Concise report

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) ≤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.
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] ≤ 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 > 1.0) 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% CI: 1.22, 1.81] on remission were considered significant predictors.
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.

**Table 1** Cox regression models for composite failure outcome after bDMARD discontinuation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable models</th>
<th>Multivariable model</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Female</td>
<td>0.76 (0.29, 1.96)</td>
<td>0.569</td>
</tr>
<tr>
<td>Age, per decade</td>
<td>0.94 (0.75, 1.18)</td>
<td>0.593</td>
</tr>
<tr>
<td>RA duration, per decade</td>
<td>0.95 (0.68, 1.34)</td>
<td>0.771</td>
</tr>
<tr>
<td>TNF inhibitor discontinuation</td>
<td>0.82 (0.36, 1.88)</td>
<td>0.645</td>
</tr>
<tr>
<td>Clinical Disease Activity Index</td>
<td>1.51 (1.06, 2.16)</td>
<td>0.022</td>
</tr>
<tr>
<td>MTX use</td>
<td>0.78 (0.41, 1.49)</td>
<td>0.456</td>
</tr>
<tr>
<td>Glucocorticoid use</td>
<td>1.76 (0.92, 3.37)</td>
<td>0.088</td>
</tr>
<tr>
<td>Time before remission, per year</td>
<td>1.48 (1.05, 2.09)</td>
<td>0.027</td>
</tr>
<tr>
<td>More recent calendar year, per year</td>
<td>1.08 (0.81, 1.43)</td>
<td>0.616</td>
</tr>
</tbody>
</table>

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 fiare 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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