

## Initial experience of tofacitinib for treating refractory moderate-to-severe ulcerative colitis

Masanao Nakamura<sup>1</sup>, Takeshi Yamamura<sup>1</sup>, Keiko Maeda<sup>2</sup>, Tsunaki Sawada<sup>2</sup>, Yasuyuki Mizutani<sup>1</sup>, Eri Ishikawa<sup>1</sup>, Takuya Ishikawa<sup>1</sup>, Naomi Kakushima<sup>1</sup>, Kazuhiro Furukawa<sup>1</sup>, Eizaburo Ohno<sup>1</sup>, Hiroki Kawashima<sup>2</sup>, Takashi Honda<sup>1</sup>, Masatoshi Ishigami<sup>1</sup> and Mitsuhiro Fujishiro<sup>1</sup>

<sup>1</sup>*Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

<sup>2</sup>*Department of Endoscopy, Nagoya University Hospital, Nagoya, Japan*

### ABSTRACT

Ulcerative colitis (UC) is an incurable, chronic inflammatory disease of the large bowel whose etiology and pathogenesis have not yet been comprehensively explained. Tofacitinib is a small molecule Janus kinase inhibitor that was introduced for treating refractory UC. We aimed to examine the efficacy and safety of tofacitinib for the treatment of 18 patients with UC. Continuous treatment rates were 50, 38, and 33% at 8, 24, and 52 weeks, respectively. Overall, 83.3% of these patients showed tumor necrosis factor (TNF) antibody failure status. When the effective status was defined as a Lichtiger index (LI) that decreased by 3 points or more or was less than 4 points and remission status was defined as an LI less than 4 points, the effective and remission rates (%) at 2, 8, and 16 weeks were 55.5 (10/18) and 22.2 (4/18), 38.8 (7/18) and 33.3 (6/18), and 38.8 (7/18) and 38.8 (7/18), respectively. Background characteristics of 2-week responders and non-responders were compared. C-reactive protein level in responders was significantly lower than that in non-responders, and the hemoglobin level in responders was significantly higher than that in non-responders. This study provides preliminary results of the effectiveness of tofacitinib even for TNF antibody and tacrolimus failure patients.

Keywords: ulcerative colitis, refractory, tofacitinib, case reports

#### Abbreviations:

UC: ulcerative colitis

JAK: Janus kinase

TOF: tofacitinib

LI: Lichtiger index

CRP: C-reactive protein

TNF: tumor necrosis factor

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Received: January 13, 2021; accepted: May 21, 2021

Corresponding Author: Masanao Nakamura MD, PhD

Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, 65

Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2172, Fax: +81-52-744-2180, E-mail: [makamura@med.nagoya-u.ac.jp](mailto:makamura@med.nagoya-u.ac.jp)

## INTRODUCTION

Ulcerative colitis (UC) is characterized by an increased frequency of bowel movements, watery diarrhea, and bloody stool, all of which have a negative effect on the quality of life.<sup>1</sup> The precise etiology of UC is unknown, and curative medical therapy is not yet available. The current treatment armamentarium includes mesalamine, glucocorticoids, immunosuppressive agents, infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab, as well as the small molecule Janus kinase (JAK) inhibitor, tofacitinib (TOF). With the availability of multiple treatment options with differences in efficacy and safety profiles, there is considerable variability in the clinical use of these drugs in the treatment of outpatients and inpatients with moderate-to-severe UC.<sup>2</sup> However, approximately 20% of patients are primary non-responders to induction therapy with biologic agents and 50% present with a secondary loss of response during follow-up.<sup>3</sup>

The choice of drug to treat UC should be determined by clinical factors, patient choice, cost, likely adherence, and local infusion capacity,<sup>4</sup> especially steroid-dependent and -resistant patients. Furthermore, clinicians should be aware of the characteristics of each medicine so that they can be administered to patients with optimal timing.

