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Long-term efficacy and safety of tofacitinib in patients with ulcerative colitis: 3-year results from a real-world study

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Background/Aims: The efficacy and safety of tofacitinib for the treatment of refractory ulcerative colitis (UC) has been demonstrated in clinical trials. Although, a series of reports with real-world evidence of its short-term efficacy and safety profiles have already been published, reports of long-term real-world data have been limited. We aimed to show our 3-year evidence on the clinical use of tofacitinib for the treatment of UC, focusing on its efficacy and safety profiles. **Methods:** A retrospective observational study was conducted on patients who started tofacitinib for active refractory UC at our hospital. The primary outcome was the retention rate until 156 weeks after initiating tofacitinib. The secondary outcomes were short-term efficacy at 4, 8, and 12 weeks; long-term efficacy at 52, 104, and 156 weeks; prognostic factors related to the cumulative retention rate; loss of response; and safety profile, including adverse events. **Results:** Forty-six patients who were able to be monitored for up to 156 weeks after tofacitinib initiation, were enrolled in this study. Continuation of tofacitinib was possible until 156 weeks in 54.3%, with >50% response rates and >40% remission rates. Among patients in whom response or remission was achieved and tofacitinib was deescalated after 8 weeks of induction treatment, 54.3% experienced relapse but were successfully rescued by and retained on reinduction treatment, except for 1 patient. No serious AEs were observed in the study. **Conclusions:** Tofacitinib is effective and safe as long-term treatment in a refractory cohort of UC patients in real-world clinical practice. **(Intest Res 2024;22:369-377)**

Key Words: Ulcerative colitis; Efficacy; Real-world evidence; Safety; Tofacitinib

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease, which is characterized as a chronic, relapsing-remitting, immune-mediated condition that requires lifelong treatment to control symptoms. Treatment strategies for UC aim to achieve sustained steroid-free remission and improve patients' quality of life.[1] Recent advances in biologic agents and small molecules for the treatment of UC have significantly improved the prognosis of patients who are refractory to conventional medications. Agents have been developed that target tumor necrosis factor (TNF)-α, interleukin-12 and -23, and α4β7 integrin to block excessive proinflammatory responses in the gut of patients with UC.

Tofacitinib is an oral synthetic small molecule that inhibits the Janus kinase pathway, which acts as a central hub in the cytokine network and modulates immune and inflammatory responses.[2] The efficacy and safety of tofacitinib for the treatment of moderate to severe refractory UC has already been demonstrated in clinical trials, including the 8-week induction studies (OCTAVE Induction 1 and 2: NCT01465763 and

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NCT01458951) and the 52-week maintenance study (OCTAVE Sustain: NCT01458574) and in long-term extension studies (OCTAVE Open: NCT01470612 and RIVETING: NCT03281304).[3-7] Since tofacitinib was first approved for clinical use in 2018, a series of reports with real-world evidence of its short-term efficacy and safety profiles have already been published.[8-14] Most of the data from those studies were consistent with those from the clinical trials. However, reports of long-term real-world data have been limited. In this study, we present our 3-year evidence on the clinical use of tofacitinib, focusing on its efficacy and safety profiles. We aimed to show the long-term sustained efficacy and safety of tofacitinib in a real-world setting for the treatment of patients who have received multiple biologics for UC.

