical subspecialty in the region with a severe shortage of trained rheumatologists in many countries.[106] Not only are many RA patients in the AP region managed by non-rheumatologists, the lack of resources also means RA clinical studies are sparse and that a big gap exists in the evidence-based management of RA in this region.

The primary aim of these treatment recommendations is to provide clinicians with an evidence-based reference for the treatment of RA in the AP region. The Steering Committee was comprised of rheumatologists from 12 AP countries representing a diverse spectrum of cultures and ethnicities, health economic statuses and practises of rheumatology in the region. A patient with RA was also invited to join the Committee so as to include patients' perspectives on the treatment of their condition in the recommendations. Because of the nature of the recommendation drafting process which required members to communicate in English, a patient from Hong Kong who was literate in the language was invited to join the Committee.

The Steering Committee did not perform a systematic review of original articles to inform recommendations. Instead, the recommendations were developed using the ADAPTE framework[12,13] appraising all international RA practice guidelines and recommendations through to December 2013. The ADAPTE Collaboration is an international collaboration of researchers, guideline developers and guideline implementers who aim to promote the development and use of clinical practice guidelines through the adaptation of existing guidelines. Having first established the scope and purpose of the current RA treatment recommendations, the Steering Committee conducted a thorough search for guidelines and relevant documentations that have been previously published. Each of these articles was then assessed for guideline quality, currency, content, consistency and acceptability/applicability for the AP region using the AGREE instrument.[15] Selected previous guidelines were rigorously and systematically reviewed and discussed by members of the Steering Committee before they were customized to create the current adapted recommendations. The generic adaptation process of ADAPTE has been shown to be valid and of high quality.[12,13]

Based on the key questions that the Steering Committee had identified regarding the treatment of RA in the AP region, 40 recommendations concerning the general RA treatment strategies, and the role of NSAIDs, corticosteroids, cDMARDs, bDMARDs and tofacitinib have been made. Specific issues relating to the safety and monitoring of cDMARDs and bDMARDs are not covered in the current report. These include screening and prophylactic treatment for latent TB, management of patients who are chronic viral hepatitis B/C carriers and precautions with other regional prevalent infectious diseases. These will be covered separately in a later instalment of the recommendations.

The role of tofacitinib, a JAK inhibitor, in RA was not originally included as one of the key questions. However, midway through the development of these recommendations, tofacitinib became available in a number of AP countries and a recommendation on the use of this agent was included in the EULAR RA treatment recommendations 2013 update. The Steering Committee therefore felt it would be appropriate to include the role of tofacitinib in RA treatment in the current recommendations.

Realizing that many Asian countries are under-resourced to allow them to adhere strictly to the recommendations made in this report, the Steering Committee added comments based on expert opinions and consensus following each recommendation in the hope that minimum care requirement is achieved for all RA patients in these countries. In addition, it is hoped that some of these region-specific comments, which may lack full evidence, may form the basis of a research agenda, which is by no means exhaustive, for clinicians in the AP region (Table 4).

It should be noted that the current report does not include recommendations for physical and occupational treatment, and alternative/complementary therapies which are widely practised by many patients in the AP region. This is partly because evidence on the role of these treatment modalities is sparse. Furthermore, in many AP countries, the physical and occupational therapy disciplines are poorly developed. However, where physical and other non-pharmacological therapies are available, clinicians should advise RA patients about their roles in protecting normal joint function. For example, the BSR 2005 guidelines mentioned that patients should be informed about alternative techniques of effective pain management, including transcutaneous nerve stimulation (TENS) and behavioral approaches.[60] Others have also found that physical therapy and exercise are beneficial in RA patients.[57] Where resources are limited and patients are unable to afford the cost of procedures such as TENS, patients may be advised to exercise at home, as leisure time physical activity has also been shown to be beneficial and should be encouraged.[22]

CONCLUSION

APLAR has developed a set of general recommendations for the best practise management of RA in the AP region. We are also hopeful that some of these recommendations, where evidence for this region may be lacking, may stimulate clinicians to embark on research studies to resolve them. Specific issues such as the prevention of reactivation or novel TB and viral hepatitis infections will be addressed in a second instalment.

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CONFLICT OF INTEREST

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CONTRIBUTIONS

All authors were involved in performing the literature search, appraisal of guideline quality, grading of evidence, evidence synthesis, development of recommendations, and writing and proofreading of recommendations.

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Low rates of biologic-free clinical disease activity index remission maintenance after biologic disease-modifying anti-rheumatic drug discontinuation while in remission in a Japanese multicentre rheumatoid arthritis registry

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Abstract

Objective. To examine in detail the outcomes of biologic DMARD (bDMARD) discontinuation while in remission occurring in daily clinical practice settings. We examined a multicentre longitudinal registry of RA patients.

Methods. We utilized data from the NinJa multicenter registry in Japan. Patients who used bDMARDs and had one or more successive visits in remission (defined by the clinical disease activity index (CDAI) $\leqslant$2.8) before discontinuation were included. The outcome of failing bDMARD-free disease control was defined as a composite of the following: re-use of bDMARDs, intensification of non-biologic DMARDs or of oral glucocorticoids, or loss of CDAI remission.

Results. Among 1037 patients who initially achieved remission on bDMARDs, 46 patients discontinued bDMARDs while remaining in remission. Of these 46 subjects, 41 (89.1%) were female, the median disease duration was 6.0 years and 31 (70.5%) had reported radiographical erosions. At the baseline, 27 (58.7%) used MTX and 19 (41.3%) used oral glucocorticoids. The bDMARD-free remission failure rate was estimated to be 67.4% at 1 year and 78.3% at 2 years. Loss of remission and reuse of bDMARDs were the more common reasons for failure. Lower CDAI within the remission range was associated with fewer failures.

Conclusion. We found a high rate of failing bDMARD-free CDAI remission, indicating difficulty of maintaining disease control, even in patients who were in remission. Modification of non-biologic treatment was observed in some of the patients who remained in remission. Considering the cost of bDMARDs, such strategies for maintaining disease control after bDMARD discontinuation may be an important option.

Key words: rheumatoid arthritis, antirheumatic agents, biologic antirheumatic agents, remission, discontinuation.

Rheumatology key messages

- Discontinuation of biologic DMARDs occurred in a small fraction of RA patients in clinical disease activity index remission.
- Loss of biologic-free clinical disease activity index remission in RA was common due to its very strict definition.
- Some biologic-free RA patients remained in clinical disease activity index remission by intensifying non-biologic treatments.

