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ORIGINAL ARTICLE

Outcomes of dose reduction, withdrawal, and restart of tofacitinib in patients with rheumatoid arthritis: a prospective observational study

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Abstract

Objective This study was designed to compare outcomes of dose reduction, withdrawal, and continuation of tofacitinib in patients with rheumatoid arthritis (RA) and to examine effectiveness of rescue with an original treatment regimen for disease flare.

Methods We prospectively enrolled 100 patients who had high or moderate disease activity and treated them with tofacitinib at 5 mg twice daily for 1 year. All patients achieving remission or low disease activity (LDA) were assigned to a withdrawal, dose-reduction, or continuation group, then followed until disease flare or end of the study. For flare cases, the original treatment regimen was reintroduced.

Results During the first year, 68 patients achieved remission or LDA (median sustained time 49.0 weeks). Subsequently, disease flare occurred at the following crude incidence rates per person-year (95% confidence interval [CI]): 0.73 (0.43–1.22) after withdrawal, 0.44 (0.25–0.77) after dose reduction, and 0.04 (0.01–0.27) during continuation. Kaplan-Meier estimates of median flare-free time (95% CI) were 7.0 months (2.8–11.2) for withdrawal and 21.0 months (4.1–37.9) for dose reduction. In the Cox regression analysis, adjusted hazard ratios (95% CIs) were 18.11 (2.38–138) for withdrawal and 9.13 (1.19–70.4) for dose reduction compared with continuation. Restart of the original treatment regimen led to rapid remission in flare cases (93% for withdrawal and 100% for dose reduction).

Conclusion After achievement of remission or LDA, the dose-reduction strategy seems preferable to immediate withdrawal of tofacitinib. Restart of the original regimen can reinduce RA control in flare cases.

Key Points

- *During the 1-year tofacitinib therapy, two-thirds of RA patients with high or moderate disease activity achieved rapid and sustained remission or low disease activity.*
- *During subsequent years, the incidence rate and adjusted hazard ratio for disease flare were significantly higher following tofacitinib immediate withdrawal than following dose reduction.*
- *Half of the patients were estimated to remain flare-free for 21 months after dose reduction and for 7 months after withdrawal of tofacitinib.*
- *Restart of the original treatment regimen rapidly restored disease control in almost all flare cases.*

Keywords Dose reduction · Drug withdrawal · JAK inhibitor · Rescue therapy · Rheumatoid arthritis · Tofacitinib

Introduction

Tofacitinib is an oral small-molecule inhibitor of Janus kinases (JAKs) that is the first targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD) approved for treatment of rheumatoid arthritis (RA) [1]. Recent phase II and III clinical trials and long-term extension studies have indicated favorable results concerning the efficacy and safety of tofacitinib for treatment of active RA, both as monotherapy and in combination with methotrexate (MTX) or other conventional

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synthetic DMARDs (csDMARDs) [2–11]. In addition, network meta-analyses of data from the clinical trials for tofacitinib and those for currently available biological DMARDs have shown that, during a 24-week period, tofacitinib has at least equal efficacy and relatively similar safety compared with biological DMARDs in active RA patients who have an inadequate response to previous DMARD treatment [12–14]. The current practical guidelines recommend that, if the treatment target, namely, clinical remission or at least low disease activity (LDA), is not achieved with a first or second csDMARD therapy, addition of a biological DMARD or tofacitinib should be considered [15, 16].

Given the current availability of efficacious DMARDs and recent improvements in RA management, namely, aggressive early treatment and the treat-to-target approach with tight control, the prognosis of RA patients has improved dramatically. Clinical remission or LDA early in the disease course has become the sole therapeutic target for every RA patient [15, 16]. While maintaining a state of remission or LDA is apparently beneficial to RA patients, adverse events and high costs associated with DMARDs, especially biological therapies, are significant burdens on patients as well as rheumatologists during life-long treatment of RA. Accordingly, current practical guidelines suggest that rheumatologists can consider tapering of DMARDs for patients who are in persistent remission [15–17]. Regarding biological DMARDs, such as tumor necrosis factor (TNF) inhibitors, abatacept, and tocilizumab, a series of clinical studies has suggested that a significant subset of RA patients who have entered remission or LDA with early treatment can successfully reduce and even withdraw these DMARDs without experiencing disease flare [18–20]. Regarding tofacitinib, however, knowledge on dose-reduction strategies is still lacking. The only data available were obtained from RA patients who had stopped tofacitinib after completing clinical trials and long-term extension studies. These patients had been on tofacitinib treatment for long periods of time before immediate discontinuation, and none of them received a dose-reduction strategy [21, 22].