METHODS

1. Study Design and Definitions

The study was conducted according to the ethical principles of the Declaration of Helsinki and was approved by the Tokyo Medical and Dental University Institutional Review Board (IRB No. M2018-059). Written informed consent was waived. We performed a retrospective observational study on Japanese patients ≥18 years old who were started on tofacitinib treatment for active refractory UC by board-certified gastroenterologists between May 2018 and October 2022 at Tokyo Medical and Dental University Hospital. Patients who were able to be monitored for up to 156 weeks after tofacitinib initiation were enrolled in this study. Based on the inclusion criteria above, we collected data on demographics; treatment history; disease type, duration, and disease activity, which was assessed by the partial Mayo score (pMS); and laboratory data. We defined remission as pMS ≤2, with individual subscore of <1 and bleeding subscore of 0. Response was defined as a decrease in pMS by at least 2 and 1 of the following conditions: (1) decrease in the bleeding subscore by at least 1; (2) bleeding subscore of <1; or (3) induction of remission, as defined above. Retention rate was defined as the proportion of patients who were maintained on tofacitinib treatment at a certain time point. Relapse was defined as symptom recurrence or a pMS >2 following remission. Failure was defined as tofacitinib discontinuation due to any of the following: relapse following remission, nonresponse to tofacitinib treatment, or adverse events (AEs). In patients who met the response criteria at week 8 and in whom tofacitinib was subsequently reduced to 5 mg twice daily (b.d.), loss of response (LOR) was defined as relapse that led to an increase in the tofacitinib dose to 10 mg b.d. and/or discontinuation of tofacitinib. For dose optimization study, patients who achieved response or remission at 8 weeks were included. We analyzed the breakdown of patients who experienced LOR in this cohort, and the patients' duration of induction and maintenance treatment, background characteristics, and disease status at the time of tofacitinib reduction.

2. Tofacitinib Treatment

Eligible patients were started on tofacitinib at 10 mg b.d. for ≥8 weeks as induction therapy and reduced to 5 mg b.d. as maintenance therapy. All immune-suppressive agents, such as thiopurines, calcineurin inhibitors, and biologic agents, were withdrawn before tofacitinib treatment, and patients who were taking corticosteroids at the start of tofacitinib treatment promptly reduced and discontinued. Patients underwent dose optimization during tofacitinib treatment upon the discretion of board-certified gastroenterologists. Among patients who responded to the induction therapy, tofacitinib was subsequently reduced to 5 mg b.d. in those who were responsive or in remission for ≥8 weeks, but it was subsequently increased to 10 mg b.d. in those who experienced disease relapse while receiving a 5 mg b.d. dose for maintenance treatment.

3. Study Outcomes

The primary outcome was the retention rate until 156 weeks after initiating tofacitinib. The secondary outcomes were short-term efficacy at 4, 8, and 12 weeks; long-term efficacy at 52, 104, and 156 weeks; prognostic factors related to the cumulative retention rate; LOR; and safety profile, including AEs.

4. Statistical Analysis

The 2 groups were compared using non-parametric tests (i.e., Mann-Whitney *U* test or Wilcoxon test) for the median values of the continuous variables and a chi-square test for categorical variables. The Kaplan-Meier method was used to draw the survival curve of the patients who were maintained on tofacitinib treatment over time. For statistical analysis, SPSS (IBM Corp., Armonk, NY, USA) version 26 was used, and the significant threshold was $P<0.05$.

RESULTS

Of the 81 patients who were initiated on tofacitinib treatment

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during the study period, 46 patients who were able to be monitored for up to 156 weeks after tofacitinib initiation, were enrolled in this study and the other 35 patients were excluded. The baseline demographics and disease characteristics of the patients are summarized in Table 1. The study population comprised 43.5% women; the median age was 36 years (range, 25–47 years) and the median disease duration was 7.2 years (range, 3.7–10.7 years). There were 29 patients (63.0%) with extensive colitis and 17 (37.0%) with left-sided colitis. At the time of tofacitinib initiation, the disease activity was moderate in 41 patients (89.1%), severe in 3 (6.5%), and mild in 2 (4.3%). The median pMS was 6 (range, 4–7), the median C-reactive protein was 1.9 mg/L (range, 0.8–9.1 mg/L), and, for cases with available endoscopic records (n = 16), the median UC endoscopic severity index was 5 (range, 4–6). There were 16 patients (34.8%) with corticosteroid-refractory disease and 29 (63.0%) with corticosteroid-dependent disease. Prior use of biologics was recorded in 42 patients (91.3%); 18 (39.1%) received 1 agent, 18 (39.1%) received 2 agents, and 6 (13.0%) received ≥3