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Introduction

Physicians grapple with whether to continue biologic DMARDs (bDMARDs) in patients achieving remission in RA. Several studies have examined the outcome of bDMARDs discontinuation while in remission, which are summarized in recent reviews [1–4]. There is wide variability in outcomes, ranging from a 1-year failure rate of ~20–90%. The variety of clinical settings and study designs, including the duration of RA, disease activity thresholds and failure criteria, are likely causes of such heterogeneity. Most studies examined the disease control outcome after protocolized discontinuation of bDMARDs. However, the disease control outcome of discontinuation spontaneously (i.e. without pre-specified protocols) occurring in clinical practice settings has not been widely studied. Therefore, we examined disease control after bDMARD discontinuation in daily clinical practice settings in Japan, using nationwide multicentre cohort data, to describe the rate of failure of bDMARD-free disease control after discontinuation, the predictors of failure and how failure definitions affect the outcome.

Methods

We utilized data from the National Database of Rheumatic Diseases by iR-Net in Japan (NinJa) multicentre registry [5]. The NinJa registry was established in 2002 and currently collects information annually from 40 participating sites throughout Japan. Among the patients in the registry, patients who used bDMARDs and who had one or more successive visits in remission (defined by clinical disease activity index [CDAI] $\leqslant$2.8) before discontinuation of their bDMARDs while remaining in remission were included. Only the first episode of remission on bDMARDs, regardless of the number of previous bDMARDs employed in treatment, was considered in order to avoid within-patient clustering of outcomes. Baseline variables, such as demographics and concurrent treatments, were ascertained at the first visit off bDMARDs. The registry, and all subsequent studies utilizing pre-existing registry data, were approved by the Sagamihara National Hospital institutional review board. No additional ethical approval was required by the central institutional review board for this specific study. Individual written consent was waived under the current Japanese ethical guidelines for epidemiological studies because of the purely observational nature of the registry.

After discontinuation of bDMARDs while in remission, four types of events were considered as failure of bDMARD-free disease control: reuse of bDMARDs, loss of CDAI remission (CDAI >2.8), addition of a new non-biologic DMARD, or increased doses of oral glucocorticoids. The outcomes were defined as the rate of the composite failure, including any one or more of the four types of failure events (Kaplan–Meier method), as well as the non-mutually exclusive (i.e. may be occurring simultaneously) individual reasons for failure (cumulative incidence function method [6]). As there was no gold standard for what constitutes failure after discontinuation of bDMARDs while in remission, we also conducted an alternative analysis looking only at reuse of bDMARDs and loss of CDAI remission as failure, thus allowing for treatment intensification of non-bDMARDs and glucocorticoids as well as analysis in which loss of CDAI low disease activity (CDAI >10) instead of remission was defined as failure. Missing CDAI was considered loss of remission. Predictors of failure after bDMARD discontinuation in remission were examined using Cox regression models for the composite failure. Predictors were defined at the time of discontinuation (i.e. first study visit off bDMARDs), and were assessed both in univariable regression and multivariable regression models. All analyses were conducted with R version 3.1.3 (www.r-project.org) and additional packages: tableone, survival and cmprsk. Hypothesis tests were considered statistically significant when *P*-value was <0.05.

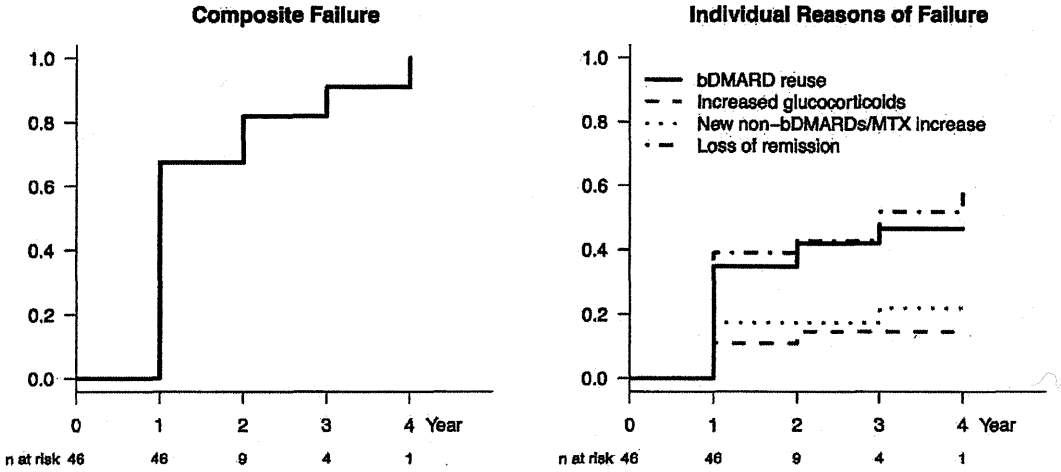
Results

Among 1037 patients who initially achieved remission on bDMARDs, 77 patients discontinued their bDMARDs after successive visits in CDAI remission. Among them, 46 had additional follow-up visits after discontinuation available for outcome assessment. In this 46-patient study cohort, 41 (89.1%) were female, the mean (S.D.) age was 57.4 years (13.1), the median RA disease duration was 6.0 years (interquartile range: 4.0–8.0), 31 (70.5% of 44 with baseline data) had radiographical erosions, 38 (82.6%) discontinued TNF inhibitors and 42 (91.3%) discontinued their first bDMARD. At baseline, treatments were as follows: MTX use by 27 patients [58.7%; median dosage among users 8.0 mg/week (interquartile range: 6.0–10.0)], any non-biologic DMARDs use by 34 patients (73.9%), oral glucocorticoid use by 19 patients [41.3%; median dosage among users 3.0 mg/day (2.0–5.0)] and NSAIDs use by 13 patients (28.3%). The baseline characteristics of the study cohort, as well as the source cohort of patients in remission, are summarized in supplementary Table S1, available at *Rheumatology* Online.

