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Investigation of the Clinical Remission Course in Ulcerative Colitis from Tofacitinib Induction to Tapering or Withdrawal in Japanese Patients: A Single-Center Retrospective Study

Miki Koroku[a] Teppei Omori[a, b] Shun Murasugi[a] Ayumi Ito[a] Maria Yonezawa[a] Shinichi Nakamura[a] Katsutoshi Tokushige[c] Yousuke Nakai[a]

[a]Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan; [b]Department of Gastroenterology and Hepatology, Kyorin University School of Medicine, Tokyo, Japan; [c]Tokyo Joto Hospital, Tokyo, Japan

Keywords
Ulcerative colitis · Tofacitinib · Partial Mayo score · Remission · Reinduction

Abstract

Introduction: Tofacitinib (TOF), a Janus kinase inhibitor, has emerged as an innovative treatment option for patients with moderate-to-severe ulcerative colitis (UC). However, the clinical course of patients who achieve induction and maintain remission followed by TOF tapering or withdrawal is unclear. We investigated the efficacy of TOF and the clinical course after TOF tapering or withdrawal in real-world clinical practice. ***Method:*** Thirty-two patients treated with TOF 20 mg/day for UC relapse between October 2018 and August 2023 were included in this single-center, retrospective observational study. Disease activity was defined by partial Mayo score (PMS), and remission was defined as PMS ≤2 and rectal bleeding score 0, other score ≤1. PMS before TOF 20 mg/day induction was compared with PMS at 8 weeks. Patients who achieved clinical remission were tapered to 10 mg/day, while those who requested for drug withdrawal were allowed. The relapse rate of the TOF 10 mg/day maintenance group and the TOF withdrawal group was compared. Both groups included patients who had maintained remission at 6 months after tapering TOF to 10 mg/day. In addition, the efficacy of TOF 20 mg/day reinduction therapy was also compared between patients who relapsed in the TOF 10 mg/day maintenance group and the TOF withdrawal group. ***Result:*** Twenty-three patients (71.9%) achieved induction of remission by 8 weeks after TOF 20 mg/day administration, with significantly lower PMS than before TOF ($p < 0.0001$). Ultimately, 27 patients (84.4%) achieved remission, 24 who achieved remission were tapered to 10 mg/day, whereas 18 were able to maintain remission for 6 months. Seven of the 18 eventually withdrew from TOF. There was no significant difference in relapse rates between the TOF 10 mg/day maintenance group ($n = 11$; follow-up, 525 [29–1,483] days) and the TOF withdrawal group ($n = 7$; follow-up, 284 [77–797] days) (5/11 [45.5%] vs. 3/7 [42.9%], log-rank test: $p = 0.7091$). All patients who received TOF 20 mg/day reintroduction therapy after relapse went into remission. ***Conclusion:*** In clinical practice, TOF 20 mg/day significantly induced induction of remission, and in patients who received 6 months of maintenance remission therapy

karger@karger.com
www.karger.com/iid

Correspondence to:
Teppei Omori, omori.teppei@twmu.ac.jp

with TOF 10 mg/day, the relapse rates between the TOF 10 mg/day maintenance group and the TOF withdrawal group were similar. After relapse, TOF 20 mg/day reintroduction therapy improved symptoms.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology that affects the colon and rectum. Multiple factors, including genetic background, environmental factors, luminal factors, and mucosal immunomodulation, are believed to contribute to the pathogenesis of UC [1]. In 2023, the global prevalence of UC was estimated at 5 million cases, and its incidence is increasing [2]. Treatments to induce remission typically include 5-aminosalicylic acid (5-ASA) drugs and corticosteroids. In steroid-resistant or steroid-dependent cases, remission induction and maintenance therapies may include small molecules (Janus kinase [JAK] inhibitors), thiopurines, and biological agents (e.g., anti-cytokines and anti-integrins) [2]. JAK inhibitors, such as tofacitinib (TOF), have emerged as innovative therapeutic modalities for patients with moderate-to-severe UC. However, the risk of infection, especially herpes zoster, has been noted in patients with UC [3]. Moreover, a study comparing TOF with TNF inhibitors in patients with rheumatoid arthritis at high cardiovascular risk found a higher risk of major adverse cardiovascular events and cancer in the TOF group, which did not meet the non-inferiority criteria [4]. In the OCTAVE program, a phase 3 randomized, double-blind, placebo-controlled trial, approximately 40% of patients who relapsed after the discontinuation of TOF, achieved remission upon its reinduction [5]. Withdrawal of TOF in UC may also reduce the risk of adverse events. However, there have been no real-world data on the risk of relapse of UC due to the withdrawal of TOF 10 mg/day or on the efficacy of TOF 20 mg/day reinduction at the time of relapse. We examined the efficacy of TOF and the clinical course after TOF tapering or withdrawal, as well as the efficacy of TOF 20 mg/day reinduction therapy in real-world clinical practice.