Table 1. Patient Baseline Demographics and Disease Characteristics

Demographics and disease characteristics	Value (n = 46)
Sex	
Male	26 (56.5)
Female	20 (43.5)
Age (yr)	36 (25–47)
Disease duration (yr)	7.2 (3.7–10.7)
Extent of disease	
Extensive	29 (63.0)
Left-sided	17 (37.0)
Severity	
Severe	3 (6.5)
Moderate	41 (89.1)
Mild	2 (4.3)
Partial Mayo score	6 (4–7)
UCEIS (n = 16)	5 (4–6)
White blood cells (/μL)	6,000 (5,000–8,250)
Hemoglobin (g/dL)	13 (10.6–14.1)
Albumin (g/dL)	3.9 (3.3–4.2)
CRP (mg/L)	1.9 (0.8–9.1)
Previous medication use	
Oral aminosalicylate	21 (45.7)
Corticosteroid	
Refractory	16 (34.8)
Dependent	29 (63.0)
Never used	1 (2.2)
Immunomodulator	40 (87.0)
Calcineurin inhibitor	13 (28.3)
Biological agent	
Naïve	4 (8.7)
1 Agent	18 (39.1)
2 Agents	18 (39.1)
3 Or more agents	6 (13.0)

Values are presented as number (%) or median (interquartile range).
UCEIS, ulcerative colitis endoscopic index of severity; CRP, C-reactive protein.

Table 2. Summary of Primary and Secondary Outcomes

Outcome	Value (n = 46)
Tofacitinib retention rate at 156 wk	25 (54.3)
Short-term efficacy	
Remission at 4 wk	14 (31.1)
Remission at 8 wk	17 (37.0)
Remission at 12 wk	20 (43.5)
Response at 4 wk	20 (44.4)
Response at 8 wk	24 (52.2)
Response at 12 wk	24 (52.2)
Long-term efficacy	
Remission at 52 wk	21 (45.7)
Remission at 104 wk	20 (43.5)
Remission at 156 wk	23 (50.0)
Response at 52 wk	24 (52.2)
Response at 104 wk	23 (50.0)
Response at 156 wk	25 (54.3)
Dose optimization study in responsive patients at 8 wk (n = 24)[a]	
Continue 10 mg b.d.	1 (4.2)
Reduced 5 mg b.d. after induction	23 (95.8)
Median period to reduction after induction (wk)	14.0 (9.0–19.0)
Continued 5 mg b.d.	10 (41.7)
Loss of response	13 (54.2)
Increased 10 mg b.d. after reduction	12 (50.0)
Median period to increase (wk)	39.5 (14.5–84.0)
Reduced 5 mg b.d. again	5 (20.8)
Median period to reduction (wk)	11.0 (9.0–18.0)
Continued 10 mg b.d.	5 (20.8)
Repeat reduce and increase	2 (8.3)
Adverse events	23 (50.0)

Values are presented as number (%) or median (interquartile range).
[a]Patients who achieved response or remission at 8 weeks were included.

agents. The most commonly used biologics were anti-TNF-α agents (e.g., infliximab, adalimumab, and golimumab); 2 patients received vedolizumab, but none used ustekinumab or other Janus kinase inhibitors. The last prior treatment was one of those biologics for most of the patients, except for 2 patients who used calcineurin inhibitor. Only 4 patients (8.7%) were biologics-naïve.

The primary and secondary outcomes are summarized in Table 2. Tofacitinib was continued until 156 weeks after initiation in 54.3% (n=25) but was discontinued in 45.7% (n=21) (Fig. 1). Twenty-three patients were in steroid-free remission, except one who had auto-immune disease taking 5 mg daily prednisolone. The others were in mild disease being able to continue tofacitinib without steroid. The reasons for discontinuation were primary failure in 71.4% (n=15), partial response in 14.2% (n=3), disease relapse in 9.5% (n=2), and AEs in 1 (4.8%) (Supplementary Table 1). The subsequent treatment after discontinuation, 7 switched to vedolizumab (3 were responsive), 4 switched to anti-TNF-α agents (2 were responsive), 3 switched to calcineurin inhibitor (2 were responsive), 3 enrolled clinical trials, 1 switched to ustekinumab (not responsive) and 3 underwent surgery.