The composite failure rate of bDMARD-free disease control was 67.4% (95% CI: 53.9, 80.3) at 1 year and 81.9% (95% CI: 67.5, 92.6) at 2 years (Fig. 1, left panel). When dissected into individual reasons for failure, which may be occurring concurrently (supplementary Table S2, available at *Rheumatology* Online), loss of CDAI remission and reuse of bDMARDs occurred in ~40% during the first 2 years, whereas non-biologic treatment intensification occurred in ~10–20% (Fig. 1, right panel). In the alternative analyses allowing for changes in the non-biologic treatment, the failure rate was 58.7% (95% CI: 45.1, 72.9) at 1 year and 77.5% (95% CI: 62.1, 89.9) at 2 years. If CDAI low disease activity was used as the failure threshold, the failure rate was 54.3% (95% CI: 40.8, 69.0) at 1 year and 68.4% (95% CI: 53.2, 82.6) at 2 years.

In the univariable Cox regression models for the composite failure of bDMARD-free disease control, the CDAI [hazard ratio (HR) 1.51 (95% CI: 1.06, 2.16) for 1 U increase, $P=0.022$, Wald test] and time between initiation of bDMARDs and initial CDAI remission (HR 1.48, 95%

FIG. 1 Composite failure and individual reasons of failure of bDMARD-free disease control over time



The left panel describes the rate of the composite failure, including all individual reasons for failure over time. The right panel shows the rate of each individual reason for failure, i.e. failure by bDMARD reuse, by increased doses of oral glucocorticoids, by initiation of a new non-bDMARD or by loss of remission. The individual reasons are partly overlapping, and thus add up to more than the composite failure rate. bDMARD: biologic DMARD.

TABLE 1 Cox regression models for composite failure outcome after bDMARD discontinuation

Variable	Univariable models		Multivariable model	
	HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Female	0.76 (0.29, 1.96)	0.569	1.33 (0.42, 4.15)	0.627
Age, per decade	0.94 (0.75, 1.18)	0.593	0.92 (0.71, 1.19)	0.518
RA duration, per decade	0.95 (0.68, 1.34)	0.771	0.92 (0.62, 1.37)	0.677
TNF inhibitor discontinuation	0.82 (0.36, 1.88)	0.645	0.74 (0.29, 1.92)	0.537
Clinical Disease Activity Index	1.51 (1.06, 2.16)	0.022	1.58 (1.04, 2.39)	0.031
MTX use	0.78 (0.41, 1.49)	0.456	1.16 (0.55, 2.46)	0.703
Glucocorticoid use	1.76 (0.92, 3.37)	0.088	1.93 (0.92, 4.05)	0.082
Time before remission, per year	1.48 (1.05, 2.09)	0.027	1.26 (0.82, 1.96)	0.294
More recent calendar year, per year	1.08 (0.81, 1.43)	0.616	0.94 (0.66, 1.33)	0.718

HR: hazard ratio; *P*: Wald test *P*-value.

CI: 1.05, 2.09 for each year; $P=0.027$) were statistically significant. In the multivariable model, only CDAI had a significant result (HR 1.58, 95% CI: 1.04, 2.39; $P=0.031$). Another suggestive finding was glucocorticoid use (HR 1.93, 95% CI: 0.92, 4.05, $P=0.082$). Time between initiation and remission became non-significant (HR 1.26, 95% CI: 0.82, 1.96; $P=0.294$). The results for all variables are summarized in Table 1.

Discussion

In order to examine the implications of bDMARDs discontinuation in CDAI remission in daily practice, we utilized a nationwide multicenter observational cohort of RA patients in Japan, and examined the rates of failure of bDMARD-free CDAI remission after discontinuation, the reasons for failure, and the predictors of failure. Among the small fraction of patients who discontinued bDMARDs in CDAI remission, the rates of failure during the following years were high at 67.4%, leaving only 32.6% of patients remaining in CDAI remission without treatment intensification at 1 year. Among the reasons for failures, bDMARD reuse and loss of CDAI remission were similarly common, although there were some people who received intensified non-biologic treatment and maintained remission, as suggested by the lower failure rate of 58.7% when regarding non-biologic treatment intensification as non-failure. When we relaxed the CDAI threshold to low disease activity, the failure rate decreased to 54.3% during the first year.

These findings suggest that maintenance of disease activity control after discontinuation of bDMARDs is relatively difficult in daily practice, even among the selected

patients who discontinued bDMARDs in CDAI remission, which is known to be a stringent criterion. Previous studies with lower failure rates at 1 year were typically clinical trials in early RA patients [7, 8], whereas studies that examined the outcome of discontinuation in more long-standing RA patients had a failure rate more similar to that of our study, which had a patient population with a median disease duration of 6 years [9–13]. There are a couple of exceptions that had lower failure rates in established RA patients. One is a study from the CORRONA registry [14]. The definition of discontinuation and failure based on the CDAI low disease activity threshold and health care system difference are likely to explain the difference. Another is a pragmatic trial from Japan [15]. No use of glucocorticoids by protocol before discontinuation, and failure definition according to the DAS28 low disease activity threshold are the likely reasons. Our results were sensitive to definitions of failure, underscoring the importance of a detailed look at definitions of failure when examining papers in this area of research.

Some studies examined the roles non-biologic DMARDs play after discontinuation of bDMARDs [16, 17]. In one such study [16], addition of bucillamine (D-pen-like DMARD, available in Japan and South Korea) at the discontinuation of infliximab decreased flare rate compared with discontinuation without additional medications. In our study, a small proportion of patients utilized additional non-biologic DMARDs and/or increased oral glucocorticoids during the study follow-up and remained in remission. When non-biologic medication modifications were considered non-failure, the composite failure rate was reduced by ~10% for the first year, although the second year result was not very different. Had this practice been more common, the successful maintenance of disease control after bDMARD discontinuation might have been better.

In terms of the predictors of failures, the baseline CDAI at the time of discontinuation was significant in the multivariable analysis. This indicates, even within the remission range, that lower CDAI was associated with better outcomes after discontinuation, confirming the need for deep remission for successful discontinuation [1, 15, 18]. One may argue that this is an artifact due to the failure definition, which also uses the CDAI remission threshold. However, considering the implication of sustained disease activity control on the structural progression [19], this is still clinically important.

Another interesting finding in the univariable analyses was the more frequent failures observed when a longer time was required to reach remission on bDMARDs. This is consistent with clinical intuition and is in line with a study based on the BeSt trial [8], in which longer treatment durations on a bDMARD were associated with increased failure after discontinuation. The study was a pragmatic trial in which treatment discontinuation was allowed only if a certain duration of successful disease control was observed, making longer treatment durations a surrogate marker of the time required to reach sufficient disease activity suppression. This effect was not significant after adjusting for CDAI, which may suggest longer bDMARD treatment durations before reaching remission influence the outcome mainly through adversely affecting the baseline CDAI.

