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Original article

Discontinuation of tofacitinib after achieving low disease activity in patients with rheumatoid arthritis: a multicentre, observational study

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Abstract

Objective. To determine whether tofacitinib can be discontinued in patients with RA who achieve low disease activity (LDA).

Methods. RA patients with LDA after tofacitinib treatment in a phase III and long-term extension study were enrolled in this multicentre, non-randomized, open, prospective, observational study. The decision of discontinuation or continuation of tofacitinib was determined based on patient–physician decision making with informed consent. The primary endpoint was the proportion of patients who remained tofacitinib-free at post-treatment week 52. Clinical outcome was compared between those who continued and those who discontinued tofacitinib. The last observation carried forward method was used for patients who could not discontinue tofacitinib before week 52.

Results. Of 64 patients, 54 discontinued and 10 continued tofacitinib therapy. At post-treatment week 52, 20 of the 54 patients (37%) of the discontinuation group remained tofacitinib-free without disease flare. Disease activity at post-treatment week 52 was higher in the discontinuation group than the continuation group. Among the discontinuation group, the RF titre at baseline was significantly lower in patients who remained tofacitinib-free than those who did not (40 *vs* 113 U/ml). In fact, a higher proportion of patients with lower RF remained tofacitinib-free at week 52 compared with those with higher RF at baseline. In patients who could not achieve tofacitinib-free status, re-initiation of tofacitinib or other biologics improved disease activity.

Conclusion. It is possible to discontinue tofacitinib without flare in about a third of patients with RA. A low RF predicts maintenance of LDA after discontinuation of tofacitinib.

Key words: tofacitinib, rheumatoid arthritis, discontinuation, rheumatoid factor

CLINICAL SCIENCE

Rheumatology key messages

- Tofacitinib can be discontinued in about a third of RA patients who achieve low disease activity.
- RA remission can be maintained after discontinuation of tofacitinib.
- A low RF titre at baseline is associated with successful discontinuation of tofacitinib.

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Introduction

RA is an autoimmune disease characterized by synovitis and joint destruction. With the development of biologic DMARDs (bDMARDs), clinical remission has become the primary goal in the treatment of the disease, and both structural and functional remissions have become possible [1].

The treatment efficacy of small-molecule inhibitors that selectively target Janus kinase 1 (JAK1) and JAK3 for RA has been demonstrated and these agents were recently categorized as targeted synthetic DMARDs (tsDMARDs). JAK is a tyrosine kinase known to play important roles in cytokine receptor binding triggered signal transduction through the translocation of signal transducers and activation of transcription to the cell nuclei. To date, the JAK family consists of four members: JAK1, JAK2, JAK3 and Tyk2 and >40 different cytokines and growth factors have been shown to activate specific combinations of JAKs and signal transducers and activators of transcription (STATs) [2]. Tofacitinib, which is selective for JAK1 and JAK3 [3, 4], is the first oral tsDMARD approved for RA treatment. The efficacy of tofacitinib in RA is similar to that of biologics [5–9], suggesting it is suitable as a common treatment for RA. On the other hand, tofacitinib not only acts on lymphocytes [10], but also on dendritic cells [11] and macrophages [12]. Thus tofacitinib directly affects adaptive immunity as well as innate immunity, which can possibly result in greater immunosuppression than anticipated.

Similar to bDMARDs, tsDMARDs can also induce clinical remission in some patients with RA. However, the high cost of some bDMARDs and concern about long-term safety related to the inhibition of particular molecules may limit the use of bDMARDs and can lead to discontinuation after long remission [13]. While data on tofacitinib are limited, previous studies on TNF inhibitors, such as etanercept and adalimumab, in combination with MTX, have demonstrated that treatment with these agents reduces disease activity, allowing their discontinuation without clinical flare in randomized controlled trials [14–16], in subanalyses of randomized controlled trials [17–19] and uncontrolled studies [20–22]. Moreover, there are a few reports showing that biologic-free disease control can be maintained after attaining sustained clinical remission with abatacept [23] and tocilizumab [24]. Thus the tapering of DMARDs and even their discontinuation appears an interesting concept for achieving a more tailored and dynamic treatment approach for RA, especially in patients who achieve full disease control with DMARD treatment [25]. To our knowledge, there are currently no studies on discontinuation of tsDMARDs.