The comparison of the baseline demographics and disease characteristics between cases of tofacitinib treatment nonfailure and failure are summarized in Table 3. The median disease duration at baseline was significantly longer in nonfailure cases than in failure cases. The other variables did not significantly differ between the 2 groups. Among the nonfailure cases that continued receiving tofacitinib treatment for 156 weeks, the pMS immediately improved as early as 4 weeks and kept improving until 156 weeks (Fig. 2). Overall, continuation of treatment for 156 weeks was achieved in 95% of the quick responders at 4 weeks but in only 24.0% (n=6) of the nonresponders at 4 weeks (Supplementary Table 2).

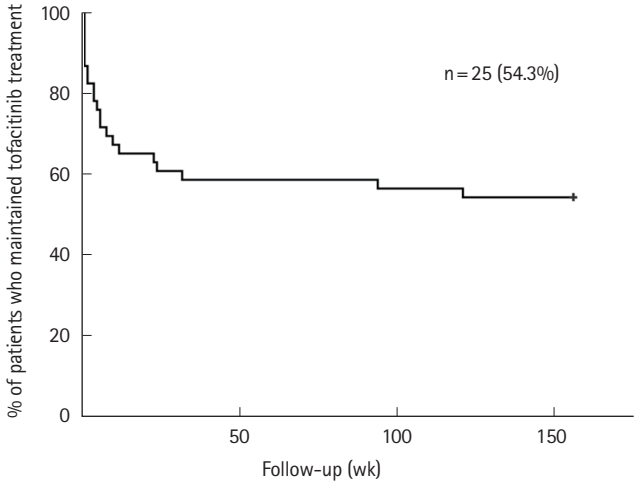

Fig. 1. Survival curve of patients who maintained tofacitinib treatment over time up to 156 weeks after initiation of tofacitinib treatment (n=46).

The time series data on the short-term and long-term efficacy of tofacitinib are summarized in Fig. 3. For short-term efficacy, the remission rate was 31.1% (n=14) at 4 weeks, 37.0% (n=17) at 8 weeks, and 43.5% (n=20) at 12 weeks and the response rate was 44.4% (n=20) at 4 weeks and 52.2% (n=24) at 8 and 12 weeks. For long-term efficacy, the remission rate was 45.7% (n=21) at 52 weeks, 43.5% (n=20) at 104 weeks, and 50.0% (n=23) at 156 weeks and the response rate was 52.2% (n=24) at 52 weeks, 50.0% (n=23) at 104 weeks, and 54.3% (n=25) at 156 weeks. Our results showed that the remission rate continued to exceed 40% after 12 to 156 weeks, and the response rate continued to exceed 50% after 8 to 156 weeks.

In dose optimization study, 24 patients who achieved response or remission at 8 weeks were included (Supplementary Fig. 1). In 95.8% (n=23) of those patients, tofacitinib was reduced to 5 mg b.d. after a median of 14 weeks (range, 9–19 weeks) after induction. LOR was observed in 54.2% (n=13) after a median of 39.5 weeks (range, 14.5–84.0 weeks) of maintenance treatment. Tofacitinib was increased to 10 mg b.d. for reinduction in 50% (n=12), but it was discontinued in 4.2% (n=1). Of the 12 patients who received reinduction treatment, 29.1% (n=7) successfully achieved remission again, and tofacitinib was reduced to 5 mg b.d. after a median of 11 weeks (range, 9–18 weeks) of the reinduction treatment. Conversely, 5 of the 12 reinduction cases (20.8%) continued 10 mg b.d. and retained tofacitinib treatment. The characteristics of the patients in dose optimization study are summarized in Supplementary Table 3; disease duration was significantly longer in nonfailure cases than in the LOR cases. For further analysis, we compared the data at the time of dose reduction in each patient, but we found no clear difference and no predictable factor for LOR in our cohort (Supplementary Table 4).