Our study had a small sample size, mainly due to the strict inclusion criteria (based on successive visits in CDAI remission). Patients were not allowed to have visits with non-remission disease activity or missing CDAI once they entered remission at some point. This was required in order to ensure that the patients were indeed in good disease control before the time of discontinuation. The study sample was mostly limited to the first bDMARD users, as we focused on the first episode of remission and discontinuation. We did not examine tapering (dose reduction) of bDMARDs, which some of the recent studies [17, 20] looked at, as it further complicates outcome definitions. Due to the annual nature of the data collection in the NinJa registry, we had to define loss of CDAI remission as the any non-remission-range CDAI recorded at the annual data points. This may have captured transient loss of CDAI remission that did not require additional treatment. The significance of such transient loss of remission after bDMARD discontinuation is unknown, and the rate of failure may have been slightly overestimated by this. Nonetheless, our study is unique in that we observed outcomes of bDMARD discontinuation, including non-biologic treatment modifications spontaneously occurring in clinical practice without pre-specified protocols.

In conclusion, we found a high rate of failure of bDMARD-free CDAI remission after discontinuing bDMARDs in daily practice, even in patients who were in CDAI remission. The most common reasons of failure were restarting bDMARDs and loss of CDAI remission. This result indicates the difficulty of maintaining tight disease control off bDMARDs in established RA patients being treated with bDMARDs in daily practice. Modifications of non-biologic treatment were observed in some of the patients who remained in remission. Considering the cost of bDMARDs, such treatment strategies employed to maintain disease control after bDMARD discontinuation might need further investigation in addition to investigation of more conservative bDMARD dose reduction strategies.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Incidence and Predictors of Biological Antirheumatic Drug Discontinuation Attempts among Patients with Rheumatoid Arthritis in Remission: A CORRONA and NinJa Collaborative Cohort Study

Kazuki Yoshida, Helga Radner, Maria D. Mjaavatten, Jeffrey D. Greenberg, Arthur Kavanaugh, Mitsumasa Kishimoto, Kazuo Matsui, Masato Okada, George Reed, Yukihiko Saeki, Shigeto Tohma, Joel Kremer and Daniel H. Solomon

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ABSTRACT. ***Objective.*** We conducted a longitudinal observational study of biological disease-modifying antirheumatic drugs (bDMARD) to describe the proportions of patients with rheumatoid arthritis in remission who discontinued these agents, and to assess the potential predictors of the decision to discontinue.

Methods. We used data from the US COnsortium of Rheumatology Researchers Of North America (CORRONA) and the Japanese National Database of Rheumatic Diseases by iR-net in Japan (NinJa) registries, and ran parallel analyses. Patients treated with bDMARD who experienced remission (defined by the Clinical Disease Activity Index ≤ 2.8) were included. The outcome of interest was the occurrence of bDMARD discontinuation while in remission. The predictors of discontinuation were assessed in the Cox regression models. Frailty models were also used to examine the effects of individual physicians in the discontinuation decision.

Results. The numbers of eligible patients who were initially in remission were 6263 in the CORRONA and 744 in the NinJa. Among these patients, 10.0% of patients in CORRONA and 11.8% of patients in NinJa discontinued bDMARD while in remission over 5 years, whereas many of the remaining patients lost remission before discontinuing bDMARD. Shorter disease duration was associated with higher rates of discontinuation in both cohorts. In CORRONA, methotrexate use and lower disease activity were also associated with discontinuation. In frailty models, physician random effects were significant in both cohorts.

Conclusion. Among patients who initially experienced remission while receiving bDMARD, around 10% remained in remission and then discontinued bDMARD in both registries. Several factors were associated with more frequent discontinuation while in remission. Physician preference likely is also an important correlate of bDMARD discontinuation, indicating the need for standardization of practice.

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Key Indexing Terms:

RHEUMATOID ARTHRITIS ANTIRHEUMATIC AGENTS AFFILIATIONS
BIOLOGICAL ANTIRHEUMATIC AGENTS REMISSION DISCONTINUATION

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Discontinuation of biological disease-modifying antirheumatic drugs (bDMARD) has attracted attention because of the potential to induce bDMARD-free disease control, along with the high costs and potential adverse effects. Multiple studies[1–9,10,11,12,13,14,15,16,17] and reviews[18,19,20,21,22] have suggested the feasibility of this strategy for some patients, mostly in clinical trial settings. Backed by such evidence supporting the possibility of bDMARD treatment discontinuation, the updated European League Against Rheumatism (EULAR) recommendation for the treatment of rheumatoid arthritis (RA) now includes the consideration of bDMARD tapering after achieving continued remission[23].

Little has been written about the incidence of bDMARD discontinuation while in remission in typical practice and what patient factors might influence the decision to discontinue. Most prior studies were clinical trials that protocolized discontinuation[19]; thus, they do not necessarily represent a typical practice pattern. Therefore, to clarify how often bDMARD are discontinued during remission in daily clinical practice and to identify predictors of discontinuation, we conducted a parallel analysis of patients enrolled in clinical registries in the United States and Japan.

MATERIALS AND METHODS

Data sources. We conducted a retrospective observational analysis of data from 2 clinical practice registries: the COnsortium of Rheumatology Researchers Of North America (CORRONA), which started in 2001[24], and the National Database of Rheumatic Diseases by iR-net in Japan (NinJa), which started in 2002[25]. The CORRONA database is a multicenter registry of clinically diagnosed patients with prevalent RA from 104 rheumatology practice sites in the United States with a data collection interval of 3–6 months. The NinJa database is a similar registry of clinically diagnosed patients with prevalent RA from 42 rheumatology practice sites (including both rheumatologists and orthopedists) in Japan with a fixed data collection interval of 1 year. Both registries and subsequent analyses were approved by each participating site's institutional review board or the respective central review board when not available. All patients provided written informed consent for CORRONA. For NinJa, individual written consent was waived under the current Japanese ethical guideline because of the purely observational characteristic of the registry. The most recent data used in the analysis were the 2013 data. In the United States, bDMARD were indicated at the discretion of the treating physicians, whereas in Japan, active disease (roughly defined as Disease Activity Score in 28 joints with erythrocyte sedimentation rate > 3.2) after nonbiological DMARD treatment was required. The datasets from these 2 registries were analyzed separately in most analyses because they were expected to differ in unmeasurable ways attributable to different practice settings across 2 countries.