When discontinuation of bDMARDs or tsDMARDs is considered after improvement in disease severity, several clinical questions may arise [25]. For instance, the appropriate strategy for tapering, cost-effectiveness, radiographic changes, long-term effects of not only clinical outcome but also cardiovascular events, predictive factor for discontinuation without disease flare and treatment strategy of flare after discontinuation. In this observational study, we focused on two important clinical questions: how many patients can maintain low disease activity (LDA) following discontinuation of bDMARDs or tsDMARDs and what are the predictors of long-term discontinuation?

To address these questions, we conducted the present prospective study in RA patients who had completed a phase III and long-term extension study of tofacitinib [26]. To our knowledge, this is the first study that examines potential discontinuation of tofacitinib following the achievement of LDA.

Methods

Patients

The subjects were RA patients who had completed a phase III and long-term extension study of tofacitinib [26] and achieved LDA [Simplified Disease Activity Index (SDAI) $\leqslant 11.0$]. RA was diagnosed in all patients according to the 1987 revised criteria of the ARA or the 2010 classification criteria of the ACR/EULAR [27–29]. This study was approved by the Human Ethics Review Committee of the University of Occupational and Environmental Health, Japan (approval #H24-049) and was conducted as a multicentre, non-blinded, prospective, observational study between August 2013 and October 2014. All subjects provided a signed consent form. The observation period of the study was 52 weeks.

Study design

Tofacitinib was either discontinued or continued after study enrolment, according to the discretion of the attending physician and the patient. For this reason, selection bias exists between the discontinuation group and the continuation group. Patients of both groups were followed up periodically for disease activity. With regard to the discontinuation group, patients with flare were rescued by re-administration of tofacitinib or other treatments (e.g. other DMARDs, together with a higher dose of MTX). Disease flare was defined based on the discretion of the investigator (usually based on the SDAI). Patients who were rescued by re-administration of tofacitinib or other treatments were defined as the tofacitinib-free failure group (patients' disposition; Supplementary Fig. S1, available at *Rheumatology* Online) and patients who remained tofacitinib-free without additional treatments and continued to show LDA were defined as the successful tofacitinib-free group.

Clinical efficacy and outcome

The primary outcome was the proportion of patients who remained tofacitinib-free at week 52 after discontinuation. The secondary outcomes included efficacy and safety at week 52. Disease activity was assessed using the SDAI [30, 31] and functional impairment was assessed using the HAQ disability index (HAQ-DI) [32].

Statistical analysis

The patients' characteristics are expressed as mean (S.D.) or number (%) of patients. The last observation carried forward method was used for patients who could not discontinue tofacitinib before week 52. The paired *t* test was used to detect differences in disease activity and functional impairment between baseline and week 52 in the two groups. Univariate analysis was performed to identify the prognostic factors for persistent discontinuation of tofacitinib. The optimal cut-off value for the prognostic factor was calculated using receiver operator characteristic curve analysis. All reported *P*-values are two-sided and not adjusted for multiple testing. The level of significance was $P < 0.05$. All analyses were conducted using JMP version 11.0 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Sixty-four patients treated with tofacitinib that achieved LDA at the end of the clinical trial participated in the study, and the decision to either discontinue ($n = 54$) or continue ($n = 10$) tofacitinib was selected by the patient and attending physician. The baseline characteristics of the patients are summarized in Table 1. The mean age of the patients in the discontinuation group was 58.7 years and most patients were female (77.8%). The duration of tofacitinib treatment was 4.2 years.

For the discontinuation group, the mean disease activity at baseline was 2.8 for the SDAI and 2.5 for the 28-joint DAS with ESR (DAS28-ESR).

Since the decision on discontinuation or continuation of tofacitinib was fully based on patient–physician decision making, selection bias existed between the two groups. The baseline disease activity according to the SDAI and DAS28-ESR was lower in the discontinuation group than the continuation group [point estimation −3.3 (95% CI −5.4, −1.2), $P = 0.002$ for SDAI; point estimation −1.1 (95% CI −1.1, −0.04), $P = 0.04$ for DAS28-ESR]. Also, the evaluator global assessment of disease activity and swollen joint count were significantly different between the two groups (Table 1).