In terms of safety, 36 AEs were recorded in 23 patients (50.0%) throughout the period of tofacitinib treatment (Table 4). The most common AEs were nonserious infections (n=21, 45.7%), including herpes zoster (n=3, 6.5%) and COVID-19 (n=4, 8.7%). All the patients who developed herpes zoster were successfully treated with an antiviral medication; the dose of tofacitinib was 10 mg b.d. in 1 patient and 5 mg b.d. in the rest. Of the 8 patients (17.4%) who developed dyslipidemia, 4 patients were started on medication. In 1 patient, to-

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Table 3. Patient Baseline Demographics and Disease Characteristics by Non-Failure versus Failure

Variable	Non-failure (n = 25)	Failure (n = 21)[a]	*P*-value
Sex			
Male	15 (60.0)	11 (52.4)	0.412
Female	10 (40.0)	10 (47.6)	
Age (yr)	33.5 (29.0–53.0)	29.0 (18.5–39.5)	0.164
Disease duration (yr)	8.9 (5.4–12.4)	5.9 (1.9–9.9)	0.045
Extent of disease			
Extensive	16 (64.0)	13 (61.9)	1.000
Left-sided	9 (36.0)	8 (38.1)	1.000
Severity			
Severe	1 (4.0)	2 (9.5)	0.585
Moderate	22 (88.0)	19 (90.5)	1.000
Mild	2 (8.0)	0	
Partial Mayo score	5 (3–7)	6 (5–7)	0.109
UCEIS (n = 16)	5.0 (3.8–6.3)	5.0 (4.1–5.9)	1.000
White blood cells (/μL)	5,600 (3,700–7,500)	6,400 (4,775–8,025)	0.251
Hemoglobin (g/dL)	13.2 (11.9–14.5)	12.2 (10.9–14.5)	0.076
Albumin (g/dL)	3.9 (3.5–4.3)	3.9 (3.4–4.4)	0.674
CRP (mg/L)	1.9 (0–4.2)	1.9 (0–8.9)	0.938
Previous medication use			
Oral aminosalicylate	12 (48.0)	9 (42.9)	0.774
Corticosteroid			
Refractory	8 (32.0)	8 (38.1)	0.760
Dependent	16 (64.0)	13 (61.9)	1.000
Never used	1 (4.0)	0	
Immunomodulator	21 (84.0)	19 (90.5)	0.673
Calcineurin inhibitor	4 (16.0)	9 (42.9)	0.056
Biological agent			
Naïve	4 (16.0)	0	0.114
1 Agent	8 (32.0)	10 (47.6)	0.367
2 Agents	9 (36.0)	9 (42.9)	0.764
3 Or more agents	4 (16.0)	2 (9.5)	0.673

Values are presented as number (percent) or median (interquartile range). Differences in medians between the 2 groups were compared by non-parametric test (Mann-Whitney test or Wilcoxon test), and comparison between categorical variables were performed using chi-square test.
[a]Failure was defined as tofacitinib discontinuation due to any of the following: relapse following remission, nonresponse to tofacitinib treatment, or adverse events. Twenty-five patients continued tofacitinib until 156 weeks after initiation, and 21 patients discontinued tofacitinib before 156 weeks.
UCEIS, ulcerative colitis endoscopic index of severity; CRP, C-reactive protein.

facitinib was discontinued immediately after starting treatment because of dyspnea. No hypoxemia was observed, and no pneumonia or other organic lung damage was evident. There were no serious AEs recorded, such as cancer, venous thromboembolism, death or others that required hospitalization during tofacitinib treatment.

DISCUSSION

In this study, we present real-world data on treatment-refractory UC cases treated with tofacitinib. To the best of our knowledge, our data provide one of the longest follow-up periods among the published real-world studies and present new in-