Study cohort definition. Patients with RA who had 2 or more consecutive visits while receiving bDMARD (or patients who were already receiving bDMARD at the first recorded visit) and who fulfilled the Clinical Disease Activity Index (CDAI) remission defined as CDAI ≤ 2.8 of at least 1 point while receiving bDMARD were eligible for the study cohorts. Once in the study cohorts, reentry for subsequent bDMARD use was not allowed to avoid within-patient correlated data. Patients receiving rituximab (RTX) were excluded because "discontinuation" is difficult to define because RTX is often used intermittently as needed. The cohort assembly process is described in Figure 1.

The index date was defined as the first of successive visits in CDAI remission (CDAI ≤ 2.8) while receiving bDMARD, and the followup continued until one of the outcomes of interest, competing risk events, or censoring occurred. The baseline characteristics of the study cohorts on the index date are described with summary statistics in Table 1.

Endpoint definition. The outcome of interest was defined as the discontinuation of bDMARD while remaining in CDAI remission (i.e., a visit in CDAI remission while receiving bDMARD immediately followed by a visit in CDAI remission while not receiving bDMARD). Importantly, we examined the time period preceding the occurrence of discontinuation rather than what happened after discontinuation. We examined the latter in a separate article[26]. Censoring occurred administratively (end of registry data) or by loss to followup. Two alternative endpoints were considered as competing risk events[27], which preclude the occurrence of the event of interest: (1) when patients experienced loss of CDAI remission while still receiving bDMARD ("loss of remission") or (2) when the treatment was changed to different bDMARD without reported loss of CDAI remission ("switch", presumable loss of CDAI remission occurring between study intervals[28]). Lack of CDAI data during followup was considered "loss of remission." The endpoints are explained graphically in Appendix 1.

Statistical analyses. Analyses were conducted separately for each registry. Description of occurrence of bDMARD discontinuation was performed with 2 methods: the cumulative incidence function method and the cause-specific Kaplan-Meier method[27]. The cumulative incidence function method describes the occurrence of the event of interest taking into account the cohort attrition to the competing risk events ("loss of remission" and "switch"); thus, it describes the proportion with respect to the initial cohort at the start of followup. The denominator is always the initial cohort size to describe the proportion of discontinuation among those who were initially in remission at the start of followup.

On the other hand, the cause-specific Kaplan-Meier method, by handling competing risk events as regular censoring (i.e., excluding patients as soon as they experience "loss of remission" or "switch"), describes the incidence of event of interest among those who had not experienced any of the competing risk events at each timepoint. The denominator here decreases over time as we lose people to "loss of remission" and "switch." This method describes the proportion of discontinuation among those who remained in remission while receiving bDMARD at each timepoint.

In short, both analyze the same numerator (occurrence of discontinuation), but with respect to different denominators. The former uses the constant initial cohort size as the denominator, whereas the latter uses a dynamically decreasing cohort of those who are still in remission while

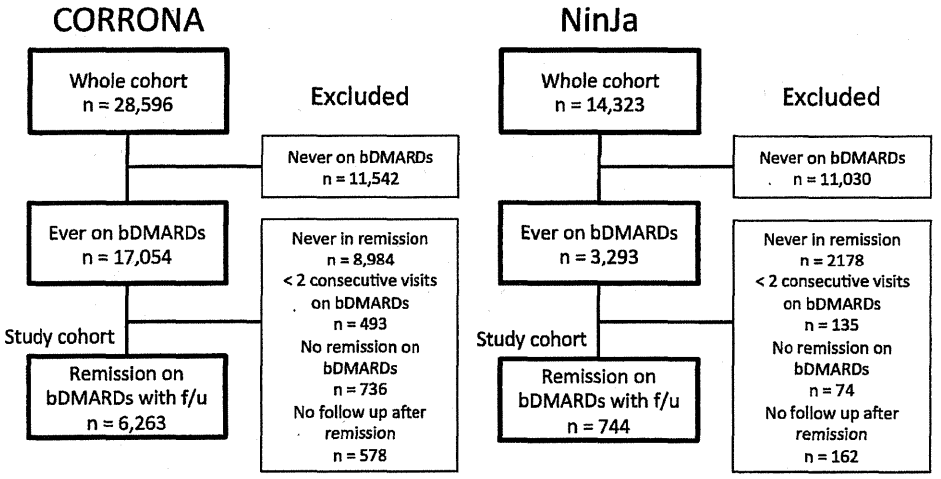

Figure 1. The cohort assembly process. Among all bDMARD users, patients who experienced CDAI remission while receiving bDMARD with followup visits were included in the study. CORRONA: COnsortium of Rheumatology Researchers Of North America; NinJa: National Database of Rheumatic Diseases by iR-net in Japan; bDMARD: biological disease-modifying antirheumatic drugs; CDAI: Clinical Disease Activity Index; f/u: followup visits; Remission: remission by the CDAI (CDAI ≤ 2.8).

receiving bDMARD at each timepoint. In the presence of substantial competing risk events, the cause-specific Kaplan-Meier estimator will overestimate the incidence, but it does answer one of the relevant questions: the incidence of physicians' decisions to discontinue given the ideal patients who remain in remission while receiving bDMARD indefinitely and who do not experience any of the competing risk events.