Clinical efficacy and outcome

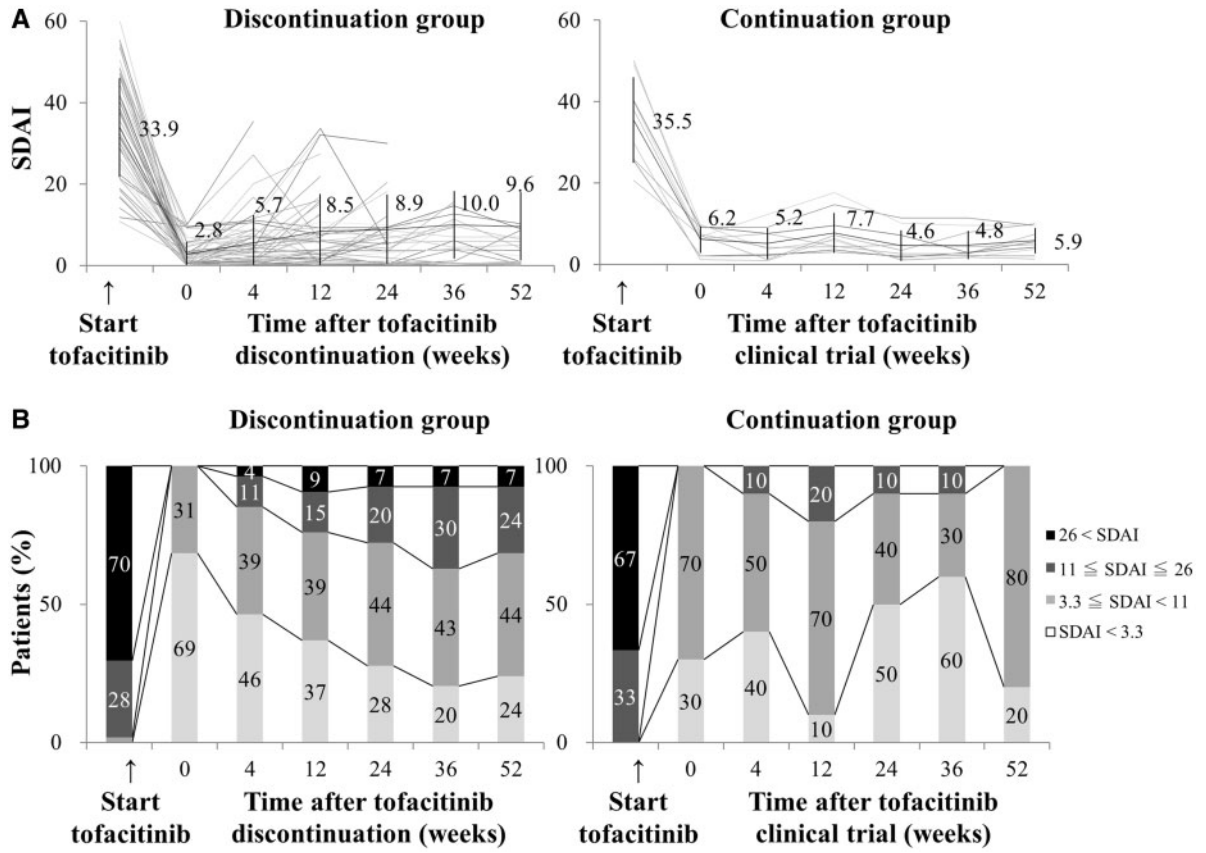
Of the 54 patients who discontinued tofacitinib at study enrolment, 20 (37.0%) remained tofacitinib-free after 52 weeks. Fig. 1A shows the serial changes in the SDAI after 52 weeks and those in the DAS28-ESR are shown in Supplementary Fig. S2A, available at *Rheumatology* Online. Before participation in the study, tofacitinib significantly improved the SDAI in both groups. Discontinuation of tofacitinib resulted in a significant increase in the SDAI