To address this issue, we performed a long-term prospective observational study that compared clinical outcomes of dose reduction, withdrawal, and continuation of tofacitinib in RA patients who had achieved remission or LDA through an initial year-long course of induction therapy. The effectiveness of reintroducing the original tofacitinib therapy in flare cases was also examined.

Patients and methods

Patients

Tofacitinib was launched on July 30, 2013, in Japan. During the period from August 15, 2013, through August 15, 2017, we enrolled all patients with RA who were scheduled to start tofacitinib therapy under the care of the rheumatology department of NHO Kumamoto Saishunsou National Hospital. All participants were required to be over 18 years of age, fulfill the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria for diagnosis of RA [23, 24], and have a high or moderate clinical disease activity index (CDAI) (CDAI > 10). Exclusion criteria have been described elsewhere [25].

Study design

All participants received induction therapy with tofacitinib at a 5-mg twice-daily regimen for 1 year. At the end of induction therapy, we identified patients who had achieved and maintained remission (CDAI ≤ 2.8) or LDA (CDAI < 2.8 and ≤ 10) and then assigned these patients to withdrawal, dose-reduction, and continuation groups for tofacitinib according to the discretion of each treating physician and the preference of each patient. For patients assigned to the dose-reduction group, tofacitinib was continued at a 5-mg once-daily regimen. For patients who were receiving MTX at enrollment, a continuous stable dose of MTX (6 to 12 mg/week) was allowed during follow-up. Patients who were receiving prednisolone at enrollment were likewise allowed to continuously receive the same dose (2 to 7.5 mg/day) concomitantly throughout the study period.

Patients in all groups received periodic follow-up to assess disease activity. Follow-up started on the first day of withdrawal or dose reduction of tofacitinib. For patients in the continuation group, the start of follow-up was set as the first day of the second year of tofacitinib therapy. The end of follow-up was set as the earliest of the following events: disease flare, loss to follow-up, death, or the last follow-up visit prior to the end of January 2019. For patients in the dose-reduction and continuation groups, follow-up was also ended if tofacitinib was discontinued due to adverse events or other reasons (patient preference, hospital transfer, etc.). Loss to follow-up was defined as missing at least two scheduled visits without any contact.

RA disease activity

CDAI was used to quantify RA disease activity [26]. Cut-off values for disease activity states were defined as follows: high disease activity, CDAI > 22; moderate disease activity, CDAI > 10 and ≤ 22; LDA, CDAI > 2.8 and ≤ 10; and remission, CDAI ≤ 2.8 [27]. After withdrawal or dose reduction of tofacitinib, CDAI assessments were performed every month. Disease flare was defined as a worsening of CDAI values (a return to moderate or high CDAI) during follow-up.

Rescue therapy for patients with flares during follow-up

All patients who had disease flares during follow-up started rescue therapy as follows: restart of tofacitinib for patients in the withdrawal group, return to the original tofacitinib dose (5 mg twice daily) for patients in the dose-reduction group, and change of tofacitinib to other DMARDs for patients in the continuation group. When these rescue therapies failed to control disease activity, patients were retreated with other DMARDs. The choice of other DMARDs used for rescue therapy was left to the discretion of each treating physician.

Statistical analysis

To compare baseline patient characteristics between the tofacitinib withdrawal, dose-reduction, and continuation groups, we calculated mean (95% confidence interval (95% CI)), median (interquartile range [IQR]), and patient numbers (%). In univariate analyses for categorical variables, clinical differences among the three treatment groups were assessed using Fisher's exact probability test with a post hoc Holm test. Parametric and nonparametric data comparisons among the three treatment groups were performed using either one-way ANOVA (analysis of variance) with post hoc Turkey's HSD (honesty significant difference) test and the Kruskal-Wallis test with a post hoc Steel-Dwass test, respectively.

Probabilities of flare-free survival during follow-up for each treatment group were computed from life tables using the Kaplan-Meier approach. Median and mean flare-free survival time (95% CI) as well as probability of flare-free survival at 12 months (95% CI) was calculated. Log-rank test with post hoc Holm test was used for multiple comparisons among the treatment groups. Crude incidence rates (IRs) of flare and 95% CI were also calculated by dividing the number of incidence cases by the number of corresponding follow-up person-years (PYs) for each treatment group.