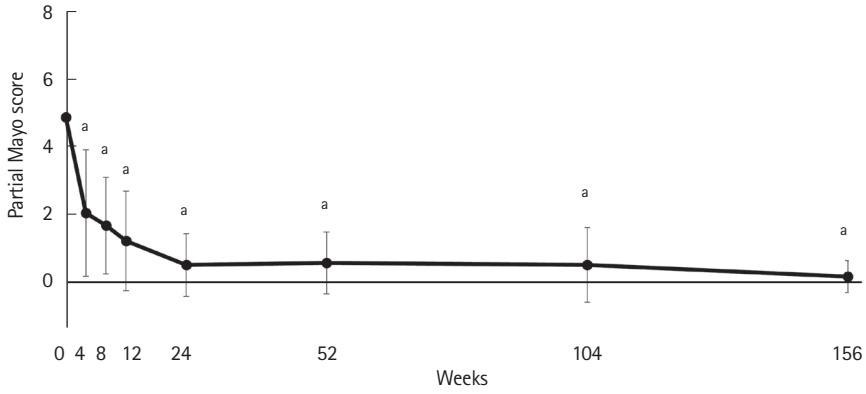

Fig. 2. Efficacy of tofacitinib (n = 25). Tofacitinib treatment non-failure patients showed significantly improved partial Mayo score from as early as 4 weeks after tofacitinib initiation, which continued until 156 weeks. [a]Wilcoxon test: $P < 0.001$ compared to week 0.

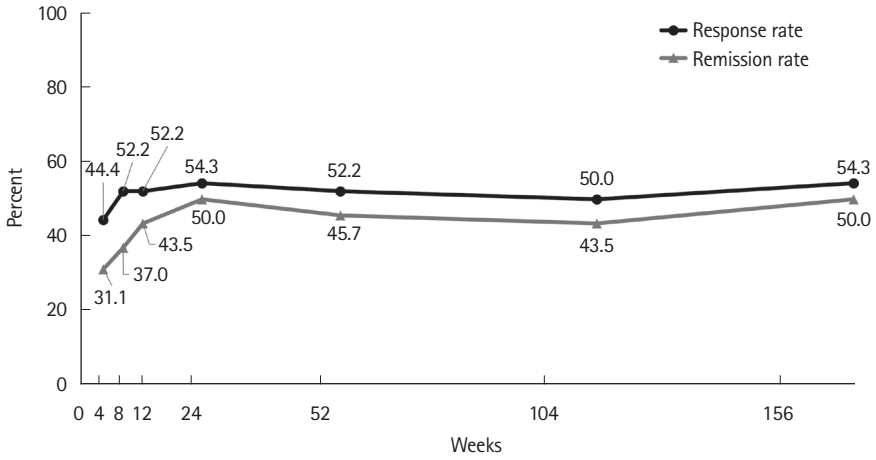

Fig. 3. Time-series data of short-term and long-term efficacy of tofacitinib (n = 46). Remission rate was 31.1% at 4 weeks, 37.0% at 8 weeks, and 43.5% at 12 weeks. Remission rate continued to exceed 40% from 12 through 156 weeks. Response rate was 44.4% at 4 weeks and the rate continued to exceed over 50% from 8 weeks through 156 weeks (n = 46).

formation on the long-term efficacy and safety of tofacitinib treatment in clinical practice. Although most of the cases in our study were biologic treatment failures, with more than half having received prior multiple biologics, 54.3% were able to continue tofacitinib and were responsive or in remission after 156 weeks of follow-up. Previous real-world studies in Europe and Asia have reported >40% rates of response and remission for up to 1 year.[8-14] In this long-term study, the response rate exceeded 50% after 8–156 weeks, and remission rate exceeded 40% after 12–156 weeks; these results were consistent with those of a 2-year real-world study in Europe.[15] The results of a previous report by the authors suggested that treatment status at 4 weeks could predict 52-week efficacy.[8] In this present study, upon assessment at 4 weeks of treatment, tofacitinib could be continued for 156 weeks in 95% of the responders but in only 24% of the nonresponders; this suggested that the response status early in the treatment period (i.e., 4 weeks) could predict the 3-year treatment success.

The results of dose optimization study implied that once the treatment was effective, the probability of successful reinduction and longer treatment retention for as long as 156 weeks remained high, even for cases of disease relapse within a year. In the OCTAVE Open study, in which tofacitinib was de-escalated to 5 mg b.d. in 8-week remitters, 25.4% relapsed after 12 months and 57.9% to 64.9% responded to 10 mg b.d. of tofacitinib reinduction treatment.[4] Although our study was based on real-world data and differed from the conditions of a phase III trial, only 1 study on tofacitinib reinduction treatment after LOR can be found. Yu et al.[16] reported a real-world study that showed a 56% cumulative disease relapse rate after tofacitinib de-escalation within 12 months of its initiation among patients with moderate to severe UC; 63% of those cases were