TABLE 1 Baseline characteristics of participating patients

Characteristic	Discontinuation group (n = 54)	Continuation group (n = 10)	*P*-value
Age, years	58.7 (11.0)	57.8 (13.7)	0.83
Gender, female, *n* (%)	42 (77.8)	8 (80.0)	1.00
Disease duration, years	6.1 (6.2)	13.0 (9.9)	0.06
Duration of tofacitinib administration, years	4.2 (0.7)	4.2 (0.7)	1.00
Steinbrocker's classification stage, %			0.06
I	24.1	0.0	
II	38.9	50.0	
III	16.7	0.0	
IV	20.4	50.0	
Prior use of biologics, *n* (%)	17 (31.5)	4 (40.0)	0.72
MTX use, *n* (%)	36 (66.7)	7 (70.0)	1.00
MTX dose, mg/week	8.3 (2.1)	7.9 (1.9)	0.56
Oral steroid use, *n* (%)	10 (18.5)	5 (50.0)	0.05
Oral steroid use, mg/day[a]	3.5 (1.5)	3.8 (2.2)	0.71
MMP3, ng/ml	54.6 (29.5)	78.3 (45.4)	0.07
Swollen joint count (0–28)	0.2 (0.6)	1.3 (1.3)	<0.001
Tender joint count (0–28)	0.5 (1.4)	0.8 (1.3)	0.60
ESR, mm/h	24.9 (17.5)	30.6 (22.6)	0.37
CRP, mg/dl	0.2 (0.4)	0.6 (1.2)	0.26
RF, U/ml	88.4 (133.0)	271.7 (289.9)	0.10
ACPA, U/ml	127.0 (233.1)	176.5 (133.1)	0.61
GH, VAS 0–100 mm	14.8 (19.8)	20.9 (13.1)	0.35
EGA, VAS 0–100 mm	4.3 (5.5)	13.4 (8.6)	0.01
SDAI	2.8 (3.0)	6.2 (3.2)	0.002
DAS28-ESR	2.5 (0.8)	3.1 (0.6)	0.04
HAQ-DI	0.3 (0.4)	0.7 (0.8)	0.14

All data are presented as mean (S.D.) unless stated otherwise. [a]Prednisolone equivalents. GH: patient's global assessment of disease activity; VAS: visual analogue scale; EGA: evaluator global assessment of disease activity.

FIG. 1 Clinical outcome evaluated by the SDAI after discontinuation of tofacitinib



(**A**) Serial changes in the SDAI. (**B**) Serial changes in disease activity stratified according to the SDAI.

from 2.8 at baseline to 8.9 at week 24 and 9.6 at week 52. Fig. 1B shows changes in disease activity stratified by the SDAI (high, $\geqslant$26; moderate, 26–$\geqslant$11; low, 11–>3.3; remission, <3.3). In the discontinuation group, the SDAI LDA rate was 72% (39/54) at week 24 and 68% (37/54) at week 52 (Supplementary Fig. S2B, , available at *Rheumatology* Online, shows changes in disease activity stratified by the DAS28-ESR). Continuation of tofacitinib did not change the SDAI (Fig. 1A and B). The SDAI was lower in the continuation group than the discontinuation group ($P = 0.02$).

Discontinuation of tofacitinib significantly increased the HAQ-DI from 0.3 at baseline to 0.5 at week 52 (Fig. 2A). With regard to patients in the discontinuation group, 61% at week 52 achieved functional remission, defined as HAQ-DI $\leqslant$0.5 (Fig. 2B). Changes in the HAQ-DI score were comparable between the two groups ($P = 0.28$). No serious adverse events, such as infection, were reported in either group.

The above results suggest that discontinuation of tofacitinib is possible in some RA patients after achieving LDA or clinical remission.