Cox proportional hazard regression analysis was used to calculate hazard ratios (HRs) for disease flare associated with each treatment strategy (withdrawal or dose reduction versus continuation of tofacitinib), adjusting for confounders. As potential confounders, we used baseline patient characteristics that could influence the main effect (treatment effect on the occurrence of disease flare) or that could be considered clinically relevant variables. These included age, sex, RA duration, anti-CCP positive, stages III/IV, time of sustained remission or LDA prior to the start of tofacitinib withdrawal or dose reduction, CDAI and HAQ at the start of tofacitinib withdrawal or dose reduction as well as at the time of tofacitinib initiation, previous use of biological DMARDs, and concurrent use of MTX and prednisolone. We first performed univariate Cox regression analysis for each of these cofounders and treatment during follow-up. To provide adjusted estimates for the treatment effect on disease flare, all confounders with p values < 0.20 in univariate models were introduced into multivariate Cox regression analysis. Multivariate Cox modeling was designed using a backward stepwise selection procedure with a cut-off significance level of 0.05 for deleting variables in the model. Risk differences are presented as adjusted HRs with 95% CI. The proportional hazard assumption was checked using log-minus-log plots of log cumulative hazard curve function and scaled Schoenfeld residual plots for exposure variables over time.

For all tests, a probability value (p value) of < 0.05 was considered to indicate statistical significance. All calculations were performed using PASW Statistics version 22 (SPSS Japan Inc., Tokyo, Japan) and Easy R (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [28].

Results

Patient characteristics

As shown in Fig. 1, a total of 100 patients with high or moderate CDAI were enrolled in this study and started the 1-year induction therapy with tofacitinib at a 5-mg twice-daily regimen. Among them, 32 patients withdrew tofacitinib within 1 year due to inefficacy ($n = 24$), adverse events ($n = 4$), or patient preference ($n = 4$). The adverse events included lymphopenia (two cases), cryptogenic organizing pneumonia (one case), and systemic rash (one case). The remaining patients ($n = 68$) achieved and maintained remission (53 patients, 77.9%) or LDA (15 patients, 22.1%) during the 1-year treatment. At the end of the induction therapy, these patients were assigned to the withdrawal group ($n = 19$), the dose-reduction group ($n = 31$), or the continuation group ($n = 18$), depending on the discretion of each treating physician and the preference of each patient. The median time of sustained remission or LDA at the start of tofacitinib withdrawal or dose reduction was 49.0 weeks (IQR 45.0–49.0). Because these groups were not randomly assigned, there were differences in several RA-related characteristics between these groups (Table 1). RA duration, time of sustained remission or LDA at the start of tofacitinib withdrawal or dose reduction, previous use of biological DMARDs, concurrent use of MTX and prednisolone, and CDAI and HAQ at tofacitinib initiation as well as at the start of withdrawal or dose reduction were significantly different among the treatment groups. The data indicated that disease activity was more controlled with the 1-year induction therapy in the tofacitinib withdrawal and dose-reduction groups compared with the continuation group. MTX was more often used concurrently with tofacitinib in the first two groups.