Cause-specific hazard Cox regression[27] was performed to assess the potential link between patient characteristics and bDMARD discontinuation while in remission. Models were developed in each registry separately because of heterogeneities in the patient population, data collection method, and healthcare system. Clinically meaningful baseline variables at the index date were included in the models: sex, race (assumed Asian in NinJa because it was not available), age, disease duration of RA, presence of erosive disease, classes of biologic agents, CDAI, concurrent methotrexate (MTX) use, concurrent oral glucocorticoid use, estimated time between the initiation of bDMARD and the index visit, and the calendar year of the index date. Patients without missing data in these variables were included in this part of the analysis. Continuous variables were kept as such after checking for nonlinearity by inclusion of squared terms. The bDMARD were classified into tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) and non-TNF inhibitors (abatacept, anakinra, and tocilizumab). They were assumed to be initiated at the midpoint between the last visit without bDMARD and the first visit with bDMARD. For those who were already being treated with bDMARD during the enrollment into the registries, the bDMARD were assumed to have been initiated prior to the enrollment by one-half of the median followup interval. Seropositivity was not included in the final models because of the unavailability in NinJa, and erosion was not included in the final models because of the high rate of missing data in CORRONA. As measures of overall prediction performance of the models, C statistics (akin to the area under the curve of receiver-operating characteristics analysis, a measure of the model's discrimination capability) and Nagelkerke pseudo R^2 (interpreted as the amount of variability in the time-to-event outcome explained by the model) were calculated[29]. To examine physician practice variability, physician random effects were assessed in terms of the intraclass correlation coefficient (ICC). Presence of significant random effects suggests that some physicians are more likely to attempt bDMARD discontinuation given patients with similar baseline characteristics. A combined dataset analysis was also conducted, and variables were tested for statistically significant effect modification between the 2 registries. As a sensitivity analysis, available information regarding the reasons for discontinuation was used to exclude patients who had recorded adverse events at the time of discontinuation. We also performed sensitivity analysis excluding non-TNF inhibitors.

All analyses were conducted with R version 3.1.1 (www.r-project.org) with additional analysis packages: tableone, survival, and cmprsk. Where hypothesis testing was used, results were considered statistically significant when $p < 0.05$.

RESULTS

Numbers of eligible patients in study cohorts and baseline characteristics. The total numbers of patients with RA with 2 or more consecutive study visits were 28,596 in CORRONA and 14,323 in NinJa. The numbers of patients who were treated with bDMARD at any point during the followup were 17,054 (59.6% of total) in CORRONA and 3293 (23.0% of total) in NinJa. The numbers of patients eligible for the followup were 6263 (36.7% among bDMARD users) in CORRONA and 744 (22.6% among bDMARD users) in NinJa (Table 1). Concurrent MTX was used in 63.5% in CORRONA versus 69.4% in NinJa. Nonsteroidal antiinflammatory drugs were used in 56.4% in CORRONA and 40.7% in NinJa. Glucocorticoids were used in 19.0% in CORRONA and 37.8% in NinJa. Most of the study cohorts were in their first instance of bDMARD while in the registry (90.9% in CORRONA and 92.7% in NinJa) because we did not allow the reentry of the same patients multiple times.

Discontinuation over time. In the cumulative incidence function method accounting for competing risk events ("loss of remission" or "switch" before discontinuation), 5-year bDMARD discontinuation while in remission occurred in 10.0% of patients in CORRONA, whereas it occurred 11.8% in NinJa (Figure 2). These proportions were estimated with

Table 1. Baseline characteristics of patients with RA receiving bDMARD with at least 1 visit in remission from CORRONA and NinJa. Values are n (%) or median (interquartile range) unless otherwise specified.

Characteristics	CORRONA, n = 6263	NinJa, n = 744
Female	4727 (75.8)	589 (79.2)
Race		
White	5698 (91.0)	0 (0.0)
Black	335 (5.3)	0 (0.0)
Others	230 (3.7)	744 (100.0)
bDMARD		
TNF inhibitors	5728 (91.5)	586 (78.8)
Non-TNF inhibitors	535 (8.5)	158 (21.2)
MTX use	3974 (63.5)	516 (69.4)
Dose among users, mg/week	15 (10–20)	8 (6–8)
NSAID use	3534 (56.4)	303 (40.7)
Glucocorticoid dose category		
0 mg	5075 (81.0)	463 (62.2)
1–4 mg	543 (8.7)	193 (25.9)
5–9 mg	501 (8.0)	77 (10.3)
10+ mg	144 (2.3)	11 (1.5)
Erosion*	2690 (55.1)	585 (81.8)
Age, yrs, mean (SD)	56.7 (13.5)	56.3 (13.8)
Age at RA onset, yrs, mean (SD)	46.2 (14.1)	47.0 (14.7)
RA disease duration, yrs	8.0 (4.0–15.0)	6.0 (3.0–12.0)
CDAI	1.5 (0.8–2.2)	1.6 (0.8–2.3)
TJC, 0–28		
0	5754 (91.9)	641 (86.7)
1	449 (7.2)	84 (11.4)
2	60 (1.0)	14 (1.9)
SJC, 0–28		
0	5650 (90.2)	622 (84.2)
1	467 (7.5)	91 (12.3)
2	146 (2.3)	26 (3.5)
PtGA, 0–100	5.0 (2.0–12.0)	5.0 (1.0–10.0)
PGA, 0–100	4.0 (1.0–7.0)	4.0 (1.0–7.0)
BMI, kg/m^2	27.2 (23.8–31.4)	22.0 (20.1–24.1)
Time since bDMARD, days	174.5 (62.5–394.5)	182.6 (182.6–547.9)
Followup duration, days	371.0 (189.8–777.0)	365.2 (365.2–730.5)

* Missing in 21% in CORRONA and 3% in NinJa. RA: rheumatoid arthritis; bDMARD: biological disease-modifying antirheumatic drugs; CORRONA: COnsortium of Rheumatology Researchers Of North America; NinJa: National Database of Rheumatic Diseases by iR-net in Japan; TNF: tumor necrosis factor; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; CDAI: Clinical Disease Activity Index; TJC: tender joint count; SJC: swollen joint count; PtGA: patient's global assessment; PGA: physician's global assessment; BMI: body mass index.

respect to the initial cohort sizes (6263 for CORRONA and 744 for NinJa).

In the cause-specific Kaplan-Meier analysis censoring competing risk events, 5-year bDMARD discontinuation among those who remained in remission without experiencing competing risk events was estimated to be 38.9% in CORRONA and 30.6% in NinJa (Figure 3). These proportions are higher because these were estimated regarding those who were still in remission while receiving bDMARD at each timepoint (this denominator shrank over time).