Factors that influence sustained discontinuation

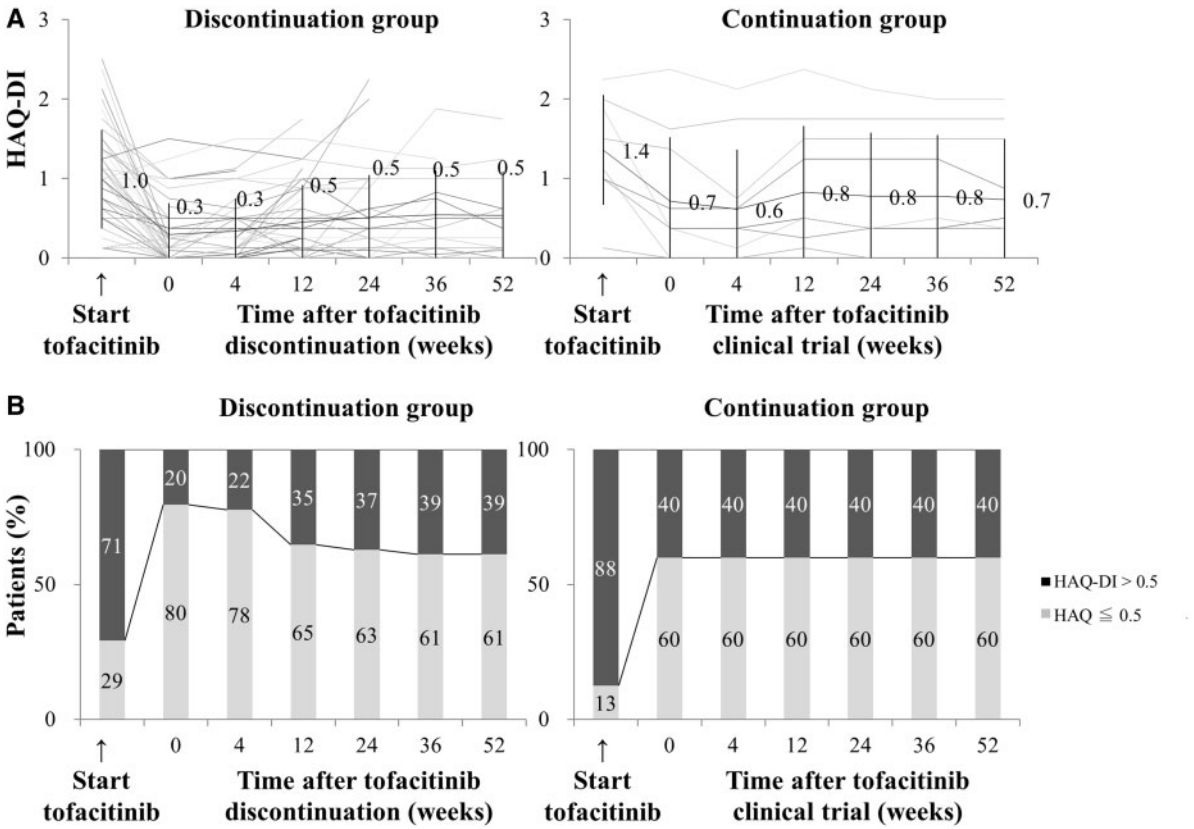
To determine the factors related to being tofacitinib-free, we compared various background factors between the successful tofacitinib-free group ($n = 20$) and the tofacitinib-free failure group ($n = 34$). Univariate analysis showed that only the RF titre at baseline ($P = 0.02$) correlated with being tofacitinib-free at week 52 (Table 2). The mean RF titre was significantly lower in the successful tofacitinib-free group (40.0 U/ml) than the tofacitinib-free failure group (113.3 U/ml). Similarly, the mean titre of ACPA at baseline was 60.6 IU/ml in the successful tofacitinib-free group compared with 165.2 IU/ml in the tofacitinib-free failure group ($P = 0.12$). The concomitant use of glucocorticoids was 5.0% in those who maintained discontinuation, compared with 26.5% in those who failed to do so ($P = 0.07$). These results suggest that a low RF titre before discontinuing tofacitinib can potentially predict tofacitinib-free disease control.

Subsequent receiver operator characteristics analysis for estimation of sustained discontinuation indicated a cut-off value for RF of 32 U/ml (Supplementary Fig. S3; CI 0.53, 0.83, relative risk 2.5, odds ratio 4.2, sensitivity 64.7%, specificity 69.7%, positive predictive value 52.4%, negative predictive value 79.3%, area under the curve 0.70).

Subgroup analysis based on RF titre

Based on the above results, disease activity was also investigated at 1 year after tofacitinib discontinuation in patients with low RF titre (<32 U/ml). While 52.4%

Fig. 2 Clinical outcome evaluated by the HAQ-DI



(**A**) Serial changes in the HAQ. (**B**) Serial changes in the proportion of patients with HAQ-DI $\leqslant$0.5.

remained successfully tofacitinib-free after 52 weeks in patients with low RF titre, 20.7% remained successfully tofacitinib-free in patients with high RF. As shown in Fig. 3A and B, only a gradual increase was noted in patients with a low RF titre. Considered together, the above data suggest that discontinuation of tofacitinib is possible in patients with a low RF titre. On the other hand, the results showed that high RF titre is associated with flare disease activity.