Methods

Thirty-two patients with UC treated with TOF for UC exacerbations at Tokyo Women's Medical University Hospital between October 2018 and March 2023 were included in this single-center, retrospective observational study. The medical records through March 2024 were reviewed, including those of patients who withdrew from TOF during the course of the study (shown in Fig. 1). Eligibility criteria were partial Mayo score (PMS) >3 or Mayo endoscopic subscore (MES) ≥2 and use of 20 mg/day of TOF as remission induction therapy. Exclusion criteria were concomitant use of biologics other than TOF, immunomodulators, other JAK inhibitors, or concomitant granulocyte and monocyte adsorption. In addition, patients who underwent treatment intensification other than TOF in this study were considered relapsed. The PMS before TOF introduction was compared with PMS at 4 and 8 weeks. Patients who reached clinical remission were tapered to 10 mg/day, and those who requested for drug withdrawal during maintenance therapy at 10 mg/day were allowed. Prior to drug withdrawal, colonoscopy was performed in all but 2 patients to confirm mucosal remission (MES0). The clinical background of the TOF 10 mg/day maintenance group and the TOF withdrawal group was also compared, as well as the relapse rate in both groups. Both groups included patients who had maintained remission at 6 months after tapering to 10 mg/day of TOF. Relapse in the TOF 10 mg/day maintenance group (observation period from after 6 months of TOF 10 mg/day) and the TOF withdrawal group (observation period from the time of TOF discontinuation) was compared. In addition, the efficacy of TOF 20 mg/day reintroduction therapy was compared in patients who relapsed after tapering or withdrawal. Disease activity was defined by PMS, with remission defined as PMS ≤2 and a rectal bleeding score of 0, other score ≤1 point. Relapse was defined as failure to meet the definition of remission, requiring therapeutic intervention with advanced therapy (ADT) such as biologics or oral corticosteroids.

Statistical Analysis

Numerical data are expressed as the median and range. Fisher's exact test was used for the univariate analysis of background factors. The Wilcoxon signed-rank test was used for changes in clinical symptoms over time. $p < 0.05$ was considered significant. Cumulative remission induction rate and cumulative relapse rate were determined using the log-rank test and survival time analysis. JMP statistical analysis software (version 11; SAS, Cary, NC, USA) was used for all analyses.

Results

Of the 32 patients, 21 (65.6%) were male; 16 (50%) had left-sided colitis, and 16 (50%) had total colitis type, PMS of 6 (2–8), and MES of 2 (1–3). Eleven (34.4%) were