Regression analysis for predictors of discontinuation. The results from 2 separate Cox regression models for bDMARD discontinuation attempts are shown in Table 2. Longer disease duration was associated with less frequent bDMARD discontinuation attempts (HR for each decade 0.88, 95% CI 0.79–0.99 in CORRONA and HR 0.53, 95% CI 0.33–0.85 in NinJa). Additionally, in CORRONA, MTX use was associated with more frequent discontinuation attempts (HR 1.56, 95% CI 1.28–1.90), whereas higher baseline CDAI had an inverse association (HR 0.89, 95% CI 0.80–1.00). When CDAI components were tested, tender joint count was the likely factor preventing discontinuation attempts (HR 0.75, 95% CI 0.54–1.04, p = 0.088). The C statistics were 0.60 in CORRONA and 0.66 in NinJa, and the pseudo R^2 were 0.01 in CORRONA and 0.04 in NinJa (Table 2). The physician random effects, measured as the ICC, were small but statistically significant for CORRONA (ICC 0.12, p < 0.001 by likelihood ratio test) and NinJa (ICC 0.12, p = 0.006). This

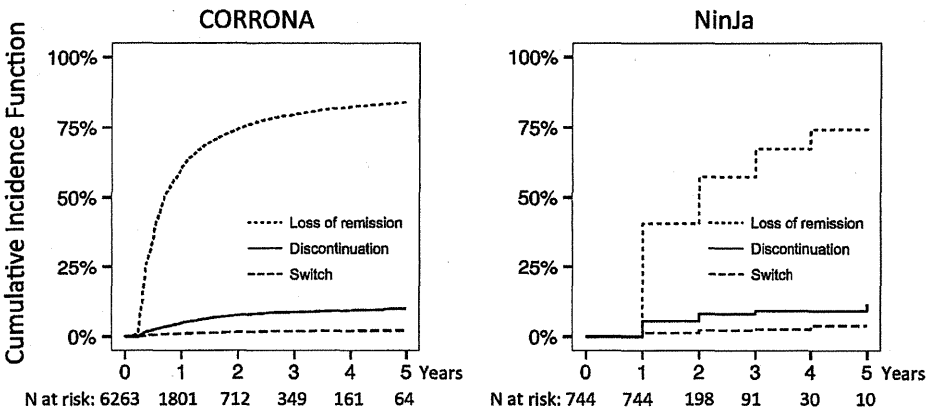

Figure 2. Discontinuation of bDMARD as well as "loss of remission" or "switch" (competing risk events) over time by the cumulative incidence function method. These proportions over time were calculated regarding the initial cohort sizes; thus, the rates of discontinuation are smaller than in Figure 3. The definitions of endpoints are explained in detail in the text and Appendix 1. CORRONA: COnsortium of Rheumatology Researchers Of North America; NinJa: National Database of Rheumatic Diseases by iR-net in Japan; bDMARD: biological disease-modifying antirheumatic drugs; N at risk: number at risk for events.

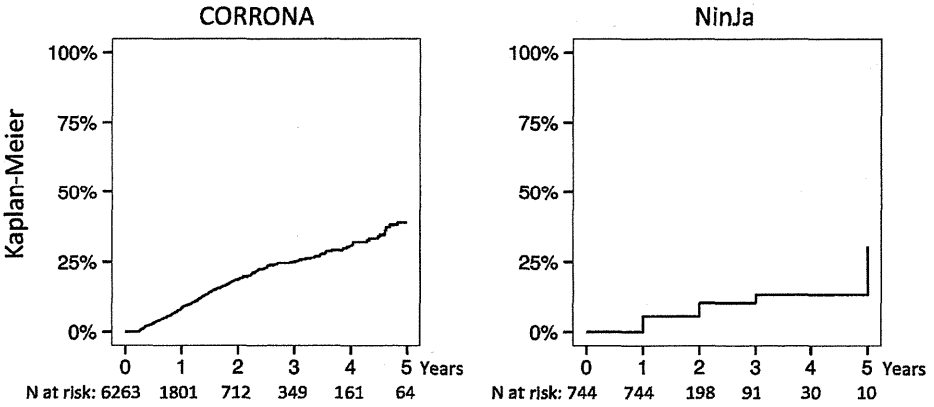

Figure 3. Discontinuation of bDMARD over time using the Kaplan-Meier method. The rates represent discontinuation of bDMARD among those who remained in remission and did not experience "loss of remission" or "switch" (competing risk events). The denominator here decreases over time; thus, the rates of discontinuation appear larger than in Figure 2. CORRONA: COnsortium of Rheumatology Researchers Of North America; NinJa: National Database of Rheumatic Diseases by iR-net in Japan; bDMARD: biological disease-modifying antirheumatic drugs; N at risk: number at risk for events.

indicates that physicians had different tendencies toward bDMARD discontinuation attempts when they had patients with similar baseline characteristics.

In the sensitivity analysis, 109 of 501 patients in CORRONA and 28 of 56 patients in NinJa had recorded information regarding the presence or absence of adverse events at the time of discontinuation. Among these patients, 26 in CORRONA and 4 in NinJa had reported adverse events. In the Cox regression excluding these patients from the outcome definition, we obtained similar point estimates (data not shown) and p values. Exclusion of non-TNF inhibitors resulted in very similar results (data not shown).

DISCUSSION

To investigate the incidence of bDMARD discontinuation while in remission and to explore the predictors of such practice in 2 different settings, we studied multicenter registries from the United States and Japan. We found that bDMARD discontinuation within 5 years of index date among those who were initially in remission occurred in around 10%, which corresponds to around one-third of patients who remained in remission over time. Shorter RA disease duration in both cohorts and MTX use and lower baseline CDAI in CORRONA were associated with a higher incidence of bDMARD discontinuations while in remission.

Table 2. Cause-specific Cox regression models for predictors of discontinuation in CORRONA and NinJa (2 separate models).

Variable	CORRONA		NinJa	
	HR (95% CI)	p	HR (95% CI)	p
Female	1.06 (0.86–1.30)	0.613	2.19 (0.98–4.90)	0.055
Race				
White	Reference			
Black	0.96 (0.65–1.43)	0.838		
Other	1.35 (0.85–2.14)	0.202		
Age, each decade	1.04 (0.97–1.12)	0.246	1.06 (0.87–1.28)	0.568
RA duration, each decade	0.88 (0.79–0.99)	0.031	0.53 (0.33–0.85)	0.009
bDMARD class				
TNF inhibitors	Reference		Reference	
Non-TNF inhibitors	0.93 (0.63–1.38)	0.731	0.80 (0.38–1.69)	0.552
CDAI	0.89 (0.80–1.00)	0.048	0.78 (0.56–1.07)	0.118
MTX use	1.56 (1.28–1.90)	< 0.001	0.80 (0.43–1.49)	0.483
Glucocorticoid use	1.24 (0.99–1.56)	0.064	0.94 (0.53–1.66)	0.820
Time since bDMARD, yrs	0.94 (0.83–1.05)	0.255	1.25 (0.95–1.64)	0.106
Index yr	1.01 (0.97–1.05)	0.688	1.10 (0.90–1.35)	0.359
C statistics	0.60		0.66	
R^2	0.01		0.04	

CORRONA: COnsortium of Rheumatology Researchers Of North America; NinJa: National Database of Rheumatic Diseases by iR-net in Japan; RA: rheumatoid arthritis; bDMARD: biological disease-modifying antirheumatic drugs; TNF inhibitors: tumor necrosis factor inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab); Non-TNF inhibitors: non-tumor necrosis factor inhibitor biologic agents (abatacept, anakinra, and tocilizumab); CDAI: Clinical Disease Activity Index; MTX: methotrexate.