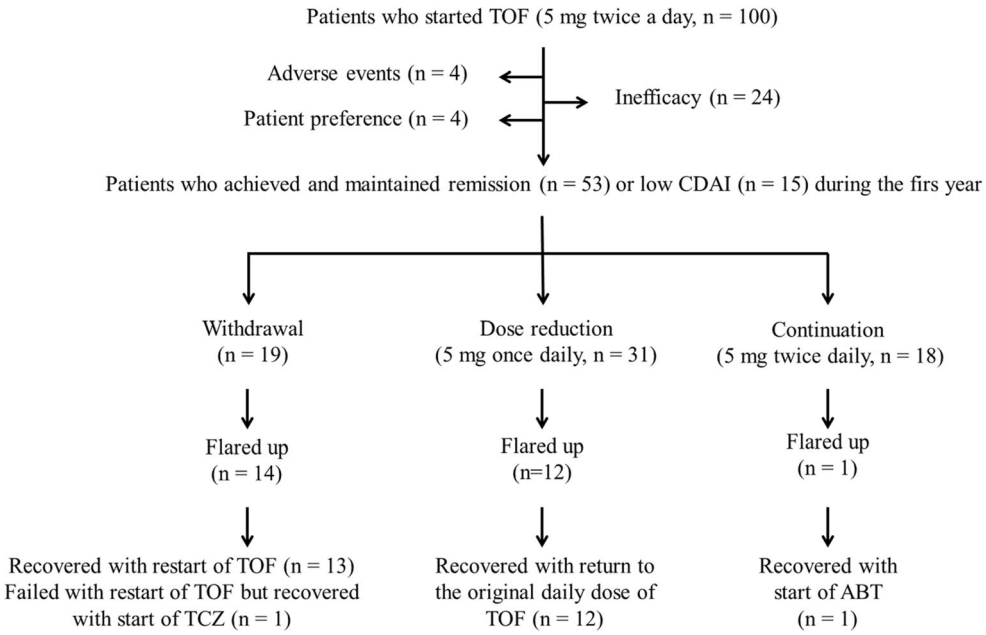

Fig. 1 Study design and patient disposition. All patients who had achieved and maintained remission or low CDAI during the first year were assigned to a tofacitinib withdrawal, dose-reduction, or continuation group, then followed for disease activity. For patients who experienced disease flare, rescue therapies were introduced. CDAI, clinical disease activity index; TOF, tofacitinib; TCZ, tocilizumab; ABT, abatacept

Outcomes of patients following withdrawal and dose reduction of tofacitinib

As shown in Table 2 and Fig. 1, disease flare was seen in 14 patients (73.7%) in the withdrawal group, 12 patients (38.7%) in the dose-reduction group, and 1 patient (5.6%) in the continuation group. Crude IRs of flare during follow-up were 0.73 per PY (95% CI 0.43–1.22) for the withdrawal group, 0.44 per PY (95% CI 0.25–0.77) for the dose-reduction group, and 0.04 per PY (95% CI 0.01–0.27) for the continuation group. No patients in the dose-reduction group or the continuation group developed severe adverse events that caused tofacitinib discontinuation. In addition, there were no cases of death or loss to follow-up in any treatment group during follow-up.

Kaplan-Meier plots for probability of flare-free survival during follow-up for each treatment group are shown in Fig. 2. Significant differences in the survival curves were observed between the treatment groups ($p < 0.001$): $p < 0.001$ for withdrawal versus continuation, $p = 0.010$ for dose reduction versus continuation, and $p = 0.008$ for withdrawal versus dose reduction. As shown in Table 2, median time of flare-free survival was 7.0 months (95% CI 2.8–11.2) for the withdrawal group and 21.0 months (95% CI 4.1–37.9) for the dose-reduction group. Since the estimated probability for the continuation group did not reach 50%, the median survival time for this group was not determined. Mean time to flare was 12.5 months (95% CI 7.1–18.4) for the withdrawal group, 15.7 months (95% CI 12.5–18.9) for the dose-reduction group, and 33.3 months (95% CI 30.1–36.5) for the continuation group. The probability of flare-free survival at 12 months was 32% (95% CI 13–52) for the withdrawal group, 66% (95% CI 46–80) for the reduction group, and 94% (95% CI 63–99) for the continuation group.

Cox regression models

Results of univariate and multivariate Cox regression analyses are shown in Table 3. In univariate analysis, the choice of treatment strategies, namely, withdrawal, dose reduction, or continuation of tofacitinib, had a significant effect on the occurrence of disease flare. In addition, we identified the trend that time of sustained remission or LDA, CDAI, and HAQ at the start of tofacitinib withdrawal or dose reduction, CDAI at tofacitinib initiation, and previous use of biological DMARDs may be associated with the risk of disease flare. In the multivariate Cox regression analysis, however, no baseline characteristics were identified as true confounders for the association between treatment strategy and disease flare. The risk of disease flare was significantly higher following tofacitinib immediate withdrawal than following dose reduction. The adjusted HRs (95% CIs) were 18.1 (2.38–138) for the withdrawal group versus the continuation group ($p = 0.005$) and 9.13 (1.18–70.4) versus the continuation group ($p = 0.03$).