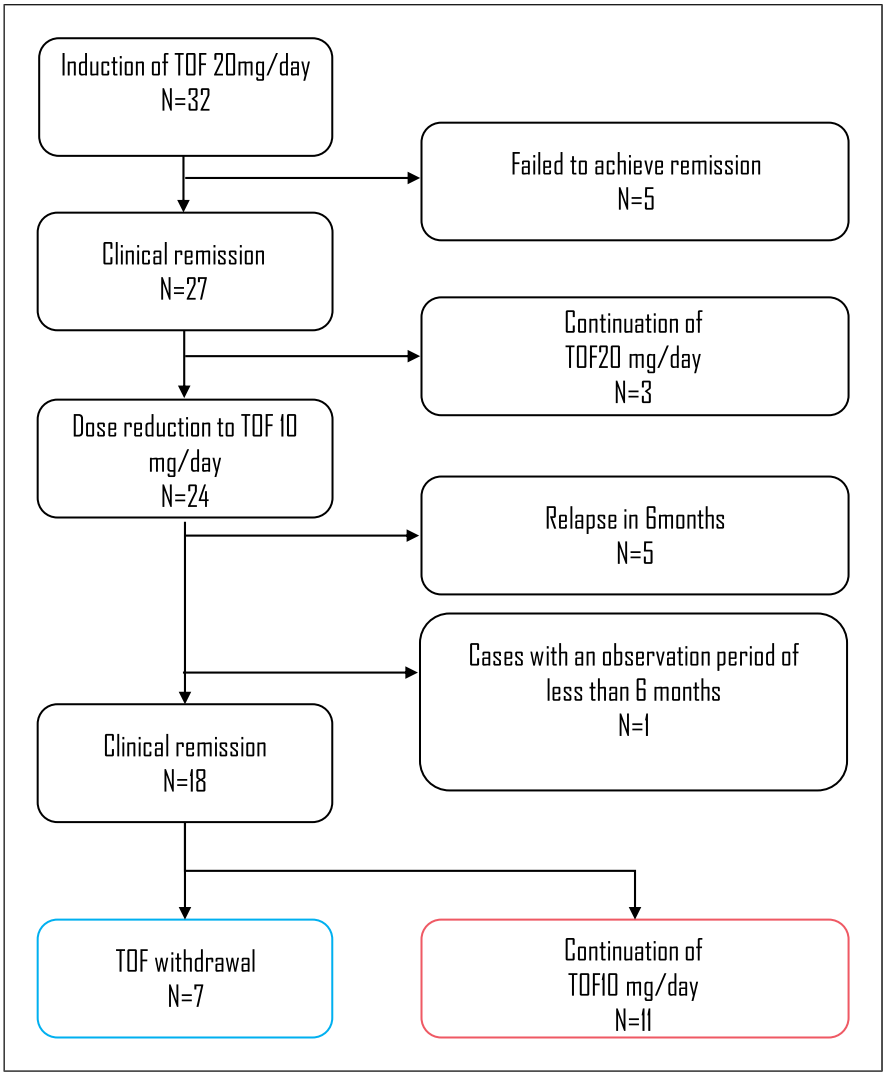

Fig. 1. Study profile of TOF withdrawal. TOF, tofacitinib.

treated with biologics, 12 (37.5%) with azathioprine, 17 (53.1%) with oral corticosteroids, 1 (3.1%) with filgotinib (FIL), and 1 (3.1%) with tacrolimus before TOF therapy. Five patients (15.6%) underwent ADT with more than one biological agent or JAK inhibitor (Table 1). Seventeen patients (53.1%) achieved induction of remission by 4 weeks after TOF administration, and 23 patients (71.9%) at 8 weeks, with a significant decrease in PMS compared to before TOF ($p < 0.0001$ at 8 weeks, Wilcoxon signed-rank test). Ultimately, 27 patients (84.4%) achieved remission, with a median time to remission of 21 (2–551) days (shown in Fig. 1, 2). Between the remission and non-remission groups, the non-remission group was significantly younger ($p = 0.011$), but there were no significant differences in clinical activity or prior treatment (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000545704). After remission, of the 27 patients, the dose was reduced to 10 mg/day in 24 (88.9%), with a median time to dose reduction of 81 (12–364) days.

Of the 24 patients whose dosage was reduced to 10 mg/day, 18 patients remained in remission for 6 months. Although 5 patients relapsed clinically within 6 months, 4 patients achieved remission following the readjustment of the dosage to TOF 20 mg/day, whereas 1 patient was switched to another agent (ustekinumab). The 1 patient was excluded from the study because the observation period was 32 days. Of the 18 patients who remained in remission at 6 months after TOF dose reduction, 7 (38.9%) went on to TOF withdrawal (364 [133–1,030] days from TOF 10 mg/day dose reduction to TOF withdrawal, shown in Fig. 1). PMS at the time of

Table 1. Baseline characteristics

	Total cohort
Sex (male/female)	21 (65.6)/11 (34.3)
Age, years	36.9 (20.4–62.8)
Disease duration, years	12.8 (1.3–23.5)
Extent of disease: E2/E3	16 (50)/16 (50)
Smoking	
No/yes/past	26 (81.3)/0 (0)/6 (18.8)
Steroid resistance/steroid independent	9 (28.1)/23 (68.8)
Mayo score	8 (4–11)
PMS	6 (2–8)
MES	2 (1–3)
Prior therapies	
5-ASA	28 (87.5)
Steroid	17 (53.1)
Thiopurine	12 (37.5)
TAC	1 (3.1)
TNFi	8 (25)
VDZ	2 (6.3)
UST	1 (3.1)
FIL	1 (3.1)
Topical	19 (59.4)
History of Bio/JAK/TAC use of 2 or more drugs	5 (15.6)
History of Bio/JAK/TAC use of 2 or more drugs	5 (15.6)

Numbers are shown in *n* (%) or median (range). 5-ASA, 5-aminosalicylic acid; Bio, biologics; E3, pancolitis; E2, left-sided colitis; JAK, Janus kinase; TAC, tacrolimus; TNFi, tumor necrosis factor inhibitor; UST, ustekinumab; VDZ, vedolizumab.