Rescue by re-administration of tofacitinib or other treatment

Finally, we investigated the serial changes in the SDAI after discontinuation failure (Fig. 4A). After discontinuation of tofacitinib, patients with flare were rescued by re-administration of tofacitinib or other treatments, such as other DMARDs or increasing the dose of MTX, as selected by the attending physician. Among the patients who failed discontinuation ($n = 34$), 5 were treated again with tofacitinib, 1 with biologics (adalimumab), 21 with MTX dose escalation and 7 with other conventional synthetic DMARDs. Overall, these treatments induced improvement, reducing the SDAI from 14.3 at disease flare to 6.8 (Fig. 4A), and 79% of these patients achieved either remission or LDA (Fig. 4B). Since tofacitinib and biologics are expensive, so majority of patients did not want to start these drugs, and only six patients started these drugs. However, re-treatment with tofacitinib or the use of biologics resulted in re-induction of LDA by 100%.

Discussion

Both the ACR and EULAR introduced the treat-to-target concept, that is, the goal of RA treatment should be remission or LDA [33]. Treatment of RA with bDMARDs or tsDMARDs is designed to achieve this goal. Tofacitinib is the first approved tsDMARD with efficacy similar to that of biologics [8]. However, treatment with bDMARDs and tsDMARDs poses financial problems associated with high cost compounded by the need for long-term use. To the best of our knowledge, this is the first report that discusses the possibility of discontinuation of tofacitinib in patients with RA after achieving LDA.

Studies from our laboratories and several other investigators have previously suggested discontinuation of bDMARDs, such as TNF inhibitors [17, 20, 21], but the consequences of discontinuation of tsDMARDs were uncertain. However, the present study showed that tofacitinib administration can be discontinued safely in 37% of RA patients who achieve LDA.

TABLE 2 Baseline characteristics of patients who sustained or did not sustain discontinuation of tofacitinib for 1 year

Characteristic	Sustained discontinuation (*n* = 20)	Failed discontinuation (*n* = 34)	*P*-value
Age, years	61.0 (9.1)	57.3 (11.9)	0.23
Gender, female, *n* (%)	17 (85.0)	25 (73.5)	0.50
Disease duration, years	5.5 (5.8)	6.4 (6.6)	0.63
Steinbrocker's classification stage, %			0.13
I	35.0	17.6	
II	45.0	35.3	
III	15.0	17.6	
IV	5.0	29.4	
Prior use of biologics, *n* (%)	7 (35.0)	10 (29.4)	0.77
MTX use, *n* (%)	15 (75.0)	21 (61.8)	0.38
Oral steroid use, *n* (%)	1 (5.0)	9 (26.5)	0.07
MMP 3, ng/ml	47.3 (29.1)	58.4 (29.4)	0.21
Swollen joint count (0–28)	0.2 (0.5)	0.3 (0.6)	0.48
Tender joint count (0–28)	0.4 (1.0)	0.6 (1.7)	0.60
ESR, mm/h	26.9 (16.2)	23.8 (18.4)	0.55
CRP, mg/dl	0.1 (0.2)	0.2 (0.5)	0.55
RF, U/ml	40.0 (45.3)	113.3 (155.5)	0.02
ACPA, U/ml	60.6 (132.0)	165.2 (269.6)	0.12
GH, VAS 0–100 mm	16.5 (25.6)	13.8 (15.8)	0.64
EGA, VAS 0–100 mm	4.0 (6.2)	4.5 (5.4)	0.71
SDAI	2.7 (3.3)	2.9 (2.9)	0.83
DAS28-ESR	2.6 (0.8)	2.5 (0.8)	0.72
HAQ-DI	0.3 (0.3)	0.3 (0.4)	0.69

All data are presented as mean (S.D.) unless stated otherwise. GH: patient's global assessment of disease activity; VAS: visual analogue scale; EGA: evaluator global assessment of disease activity.

