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

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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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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

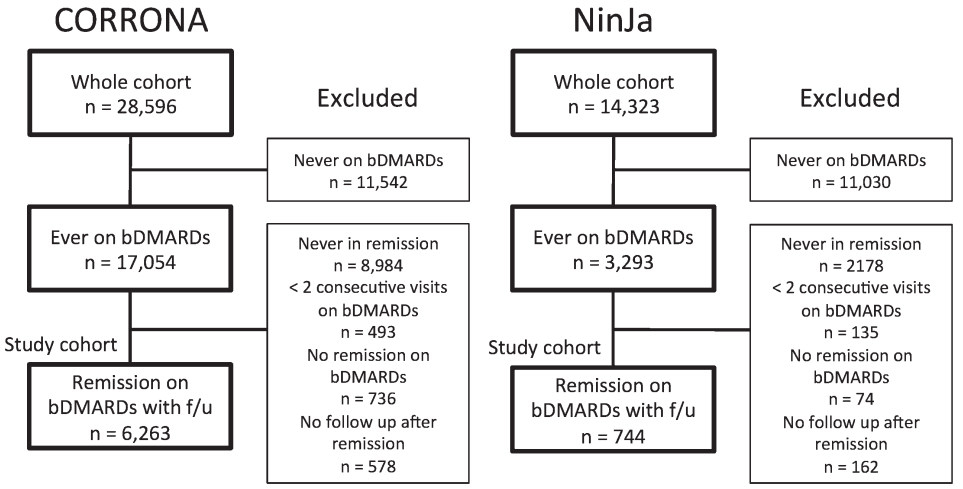

Figure 1. The cohort assembly process. Among all bDMARD users, patients who experienced CDAI remission while receiving bDMARD with followup visits were included in the study. CORRONA: COnsortium of Rheumatology Researchers Of North America; NinJa: National Database of Rheumatic Diseases by iR-net in 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

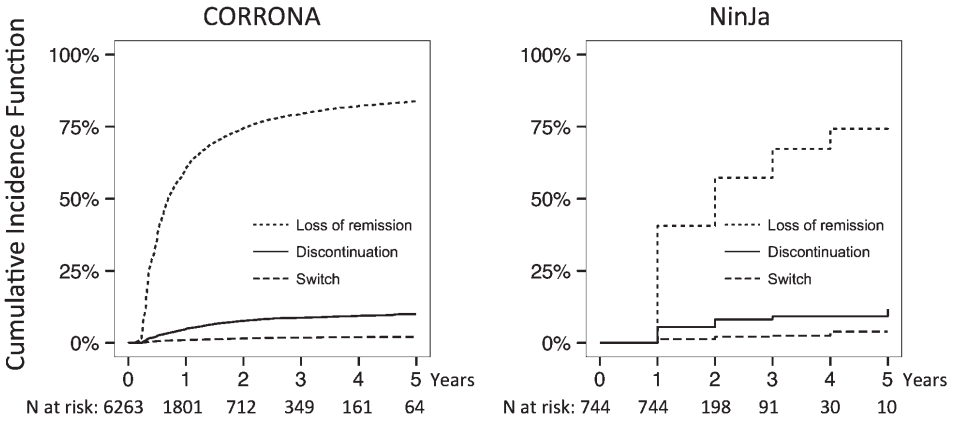

Figure 2. Discontinuation of bDMARD as well as "loss of remission" or "switch" (competing risk events) over time by the cumulative incidence function method. These proportions over time were calculated regarding the initial cohort sizes; thus, the rates of discontinuation are smaller than in Figure 3. 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.

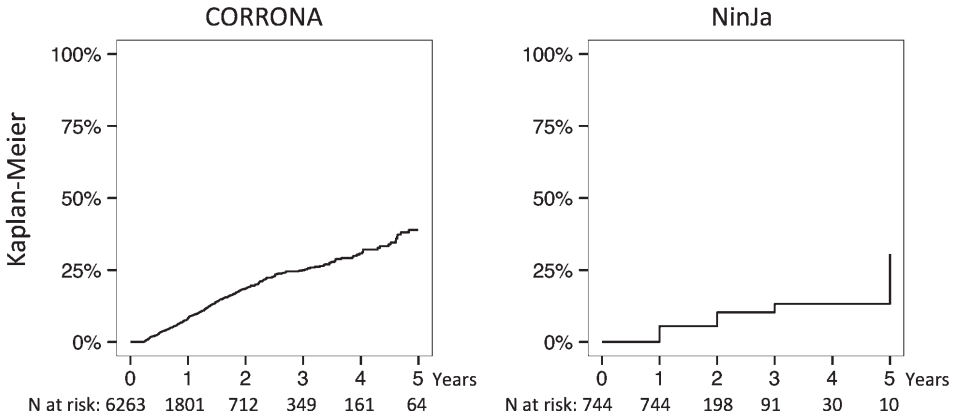

Figure 3. Discontinuation of bDMARD over time using the Kaplan-Meier method. The rates represent discontinuation of bDMARD among those who remained in remission and did not experience "loss of remission" or "switch" (competing risk events). The denominator here decreases over time; thus, the rates of 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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APPENDIX 1. The 4 potential endpoints examined in the study are "discontinuation" (event of interest), "censoring," "loss of remission," or "switch." "Index date" is the start of followup defined as the first of successive visits in remission while receiving bDMARD. "V1–5" denotes the study visits. The shaded boxes indicate visits while receiving bDMARD. "Remission/Not remission" indicates the disease activity at the corresponding visit. "bDMARD 1/bDMARD 2" indicates change in bDMARD in use. (A) If the patient discontinued bDMARD while remaining in remission, it was considered "discontinuation." It is the event of interest. (B) If the patient reached the end of followup without experiencing any of the endpoints, it was considered "censoring." (C) If the patient experienced loss of remission defined by the CDAI, it was considered "loss of remission" and the followup was terminated. (D) If the treatment was changed to a different bDMARD without reported loss of remission, it was considered "switch" and the followup was terminated. "Loss of remission" and "switch" are competing risk events that prevent the event of interest from occurring. bDMARD: biological disease-modifying antirheumatic drugs; CDAI: Clinical Disease Activity Index.