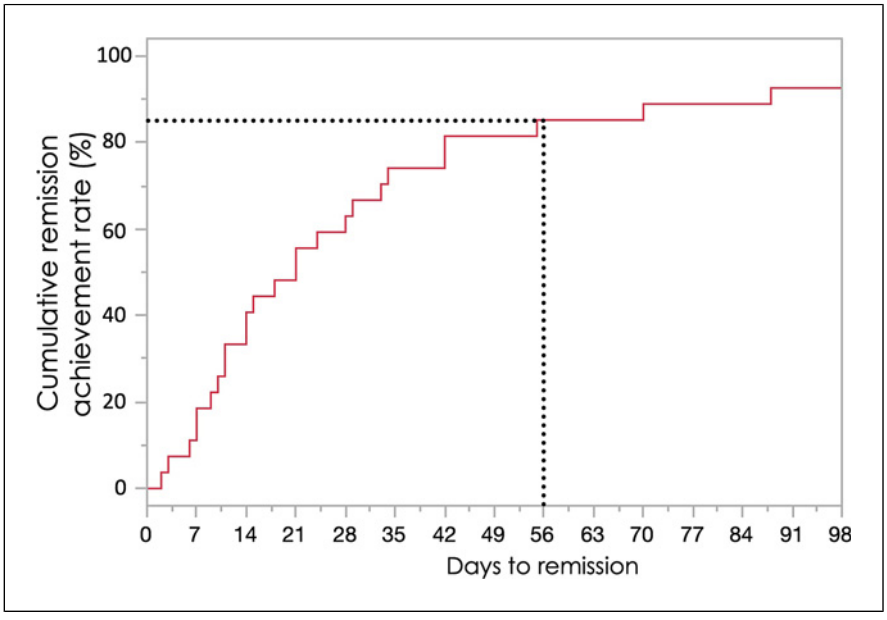

Fig. 2. Cumulative remission induction rate with TOF 20 mg/day. TOF, tofacitinib.

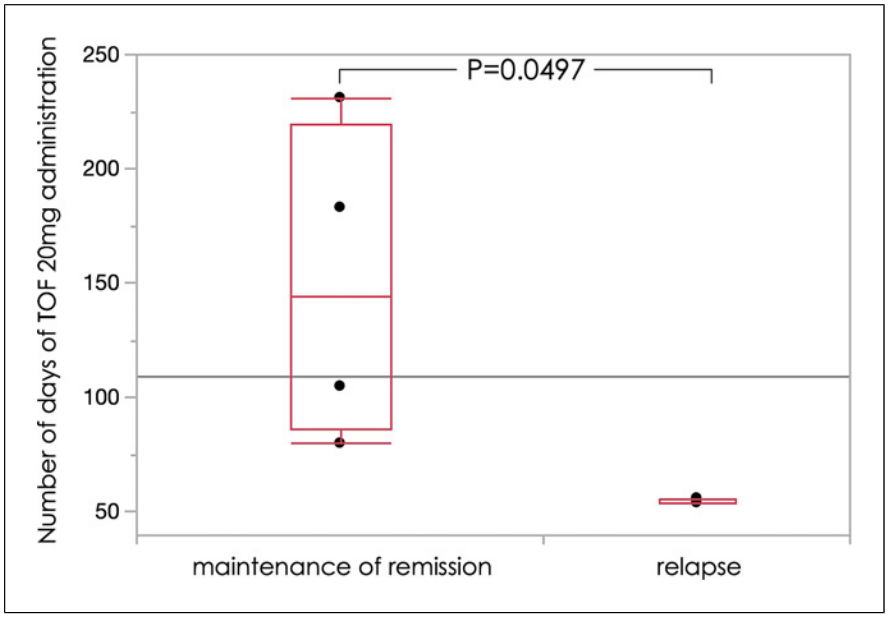

Fig. 3. Comparison of the number of days of TOF 20 mg/day at induction of remission in the remission maintenance and relapse groups after TOF withdrawal. TOF, tofacitinib.