Safety

Minor adverse events that did not cause tofacitinib discontinuation were observed in three patients in the dose-reduction group (one case of a transient increase in liver enzyme, one of bone fracture, and one of inguinoscrotal herniation) as well as in four patients in the continuation group (three cases of herpes zoster infection and one of aggravation of type 2 diabetes). In the withdrawal group, herpes zoster (one case) and a

Table 1 Clinical characteristics of RA patients at the start of tofacitinib withdrawal or dose reduction

	Withdrawal group ($n = 19$)	Dose-reduction group ($n = 31$)	Continuation group ($n = 18$)	p value[a]
Age (years), mean (95% CI)	64.9 (60.7–69.2)	64.9 (60.0–69.8)	69.0 (64.6–73.4)	0.42
Male/female	7/12	10/21	4/14	0.61
RA duration (years), mean (95% CI)	3.5 (1.2–5.8)	7.7 (5.6–9.7)	8.0 (4.2–11.7)	0.03[b]
Anti-CCP positive, number (%)	16 (84.2)	30 (96.8)	18 (100)	0.09
Steinbrocker stages III/IV, number (%)	1 (5.3)	6 (19.4)	3 (16.7)	0.38
eGFR (ml/min/1.73 m^2), mean (95% CI)	70.6 (63.7–77.5)	75.6 (70.4–80.8)	73.6 (63.8–83.4)	0.56
Sustained REM or LDA (weeks), median (IQR)	49.0 (45.0–49.0)	49.0 (45.0–49.0)	45.0 (38.5–49.0)	0.03 [c]
CDAI, median (IQR)	1.0 (1.0, 2.0)	1.5 (1.0, 2.0)	3.8 (1.7, 9.9)	< 0.001[d]
Remission (CDAI ≤ 2.8), number (%)	18 (94.7)	30 (96.8)	5 (27.8)	< 0.001[e]
HAQ, median (IQR)	0 (0, 0)	0 (0, 0)	0.38 (0.13, 0.56)	< 0.001[f]
HAQ ≤ 0.375, number (%)	19 (100)	31 (100)	12 (66.7)	< 0.001[g]
Biologic-naïve, number (%)	14 (73.7)	12 (38.7)	4 (22.2)	0.005[h]
MTX use, number (%)	19 (100)	30 (96.8)	13 (72.2)	0.004[i]
PSL use, number (%)	2 (10.5)	0	5 (27.8)	0.009[j]
Data at the time of tofacitinib initiation				
CDAI, median (IQR)	17.2 (12.2, 26.0)	16.5 (13.5, 22.1)	24.2 (17.3, 34.3)	0.03[k]
High CDAI (> 22), number (%)	6 (31.6)	8 (25.8)	11 (61.1)	0.04[l]
HAQ, median (IQR)	0.5 (0.25, 0.88)	0.25 (0.13, 0.50)	1.0 (0.47, 1.16)	< 0.001[m]
HAQ ≥ 1.0, number (%)	4 (21.1)	2 (6.5)	10 (55.6)	< 0.001[n]

[a] p values between treatment groups were determined by one-way ANOVA (analysis of variance) with post hoc Tukey's HSD (honesty significant difference) test, the Kruskal-Wallis test with the post hoc Steel-Dwass test, or Fisher's exact probability test with the post hoc Holm test. Comparisons with p values < 0.05 in post hoc tests are shown below (b–n)

[b] $p = 0.04$ for comparison of W (withdrawal) vs. D (dose-reduction)

[c] $p = 0.04$ for D vs. C (continuation)

[d] $p = 0.005$ for W vs. C; $p = 0.003$ for D vs. C

[e] $p < 0.001$ for W vs. C and D vs. C

[f] $p < 0.001$ for W vs. C and D vs. C

[g] $p = 0.008$ for W vs. C; $p = 0.001$ vs. D vs. C

[h] $p = 0.003$ for W vs. C

[i] $p = 0.02$ for W vs. C and D vs. C

[j] $p = 0.005$ for D vs. C

[k] $p = 0.03$ for D vs. C

[l] $p = 0.03$ for D vs. C

[m] $p < 0.001$ for D vs. C

[n] $p = 0.04$ for W vs. C; $p < 0.001$ for D vs. C

RA, rheumatoid arthritis; *anti-CCP*, anti-cyclic citrullinated peptide antibodies; *eGFR*, estimated glomerular filtration rate; *REM*, remission; *LDA*, low disease activity; *CDAI*, clinical disease activity index; *HAQ*, health assessment questionnaire; *MTX*, methotrexate; *PSL*, prednisolone; *IQR*, interquartile range; *95% CI*, 95% confidence interval

transient increase in liver enzyme (two cases) were observed during follow-up.