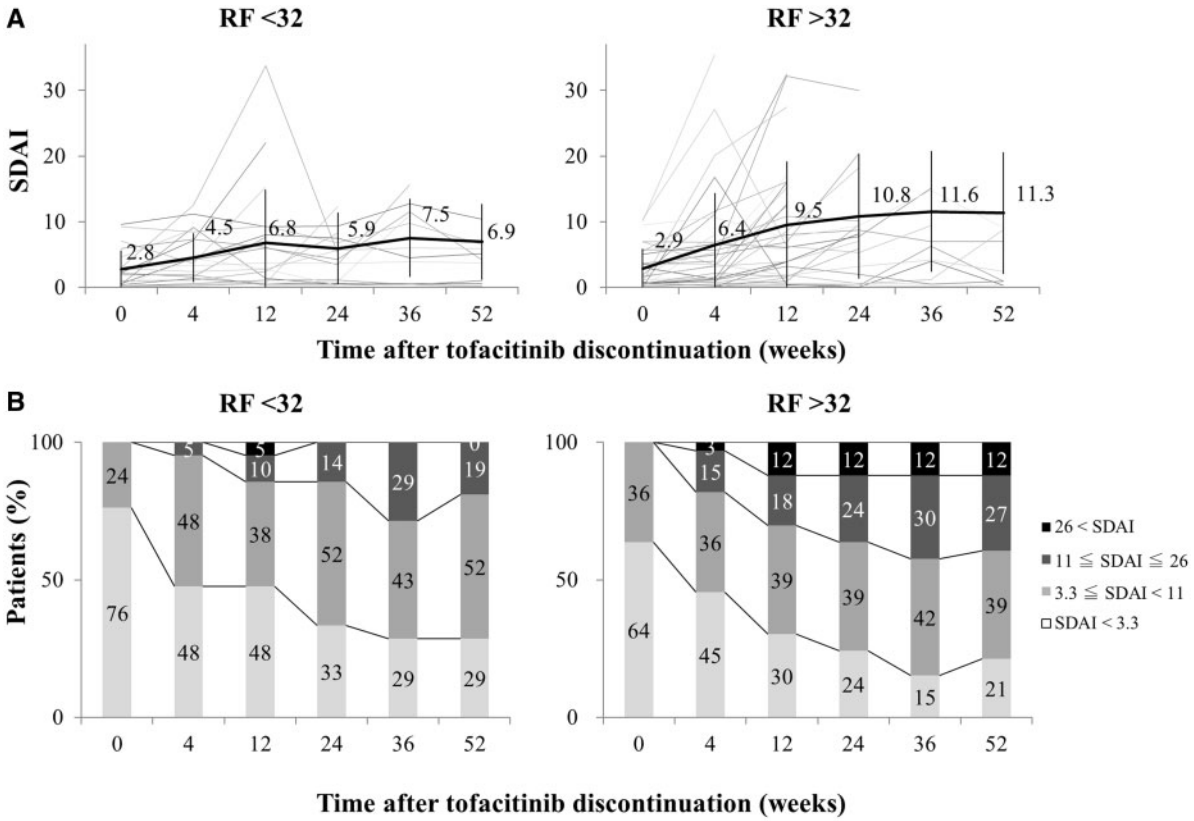
Our evaluation of clinical efficacy after tofacitinib discontinuation showed that the proportion of RA patients who achieved sustained LDA, as defined by the SDAI at week 52, was lower (68%) in those who discontinued tofacitinib than in those who remained on this regimen. This suggests that worsening of disease activity after discontinuation of tofacitinib occurs in some RA patients, such that discontinuation is not feasible in all RA patients. However, achievement of tofacitinib-free status was observed in 37% of RA patients who discontinued tofacitinib at week 52, indicating that discontinuation of treatment is feasible in as many as one-third of patients. Despite difficulties in comparing possible discontinuation of tofacitinib and biologics due to differences in baseline patient characteristics and study design, there appear to be no significant differences in sustained discontinuation of treatment between tofacitinib and bDMARDs such as infliximab [19, 21, 34] and adalimumab [17, 20, 35].

Although the prediction of disease flare is an important issue, there are no definite factors that can predict the likelihood of relapse or a persistent state of remission after discontinuation of bDMARDs [25]. Remission was associated with successful discontinuation of TNF inhibitors in the Remission Induction by Remicade in RA (RRR) study [21] and the Humira Discontinuation Without Functional and Radiographic Damage Progression Following Sustained Remission (HONOR) study [20]; on the other hand, a short disease duration was required to allow successful discontinuation in another study [36]. Schett *et al*. [37] also reported that ACPA positivity is a high relapse risk in the Reduction of Therapy in Patients with Rheumatoid Arthritis in Ongoing Remission (RETRO) study. Similar results were reported in the BeSt study [34]. The mechanisms underlying these contrasting results are unclear. In contrast to TNF inhibitors, there is no evidence for the discontinuation of tsDMARDs. In this study, we showed that 37% of the patients continued to show LDA for 52 weeks without restarting tofacitinib or other treatments and found that patients with low RF titres at baseline seem to have more chance to successfully discontinue tofacitinib. Since the power of this study was not sufficiently strong, further large-scale studies are warranted.