TOF withdrawal was 0 (0–0) in all patients, and MES before withdrawal was 0 (0–0), except in 2 patients who did not underwent colonoscopy 92 (8–165) days after TOF tapering. The time from remission induction to TOF withdrawal was 434 (189–1,213) days. 5-ASA was continued in all patients after TOF withdrawal. The reason for withdrawal of TOF was patient request in all cases, and the timing of withdrawal was decided by each attending physician; none of the withdrawals were due to adverse events. Prior to the induction of TOF, 3 patients were on biologics, three on steroids, and one on FIL as primary therapy, but after withdrawal of TOF, the only primary therapy was 5-ASA, which was continued in all patients. Three patients (42.9%) relapsed during a median observation period of 284 (77–797) days in the 7 patients who withdrew TOF. In the withdrawal group, the duration from the start of TOF 20 mg/day induction of remission was significantly shorter in the relapse group than in the non-relapse group (p = 0.0497) (shown in Fig. 3; online suppl. Table 2). On the other hand, there was no significant difference in the number of days from TOF 10 mg/day tapering to TOF withdrawal between the two groups (shown in Fig. 4). Relapses occurred at 84, 153, and 379 days. Three patients were previously treated, including two on steroids and one on vedolizumab. However, all 3 patients were in remission after TOF 20 mg/day reintroduction. One patient required 124 days to achieve remission, whereas 2 patients achieved remission induction within 7 days (Table 2).

On the other hand, in 11 patients who continued TOF 10 mg/day maintenance therapy, colonoscopy was performed 253 (0–434) days after TOF tapering in all but 3 patients, and MES was 1 (0–2). In the TOF 10 mg/day maintenance group that had been in remission for 6 months, 5 patients relapsed, 4 patients of whom were readjusted to TOF 20 mg/day after relapse, and 1 patient was treated with infliximab. In the TOF 10 mg/day maintenance group, there were no significant differences in patient background between the relapse and remission maintenance groups (online suppl. Table 3).

After 6 months of maintenance remission, there were no significant differences in patient characteristics, including duration of TOF 20 mg/day in the TOF 10 mg/day maintenance group (Table 3). There was no significant difference in relapse rate between the relapse in the TOF 10 mg/day maintenance group (observation period from after 6 months of TOF 10 mg/day) (11 patients; follow-up, 525 [29–1,483] days) and the TOF withdrawal group (observation period from the time of TOF discontinuation) (7 patients; follow-up, 284 [77–797] days) after 6 months of maintenance remission (5/11 [45.5%] patients vs. 3/7 [42.9%] patients, p = 1.0, log-rank test: p = 0.7091). There was no significant difference in the observation period (p = 0.3651). There was also no significant difference in the time to achieve induction of remission with TOF 20 mg/day or the time to taper to TOF 10 mg/day (shown in Fig. 5). Adverse events included herpes zoster in 5/32 (15.6%) and dyslipidemia in 6/32 (18.8%) during the observation period while taking TOF.

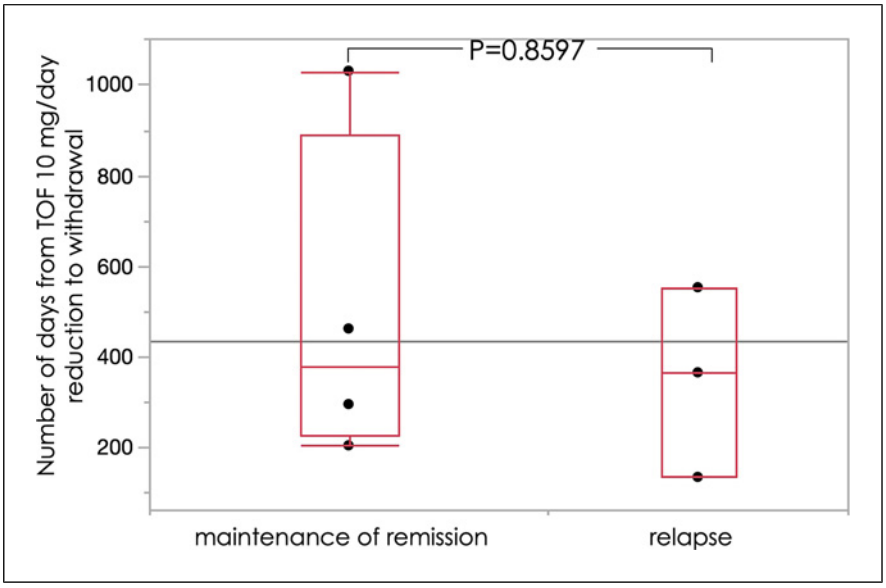

Fig. 4. Comparison of the number of days of TOF 10 mg/day during remission maintenance therapy in the remission maintenance group and the relapse group after TOF withdrawal. TOF, tofacitinib.