Rescue therapy for patients who experienced disease flare during follow-up

Among the patients who experienced disease flare after tofacitinib withdrawal, all except one regained disease control within 1 month of the reintroduction of tofacitinib at the first-year dose (Fig. 1). One patient failed to achieve a low CDAI after restarting tofacitinib but recovered disease control with the use of tocilizumab. All patients who experienced disease flare following dose reduction of tofacitinib regained remission within 1 month after returning to the first-year dose. One patient in the continuation group lost disease control during follow-up but achieved a low CDAI by replacing tofacitinib with abatacept.

Table 2 Flare of disease activity in RA patients after withdrawal or dose reduction of tofacitinib

	Withdrawal ($n = 19$)	Dose reduction ($n = 31$)	Continuation ($n = 18$)
Follow-up (months), mean (95% CI)[a]	12.2 (6.4–18.1)	10.6 (8.2–13.1)	17.3 (12.7–21.9)
Flares, number (%)	14 (73.7)	12 (38.7)	1 (5.6)
Crude IR per PY (95% CI)	0.73 (0.43–1.22)	0.44 (0.25–0.77)	0.04 (0.01–0.27)
K-M estimates for time until flare (months), median (95% CI)	7.0 (2.8–11.2)	21.0 (4.1–37.9)	NA
K-M estimates for time until flare (months), mean (95% CI)	12.5 (7.1–18.4)	15.7 (12.5–18.9)	33.3 (30.1–36.5)
K-M estimates for probability of flare-free survival at 12 months, mean (95% CI)	0.32 (0.13–0.52)	0. 66 (0.46–0.80)	0.94 (0.63–0.99)

[a] Follow-up was measured from the start of withdrawal or dose reduction of tofacitinib. For patients in the continuation group, the start of follow-up was set as the day of assignment to the treatment group

K-M, Kaplan-Meier; *IR*, incidence rate; *PY*, patient-year; *95% CI*, 95% confidence interval; *NA*, not available

Discussion

In this prospective observational study, two-thirds of RA patients achieved rapid and sustained remission or LDA during the first year of tofacitinib therapy. During subsequent years, disease flare occurred at the IR of 0.73 per PY in the withdrawal group, 0.44 per PY in the dose-reduction group, and 0.04 per PY in the continuation group. The median time to flare was 7.0 months after the withdrawal group and 21.0 months after the dose-reduction group. In the multivariate Cox regression analysis, the adjusted HR was significantly higher following tofacitinib immediate withdrawal than following dose reduction. Restarting the original treatment regimen for tofacitinib allowed rapid regain of remission in almost all cases of disease flare.

In the present study on tofacitinib therapy, the dose-reduction group had a lower IR and a lower HR for disease flare and longer flare-free time than the withdrawal group. These findings suggest that, although immediate withdrawal of tofacitinib may be a feasible strategy in RA patients who have entered clinical remission or LDA, a dose-reduction strategy seems a better option for most patients. In a recent prospective study on the use of baricitinib, another JAK inhibitor, in RA treatment, Takeuchi et al. showed that, although continuation of an original dose was more efficacious, 67% of patients maintained low CDAI or remission 48 weeks after dose reduction [29]. Similar data were obtained in the present study. According to the Kaplan-Meier approach, 66% of our patients had experienced disease flares at 12 months. Recent clinical trials and observational studies regarding biological DMARDs, mainly TNF inhibitors, have also suggested that a stepwise tapering strategy until complete withdrawal is preferable to direct withdrawal [30–37]. This strategy seems to be applicable to tsDMARDs such as tofacitinib and baricitinib.

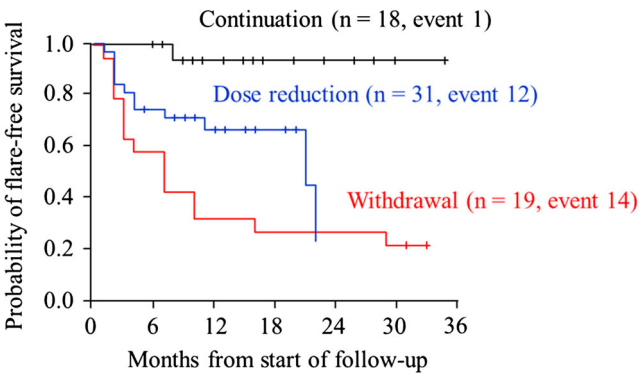

Fig. 2 Kaplan-Meier plots for probabilities of flare-free survival. Kaplan-Meier plots for proportions of patients who experienced no disease flare during follow-up are shown separately for the withdrawal, dose-reduction, and continuation groups. Log-rank test with post hoc Holm test was used for multiple comparisons of survival curves. $p < 0.001$ for the comparison of the three treatment groups ($p < 0.001$ for withdrawal versus continuation, $p = 0.010$ for dose reduction versus continuation, and $p = 0.008$ for withdrawal versus dose reduction)