The significant physician random effects results suggest an important role played by physician's preference in this decision.

The incidences of discontinuation while in remission concerning the initial cohort in remission were similar across registries (Figure 2), whereas the discontinuation among those who remained in remission was somewhat higher in CORRONA (Figure 3). Although the study design difference particularly regarding followup intervals makes quantitative comparison across registries difficult, a possible explanation for the somewhat higher rate of discontinuation while in remission among those who remained in remission in CORRONA may be the different financial burden on patients. In the United States, reimbursement for novel DMARD is more dependent on insurance plans, sometimes resulting in higher out-of-pocket cost[30], whereas in Japan the reimbursement is universal regardless of specific insurance plans, although copays (subject to capping by the catastrophic coverage) are usually required[31]. Also, patients' preferences may play different roles depending on the cultural context. For example, patients may have concerns about potential adverse effects related to therapy, or dislike the idea of needing to take medications chronically, particularly if they are feeling well, and this may differ across cultures.

Baseline MTX use was associated with higher rates of bDMARD discontinuation in remission in the CORRONA, but the association was reversed in NinJa, although nonsignificantly. The positive association seen in the CORRONA may indicate more confidence of disease control after bDMARD discontinuation on physician and/or patient sides with concurrent MTX use. This is in agreement with the 2013 EULAR recommendation[23], which states that bDMARD discontinuation should preferably occur in the presence of concurrent synthetic DMARD. The negative trend in the NinJa may occur because until early 2011, MTX was only approved for non-MTX treatment failure cases in Japan. This is likely to make the MTX users and non-users different, with the former consisting of patients who are more difficult to treat, probably explaining "reluctance" to discontinue bDMARD even though the patients were in remission.

Our study is unique in that it specifically examined the incidence and predictors of the bDMARD discontinuation attempts while in remission in typical practice settings in 2 different countries (i.e., time period before discontinuation rather than the outcome after discontinuation). Previous studies published on bDMARD down-titration and discontinuation were protocolized[12,13]. Such studies provide valuable information about the effectiveness of such discontinuation strategies; however, our study is unique in that it observed the clinical practice "as is," thereby providing insights into what the typical practice had been. Our study is also distinct from a recently published study on CORRONA[1] that examined outcomes after the discontinuation of TNF inhibitors in CDAI low disease activity.

There are several limitations that need consideration in conjunction with our current findings. The use of 2 registries gave us a unique opportunity to assess practice patterns in 2 different countries, but posed certain challenges. The harmo-

nization of data[32] is one such challenge. Ideally, registries should be designed with harmonization in mind. In our case, these 2 registries were initiated separately; thus, data harmonization had to be posthoc. We carefully chose variables and granularity of these variables so that data were available in both registries. Because differences beyond those identified by measured variables are expected, we kept the analyses separate, although the same set of analyses were conducted in each registry.

The tapering of bDMARD either by dose reduction or interval expansion is stated in the 2013 EULAR recommendation[23]. Because of the difficulty of comparing changes in dosing and interval information across registries, however, we only assessed discontinuation, but not tapering. Because studies of withdrawing medication are likely to be important in any areas in which effective but expensive therapeutic agents are used, we recommend that administrators of medication registries adopt a rich data format for discontinuation (e.g., exact date, predefined categories of reasons including discontinuation after good response, consistent dose reporting, and free text entry to identify subtleties of decisions).

The slightly higher rate of discontinuation (cause-specific Kaplan-Meier analysis) in CORRONA may be partly because of more frequent information collection (surveillance bias). Loss of remission was only assessed at study visits; thus, short-term increase in disease activity falling completely within the study visit intervals was not identified, particularly in the NinJa database where the interval was longer. Our analysis was mostly restricted to the first instance of bDMARD by not allowing reentry of the same patients for multiple bDMARD; thus, most patients were treated with TNF inhibitors, limiting generalizability to non-TNF inhibitors. The reasons for discontinuation were inconsistently reported. So in the main analysis, we used a definition of the outcome based on the disease activity. As seen in the sensitivity analysis, there were a few people who had recorded adverse events among those who discontinued while in remission.

Although several factors were associated with discontinuation, overall these models did not explain the variability in practice patterns very well. The significant physician random effects may suggest that individual physicians' preferences may influence the decision to discontinue. That is, some physicians attempt discontinuation more frequently (or less frequently) than the typical physician when treating patients with similar baseline characteristics. This is likely the case, particularly because evidence regarding bDMARD discontinuation was scarce until recently, underscoring the importance of standardizing practice through recommendations and guidelines. This finding is also in agreement with a previous study on the decision to start bDMARD, which found it was also influenced by physician preference[33]. In addition, patient preferences, such as medication beliefs, are undoubtedly important, but are not specifically identified in these data.

The topic of bDMARD discontinuation is important in light of the more effective but costly treatments. Describing the patterns of practice is worthwhile for determining how we could further improve the quality of care that we deliver. In this regard, a registry study is an attractive option, especially with multicenter registries that identify typical practice pattern. Collaboration between multiple registries can give us more opportunities to use data from different countries. It not only allows studying a wider range of patients, but also allows us to reflect upon the implication of the different practice settings and healthcare systems.

Our study revealed that around 10% of patients with RA who were initially in remission in 2 independent registries discontinued bDMARD over 5 years. If we restrict our analysis to those who remained in sustained remission, 30% of these patients discontinued bDMARD over 5 years. Although some factors predicted discontinuation among those who remained in remission, the presence of significant physician random effects suggests practice variability because of physician preference. In light of the accumulating evidence from trials settings and new practice recommendation[10], it will be important to improve the evidence basis for bDMARD discontinuation, likely leading to more standardized treatment patterns for bDMARD in typical practice.

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