Discussion

TOF, a JAK inhibitor, is used to treat moderate-to-severe UC. A phase 3 randomized, double-blind, placebo-controlled trial of TOF therapy demonstrated its efficacy compared with placebo [6]. Moreover, it produced rapid and sustained improvements in UC disease activity and patient-reported outcome, in a real-world prospective study [7]. Furthermore, in a meta-analysis of real-world evidence of TOF, clinical response and remission induction at a median of 8 weeks were achieved in 51% (95% confidence interval [CI], 41–60%) and 37% (95% CI, 26–45%) of patients, respectively [8].

Relapse following TOF tapering was reported in the RIVETING trial [9], in which patients in clinical remission after 2 years of TOF 20 mg/day maintenance were divided into a 10 mg/day tapering group and a TOF 20 mg/day maintenance group, and the percentage of patients in clinical remission at 6 months was compared. More than 75% of patients in both groups remained in remission (modified Mayo score remission) (77.1% vs. 90%). However, an MES of 1 prior to tapering was shown as a factor of difficulty in maintaining remission, especially in the 10 mg/day tapering group. In real practice reports of relapse after TOF 10 mg/day taper, the composite outcome related to disease activity in UC, such as rates of hospitalization, surgery, steroid initiation, and re-titration to TOF 20 mg/day or change in therapy, was associated with the duration of remission induction therapy of TOF 20 mg/day of less than 16 weeks and MES3 at colonoscopy, 6 months after starting TOF [10]. It has also been reported that the use of 5-ASA in TOF 10 mg/day maintenance therapy contributes to a reduced risk of UC relapse compared to the use of 5-ASA without maintenance therapy. However, 5-ASA did not contribute to relapse risk at TOF 20 mg/day maintenance therapy [11]. In TOF withdrawal and reinduction, the only data presented in UC are for patients randomized to the placebo group in the OCTAVE Sustain trial and who had a clinical response to TOF 20 mg/day induction therapy in the OCTAVE program [5]. The median time to relapse after interruption was 169 (95% CI, 94.0–179.0) days for remission cases and 123 (95% CI, 91.0–168.0) days for response cases. Moreover, 60.6% of patients in remission and 42.4% of patients in response did not relapse at 36 months after drug withdrawal [5]. However, this is not a generalization, as medication withdrawal is not usually performed immediately after the induction of remission with TOF. A similar report was made in a phase 3 randomized, double-blind, placebo-controlled trial of FIL, which has the same mechanism of action as that of TOF [12]. Discontinuation of FIL after remission induction therapy resulted in relapse at a median of approximately 15 weeks; however, clinical improvement was achieved in most patients within 12 weeks after receiving reinduction with 200 mg of FIL. These findings suggest that although the risk of relapse should be considered in UC with respect to TOF withdrawal, rapid

improvement may be achieved with reinduction of the drug. In fact, about half of the patients in this study experienced relapse after tapering or withdrawal, but there was no significant difference between the two groups, and all patients who received reinduction remission therapy with TOF 20 mg/day achieved remission. Achieving maintenance of remission with TOF is important from the concept of the treat-to-target strategy as it contributes to improving the quality of life [13]. On the other hand, whether TOF should be continued may depend on whether the previous course of treatment was refractory [14]. Therefore, it is important to identify the characteristics of patients suitable for withdrawal and the factors influencing the efficacy of subsequent reinduction. In the present study, the remission attainment rate was higher than that reported in clinical trials and real-world evidence. The patient cohort in this study had a low level of clinical activity at the time of TOF intervention, as well as a small number of patients who had experienced multiple ADTs. In addition, patients who relapsed in the withdrawal group received TOF 20 mg/day for a significantly shorter period of time before tapering to TOF 10 mg/day, which is consistent with the risk of relapse in the TOF 10 mg/day taper group. Furthermore, all cases achieved PMS0, and MES0 was confirmed in all but two cases. These factors may have influenced the fact that 57% of patients did not relapse and did not require ADT, including oral corticosteroids, during a mean follow-up of 442 days (77 to 797 days), even when 5-ASA was the only primary therapy after TOF withdrawal.

Regarding adverse events, no new safety risk signals for TOF have been reported after 9.2 years of observation [15], while rheumatoid arthritis reports caution in older adult patients with comorbidities. The older adult patients with UC are also increasing in number; therefore, caution is warranted regarding treatment of TOF in the future. In this study, herpes zoster was observed in 5 patients as an adverse event. That this study was conducted in Japanese subjects is consistent with previous reports of those with an increased risk of herpes zoster [15]. As for herpes zoster, vaccination can reduce the risk of disease, and it may be important to recommend administration beforehand when ADT, especially JAK inhibitors/TOF, is required [16]. Unfortunately, the patients enrolled in the study could not be vaccinated because the disease activity of UC was severe enough to require prompt administration of TOF.