Recently, two studies examined the outcomes of tofacitinib discontinuation during 1 year of post-treatment follow-up among RA patients who had achieved remission or low CDAI in clinical trials and long-term extension studies [21, 22]. Among these studies, one conducted in a Japanese cohort showed that 37% (20 out of 54 patients) in the discontinuation group continued without flare while tofacitinib-free [21]. In another study in Mexican patients, disease activity worsened following discontinuation of tofacitinib in 85% (17 out of 20 patients) [22]. In the present study in Japanese patients, the probability of flare-free survival at 12 months as estimated by the Kaplan-Meier approach was 32% in the discontinuation group, 66% in the dose-reduction group, and 94% in the continuation group. In the two Japanese studies, similar rates of patients remained without disease flare for 1 year following tofacitinib withdrawal, whereas in the Mexican study, the proportion of flare-free patients was lower. There were two major differences in baseline variables among these three studies. First, the rate of remission patients at the start of tofacitinib discontinuation was 94.7% in the present study, 69% in the other Japanese study, and 45% in the Mexican study. Second, the mean time of tofacitinib treatment prior to discontinuation was 4.2 years in the other Japanese study and 7.9 years in the

Table 3 Univariate and multivariate Cox regression analyses for disease flare following tofacitinib withdrawal or dose reduction

Variables at start of withdrawal or dose reduction	Unadjusted HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
Age per 1 year more	0.99 (0.96–1.03)	0.75	–	–
Male vs. female	0.94 (0.41–2.16)	0.89	–	–
RA duration per 1 year more	1.00 (0.99–1.01)	0.37	–	–
Anti-CCP positive	2.30 (0.31–17.2)	0.42	–	–
Stages III/IV	1.15 (0.40–3.34)	0.79	–	–
Sustained REM or LDA per 1 week more	1.11 (0.97–1.27)	0.12	–	–
Remission (CDAI ≤ 2.8)	2.61 (0.79–8.69)	0.12	–	–
HAQ per 1 unit more	0.03 (0.001–0.90)	0.04	–	–
Biologic-naïve vs. experienced patients	1.76 (0.82–3.77)	0.15	–	–
MTX users vs. non-users	3.14 (0.43–23.2)	0.26	–	–
PSL users vs. non-users	0.00 (0.00–Inf)	1.00	–	–
Data at tofacitinib initiation				
High CDAI (> 22)	0.42 (0.17–1.05)	0.06	–	–
HAQ per 1 unit more	0.62 (0.27–1.38)	0.24	–	–
Treatment of tofacitinib				
Withdrawal	18.1 (2.38–138)	0.005	18.1 (2.38–138)	0.005
Dose reduction	9.13 (1.18–70.4)	0.03	9.13 (1.18–70.4)	0.03
Continuation	1	–	1	–

All confounders with *p* values lower than 0.20 in the univariate Cox models were introduced into multivariate analysis. A backward stepwise selection procedure with a cut-off significance level of 0.05 was used for deleting variables in the multivariate model. None of the baseline patient characteristics remained in the final Cox model as significant confounders. The confounding effects of these characteristics were so weak that the HRs for withdrawal versus continuation and for dose reduction versus continuation did not change after adjusting for these factors

RA, rheumatoid arthritis; *anti-CCP*, anti-cyclic citrullinated peptide antibodies; *REM*, remission; *LDA*, low disease activity; *CDAI*, clinical disease activity index; *HAQ*, health assessment questionnaire; *MTX*, methotrexate; *PSL*, prednisolone; *HR*, hazard ratio; *95% CI*, 95% confidence interval; *Inf*, infinite

Mexican study, while all our patients received tofacitinib therapy for only 1 year. Such differences in disease activity and time of tofacitinib treatment at the start of discontinuation may have influenced the rate of disease flare during the first year of follow-up.