Our results showed no clear differences between patients who continued and discontinued tofacitinib in terms of functional remission as assessed by the HAQ-DI, with consideration of disease activity as well as other variables, including age and severity of joint destruction [38]. One explanation for this observation is that additional treatment was allowed in this study if the attending physician considered it necessary for potential disease flare-up, and such treatments were initiated before changes in the HAQ-DI indicated clinical worsening.

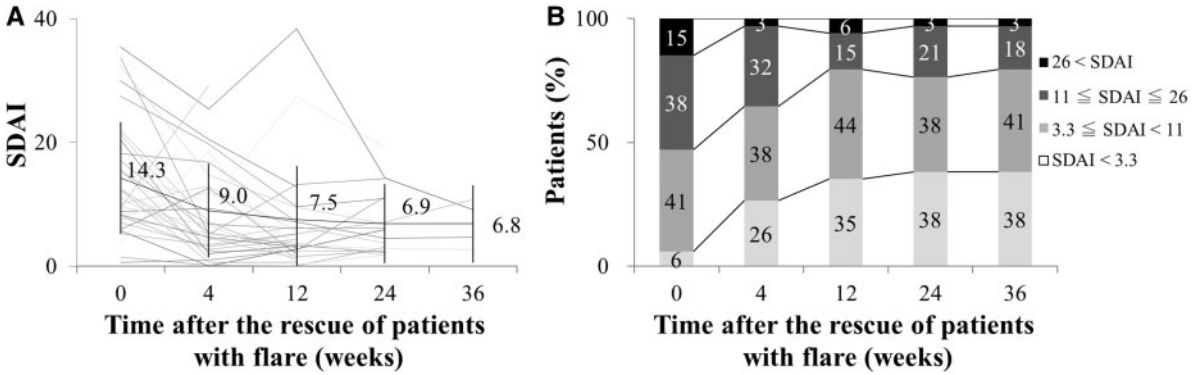
The important issue to consider when attempting to taper tofacitinib treatment is that in all RA patients who experienced flares after the tofacitinib-free period, re-

FIG. 3 Subgroup analysis according to RF titre



(**A**) Serial changes in the SDAI. (**B**) Serial changes in disease activity stratified according to the SDAI.

FIG. 4 Serial changes in the SDAI after rescue of patients with flare



(**A**) Serial changes in the SDAI after rescue by re-administration of tofacitinib or other treatments. (**B**) Serial changes in disease activity stratified according to the SDAI.

initiation of tsDMARDs or initiation of bDMARDs reduced disease activity. Discontinuation of treatment followed by re-initiation of equivalent regimens reduced disease activity without resulting in resistance to treatment; this facilitates attempts to discontinue treatment regardless of whether or not discontinuation is likely to be successful.

Our study has several limitations. The most important limitation was that this observational study did not define the disease flare by disease activity such as the SDAI. Disease flare was defined based on the discretion of the investigator (usually based on the SDAI). This limitation may reduce the generalizability of the results.

Second, selection bias can occur with an open-label, non-randomized study; also, determination of tofacitinib discontinuation was based on informed consent from patients. Disease activity was somewhat higher in patients who discontinued tofacitinib, due to the lack of baseline characteristic matching patients who continued and those who discontinued the treatment. Thus we could not compare these patient groups. Another limitation is the lack of radiographic assessment of joint destruction. Furthermore, this study included a relatively small number of patients. To elucidate the two research questions that we mentioned in the Introduction section, the study only needs an uncontrolled design. However, to elucidate the differences in disease activity between the continuation and discontinuation groups, a large and randomized control group would be needed.

Despite the above limitations, our study demonstrated that tofacitinib can be discontinued in some RA patients after achieving LDA. In particular, low RF titre was a significant predictor of achievement of tofacitinib-free status. In addition, even when disease activity flares following tofacitinib discontinuation, further control of disease activity can be achieved with re-initiation of tofacitinib. Tofacitinib, although expensive, is very likely to become a first-line option for RA patients, especially if it is possible to discontinue treatment after use for a certain period of time. Accumulation of further evidence to identify candidate patients for tofacitinib discontinuation, as described above, may help not only RA patients but may contribute to reducing medical costs.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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