Table 2. Patient characteristics and clinical outcomes in the TOF withdrawal cohort

Case	Sex	Age, years	Disease duration, years	Extent of disease	Prior therapies	At the start of treatment		Days to remission	Days to taper to 10 mg/day	Days to TOF withdrawal	Time of TOF withdrawal		Treatment after TOF withdrawal	Relapse after TOF withdrawal	Observation period (days until relapse)
						PMS	MES				PMS	MES			
1	Male	20s	8.5	E2	5-ASA + PSL + VDZ	5	2	11	54	606	0	0	5-ASA 4,800 mg	Yes	379
2	Female	30s	3.2	E2	5-ASA + PSL	7	2	28	56	189	0	0	5-ASA 3,600 mg	Yes	153
3	Female	50s	1.3	E3	5-ASA + PSL	6	3	14	56	420	0	0	5-ASA 4,800 mg	Yes	84
4	Male	20s	13.2	E2	5-ASA + AZA + GLM	3	3	55	183	1,213	0	N/A	5-ASA 4,000 mg	No	599
5	Female	40s	22.2	E3	5-ASA + UST	5	2	14	231	434	0	N/A	5-ASA 2,400 mg	No	284
6	Male	30s	3.7	E3	5-ASA + PSL + FIL	5	2	70	105	566	0	0	5-ASA 4,800 mg	No	77
7	Male	40s	7	E3	5-ASA + PSL	5	2	24	80	374	0	0	5-ASA 4,800 ng	No	797

5-ASA, 5-aminosalicylic acid; AZA, azathioprine; E3, pancolitis; E2, left-sided colitis; FIL, filgotinib; GLM, golimumab; MES, Mayo endoscopic subscore; N/A; not applicable; PMS, partial Mayo score; PSL, prednisolone; UST, ustekinumab; VDZ, vedolizumab.

Table 3. Comparison of TOF withdrawal and 10 mg/day maintenance group

	TOF withdrawal cohort, $N = 7$	TOF 10 mg/day maintenance cohort, $N = 11$	p value
Sex (male/female)	4 (42.9)/3 (57.1)	8 (72.7)/3 (27.3)	0.6267
Age, years	34.3 (28.6–55.6)	41 (33.7–62.8)	0.2651
Disease duration, years	7 (1.3–22.2)	15.8 (5.9–23.5)	0.0297
Extent of disease: E2/E3	3 (42.9)/4 (57.1)	6 (54.6)/5 (45.4)	1.0000
Smoking			
No/yes/past	6 (85.7)/0 (0)/1 (14.3)	8 (72.7)/0 (0)/3 (27.3)	1.0000
Steroid resistance/steroid independent	1 (14.3)/6 (85.7)	2 (18.2)/9 (81.8)	1.0000
Mayo score	7 (6–9)	8 (4–11)	0.4894
PMS	5 (3–7)	6 (2–8)	0.4062
MES	2 (2–3)	2 (2–3)	0.9544
Prior therapies			
5-ASA	7 (100)	11 (100)	1.0000
Steroid	3 (42.9)	4 (36.4)	1.0000
Thiopurine	1 (14.3)	7 (63.6)	0.0656
TAC	0 (0)	1 (9.1)	1.0000
TNFi	1 (14.3)	2 (18.2)	1.0000
VDZ	1 (14.3)	1 (9.1)	1.0000
UST	1 (14.3)	0 (0)	0.3889
Filgotinib	1 (14.3)	0 (0)	0.3889
Topical	5 (71.4)	8 (72.7)	1.0000
History of Bio/JAK/TAC use of 2 or more drugs	1 (14.3)	3 (27.3)	1.0000
Observation period (or days until relapse)	718 (342–1,213)	895 (300–1,732)	0.4652
Days to achieve remission with TOF 20 mg	24 (11–70)	18 (3–88)	0.3644
Days to taper from TOF 20 mg to TOF 10 mg	80 (54–231)	69 (12–231)	0.7163
Days to withdrawal from 10 mg of TOF tapering	364 (133–1,030)	–	–
Days of observation after withdrawal of TOF	284 (77–797)	–	–
Days of observation after 180 days of remission maintenance with 10 mg of TOF	–	525 (29–1,483)	–
MES after therapeutic intervention	0 (0–0)	1 (0–2)	
Interval between TOF withdrawal and colonoscopy after therapeutic intervention	92 (8–165)		
Interval between TOF tapering and colonoscopy after therapeutic intervention		253 (0–434)	
Relapse	3 (42.9)	5 (45.5)	1.0000
Days to relapse	153 (84–379)[a]	136 (29–1,401)[b]	1.0000

Numbers are shown in *n* (%) or median (range). 5-ASA, 5-aminosalicylic acid; Bio, biologics; E3, pancolitis; E2, left-sided colitis; JAK, Janus kinase; TAC, tacrolimus; TNFi, tumor necrosis factor inhibitor; UST, ustekinumab; VDZ, vedolizumab. [a]Days to relapse after withdrawal of TOF 10 mg. [b]Days to relapse after 180 days of remission maintenance with 10 mg of TOF.