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Table 4. Adverse Events Reported during Tofacitinib Treatment (n = 46)

Adverse events[a]	No. (%)
Infectious adverse event	
Nasopharyngitis	8 (17.4)
Herpes zoster	3 (6.5)
Paranasal sinusitis	3 (6.5)
Serpigo	1 (2.2)
External otitis	1 (2.2)
Herpangina	1 (2.2)
COVID-19	4 (8.7)
Dyslipidemia	8 (17.4)
Acne	5 (10.9)
Abnormal liver function tests	1 (2.2)
Dyspnea	1 (2.2)
Cancer	0
Venous thromboembolism	0

[a]Adverse events were recorded 36 in 23 patients.

able to achieve another response with tofacitinib reinduction treatment. The data presented here showed that increasing tofacitinib led to a sufficiently high long-term efficacy of reinduction treatment, which we believe should be attempted for patients experiencing LOR because of several reasons. First, the flexibility of dosing provides the opportunity to adjust the tofacitinib dosage according to disease activity from reinduction to maintenance. Second, the rapid onset of the effect allows early timing of dose adjustment.[17] Third, because tofacitinib is an oral synthetic small molecule, it does not produce antidrug antibodies and, therefore, can be considered less prone to secondary failure, which is commonly seen with biologics treatment.[18]

When choosing between the 5 mg b.d. and 10 mg b.d. doses for maintenance therapy, it is recommended to consider disease severity and previous exposure and response to biologics. Moreover, the age, sex, and comorbidities, such as venous thromboembolic events, major adverse cardiovascular events, and malignancy, should also be considered in order to avoid potentially dose-related AEs and to balance both the benefits and risks of tofacitinib treatment.[19] The safety of tofacitinib treatment has been reported in several publications.[20] Although the Food and Drug Administration has announced concerns about the risks of cancer and cardiovascular and thromboembolic events[21]; in this 3-year study, none of these were reported. A large cohort and longer-term analysis are needed to evaluate the risks of these AEs. The reason for the lower AE rates in our study compared to previous clinical trials[22,23] could be because AEs are usually underreported in real-world studies. Herpes zoster infection during tofacitinib treatment was the next AE of our concern, because the patients in our cohort were all Asians, who were previously reported to be susceptible to the infection. Three patients (6.5%) were affected with herpes zoster between 16 and 25 weeks after tofacitinib initiation. Although this rate was higher than that previously reported,[24,25] the patients were successfully treated with antiviral medication without tofacitinib discontinuation.

We acknowledge that this report has several limitations, including the small sample size, the distinct patient population from a single tertiary inflammatory bowel disease center, and the retrospective evaluation. Although our data may not be generalizable to all UC cases and our cohort comprised mostly of biologic failure cases, the efficacy was similar to that reported in other real-world studies. One of the strengths of our study was the longest analysis period among the real-world studies on the use of tofacitinib for refractory UC. Even larger cohorts and longer-term data accumulation are needed for further analysis.

In this real-world study, continuation of tofacitinib was possible until 156 weeks after initiation in 54.3% of refractory UC cases, with >50% response rates and >40% remission rates. Among patients in whom response or remission was achieved and tofacitinib was deescalated after 8 weeks of induction treatment, 54.3% experienced relapse but were successfully rescued by and retained on reinduction treatment, except for 1 patient. No serious AEs were observed in the study.

ADDITIONAL INFORMATION

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Not applicable.

Author Contribution
Conceptualization: Shimizu H, Aonuma Y. Data curation: Shi-

mizu H, Aonuma Y, Hibiya S. Formal analysis: Shimizu H, Aonuma Y, Hibiya S. Investigation: Aonuma Y. Methodology: Shimizu H, Aonuma Y. Project administration: Shimizu H. Resources: Shimizu H. Supervision: Takenaka K, Fujii T, Saito E, Nagahori M, Ohtsuka K, Okamoto R. Validation: Shimizu H, Aonuma Y, Hibiya S. Visualization: Shimizu H. Writing - original draft: Shimizu H. Writing - review & editing: Kawamoto A. Approval of final manuscript: all authors.

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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