When considering drug tapering and discontinuation for RA patients in a state of remission, one of the most critical concerns is whether, if disease flare occurs, it is possible for patients to rapidly recover their baseline conditions by restarting DMARDs at the original regimen. In the present study, all patients with disease flare during follow-up restarted the original treatment regimen of tofacitinib, and all but one regained remission within 1 month. Such rapid and remarkable recovery of disease control should encourage rheumatologists and RA patients to make a therapeutic decision in favor of dose reduction and even withdrawal of tofacitinib. The restoration of remission or LDA by returning to the original dose was also reported in the abovementioned study of baricitinib, but their success rate for original-dose rescue therapy was lower than ours (66.7% versus 100%). This might be explained by differences in remission rates at the start of dose reduction (46.0% versus 96.8%) and/or higher disease activity at the introduction of tsDMARDs (mean disease activity score [DAS28]-C-reactive protein (CRP) 5.6–6.0 versus CDAI 16.5) [29]. Immunogenicity of biological DMARDs, which is attested by the development of anti-drug antibodies, is one of the main reasons for secondary loss of efficacy [38]. Although successful reinduction of remission by restarting original treatment regimens has been reported in recent trial studies on biological DMARDs [33–36, 39–42], we cannot exclude the possibility that patients may have developed anti-drug antibodies to biological DMARDs by the time the drugs were restarted. Given that tsDMARDs, being synthetic small molecules, are not expected to be immunogenic, tofacitinib may be a more practical candidate for drug-holiday strategies.

Whether concurrent use of MTX (continuation of background treatment) can influence the risk of disease flare during tofacitinib withdrawal or dose reduction is an important issue, but data on this topic are still lacking in the literature. In the present study, MTX was concurrently used at significantly higher rates in the tofacitinib withdrawal and dose-reduction groups (100% and 96.8%, respectively) compared with the continuation group (72.2%), but the Cox regression analysis showed that background MTX treatment did not affect the

estimates of the treatment effect on disease flare. It was difficult to determine whether the risk of disease flare in patients receiving the same treatment strategy of tofacitinib may have been unaffected by the background MTX treatment because the individual treatment groups consisted of low numbers of patients for statistical analysis. Similarly, the concurrent use of prednisolone had no significant effects on estimates for the risk of disease flare associated with each treatment strategy. It was, however, difficult to yield reliable estimates of background prednisolone for the risk of flare in each treatment group.

There are several limitations to this study. The present study was performed without randomization or blinding, and the assignment of each treatment was left to the discretion of the treating physician and the preference of the patient, which can produce allocation bias. Baseline patient characteristics that might affect the true treatment effect should be considered carefully. To address this problem, we performed univariate and multivariate Cox regression analyses and showed that none of the baseline patient characteristics remained in the final regression model as significant confounders for disease flare. Considering the relatively small sample size of this study, however, it may be difficult to draw a definitive conclusion regarding predictors for disease flare. Another limitation is the lack of radiologic evaluation. Recent studies have shown that imaging-detected residual synovitis is a predictor for the risk of disease flare after tapering or discontinuing biological DMARDs [37, 43–45]. Nevertheless, the present study provides useful information regarding the treatment strategies of tofacitinib, namely, dose reduction, withdrawal, and restart, in RA patients who have achieved sustained disease control in daily clinical practice. The findings obtained from this study would be useful in designing larger confirmatory studies.

In conclusion, 1 year of tofacitinib treatment induced rapid and sustained disease control in two-thirds of RA patients. Following dose reduction, some of them experienced disease flare, but a return to the original dose allowed rapid recapture of remission in all flare cases. Considering the lower IR and lower HR for disease flare and longer flare-free time after dose reduction compared with direct withdrawal, the dose-reduction strategy seems preferable for RA patients who desire to take a drug-free holiday following the induction of sustained disease control with tofacitinib treatment.

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Compliance with ethical standards

This study was conducted in accordance with the principles of the Declaration of Helsinki (2008). The protocol of this study also meets the requirements of the Ethical Guidelines for Medical and Health Research Involving Human Subjects, Japan (2014), and has been approved by the Human Research Ethics Committees of NHO Kumamoto Saishunsou National Hospital (No. 27-3/29-7). Written informed consent was obtained from all patients prior to enrollment in this study.

Disclosures None.

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