There are several limitations to this study. First, the results were reported in a very small number of cases. Therefore, the rate of relapse in the TOF withdrawal group may be underestimated, and caution should be exercised in the interpretation of the results. Second, it is a retrospective observational study, which may be subject to selection bias. Withdrawals occur at the patient's request, the duration of medication is left to the attending physician, and the

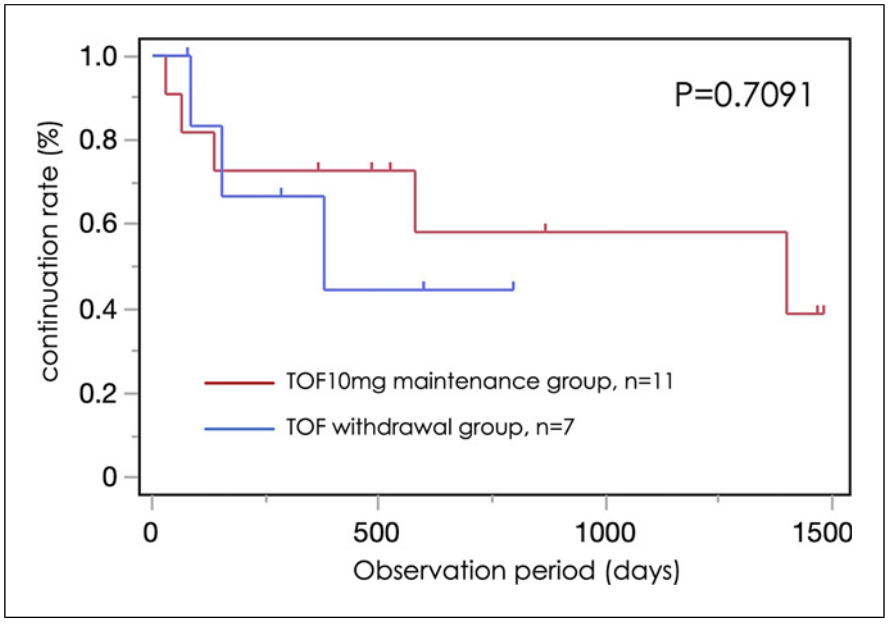

Fig. 5. Comparison of recurrences between the TOF withdrawal group and the TOF 10 mg/day maintenance group. TOF, tofacitinib.

criteria for the observation period are unclear. Therefore, patients with short observation periods were included. In the withdrawal group, colonoscopy was performed after dose reduction and before withdrawal except in two cases. However, in the 10 mg/day maintenance group, the timing of colonoscopy was not constant and was not performed at the start of 6 months of maintenance. Therefore, some patients did not reach mucosal remission, which may have affected the relapse rate. Furthermore, all patients in the maintenance and withdrawal groups were treated with 5-ASA, and the effect of 5-ASA use on maintenance of remission was unclear. Therefore, this study is preliminary, and more prospective studies with a larger number of patients are needed to select appropriate patients for TOF withdrawal.

In conclusion, in clinical practice, induction of remission with TOF 20 mg/day shows a high rate of induction of remission. In addition, in patients who received 6 months of maintenance remission therapy with TOF 10 mg/day, the relapse rate was not significantly different between the 10 mg/day maintenance group and the TOF withdrawal. After relapse, TOF 20 mg/day reintroduction therapy improved symptoms.

Statement of Ethics

This study protocol and consent procedure were reviewed and approved by the Tokyo Women's Medical University Human Ethics Review Committee (Approval No. 2023-0166). Informed consent was obtained from all patients using the opt-out method because of the retrospective design of the study. The opt-out informed consent protocol was allowed for the use of participant data for research purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

T. Omori: study concept and design. M. Koroku, M. Yonezawa, S. Murasugi, A. Ito, and T. Omori: data acquisition. M. Koroku: statistical analysis and drafting of the first version of the manuscript. T. Omori, S. Nakamura, K. Tokushige, and Y. Nakai: critical revision and approval of the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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