TOF is an oral, small molecule JAK inhibitor for the treatment of UC. Tofacitinib is a potent inhibitor of JAK1 and JAK3 with only moderate potency for JAK2 in *in vitro* assays, and JAK1/3 inhibition by TOF is proposed to block signaling for several cytokines integral to lymphocyte activation, proliferation, and function, including interleukin-2, -4, -7, -9, -15, and -21. In addition, JAK1 inhibition may also attenuate signaling by interleukin-6 and interferon gamma.<sup>5,6</sup> TOF was approved for the treatment of adults with moderate-to-severe rheumatoid arthritis prior to UC. TOF was also approved for treating adult patients with moderate-to-severe active UC in Japan in 2018; it can be applied for both induction and maintenance therapy. Post-hoc analyses of TOF treatment in Japanese patients with moderate-to-severe UC in one of two global phase III studies showed that, at week 8 of OCTAVE Induction 1, 22.4% of patients achieved remission with TOF.<sup>7</sup> However, differences in the safety profile of TOF in Japanese patients versus the global population, such as a higher risk of herpes zoster with an incidence of about 8%, have been reported.<sup>8,9</sup> Therefore, it is essential to reveal the efficacy and safety profiles of TOF in Japanese patients with UC. Here, we report the treatment details in patients who were administered TOF at Nagoya University Hospital. This study was approved by the ethics committee of Nagoya University Hospital (ID 2015–0466).

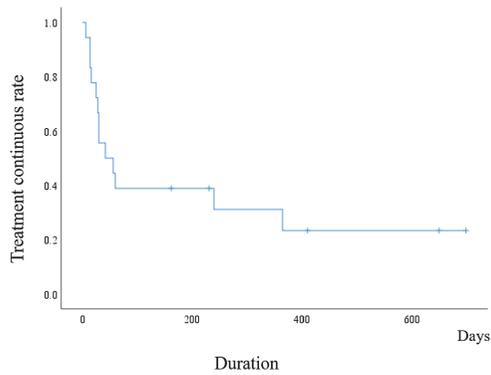
## CASE REPORTS

Of the 642 patients in the UC database in our unit, 18 consecutive patients who were administered TOF were selected for analysis. Their baseline characteristics are shown in Table 1. Four patients (22.3%) were categorized as having moderate status according to the Lichtiger index (LI) from 6 to 9 points and severe status according to the LI with more than 10 points. Fifteen patients (83.3%) had a biologic failure status. Two patients received infliximab, adalimumab, and vedolizumab; however, they still had moderate UC activity. Previous calcineurin inhibitor failure was observed in eight (44.5%) patients. Calcineurin inhibitor is a medicine inhibiting the action of calcineurin which is an enzyme that activates T-cells of the immune system and usually used for refractory UC. The treatment strategy for each patient involved administering TOF at 20 mg/day for the first 8 weeks, then at 10 mg/day for as long as possible. Four patients developed an increasing number of bowel movements after 8 weeks and the dose of TOF was increased temporarily to 20 mg/day. In clinical practice, clinicians recommended taking tofacitinib for more

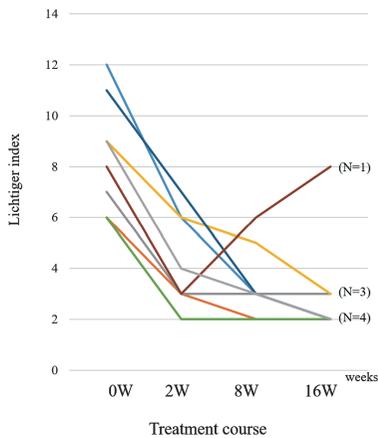
than 16 weeks and stopped it by patient's request with reference to response of tofacitinib and adverse events. The mean observation period was 171 days (range 6–699). Treatment continuation rates were 50, 38, and 33% at 8, 24, and 52 weeks, respectively (Figure 1). When effective status was defined as an LI that decreased by 3 points or more, or the LI was less than 4 points, and remission status was defined as an LI less than 4 points, the effective and remission rates at 2, 8, and 16 weeks were 55.5 (10/18) and 22.2 (4/18), 38.8 (7/18) and 33.3 (6/18), and 38.8 (7/18) and 38.8% (7/18), respectively (Figure 2a-c). Of 10 patients who discontinued tofacitinib treatment at 16 weeks, UC activity in 5 patients was improved by switching medicines (calcineurin inhibitor in 2 patients, ustekinumab in 2 patients, and steroid injection in 1 patient). The Other 5 patients received surgical treatment owing to severe UC.

**Table 1** Baseline demographic and disease characteristics

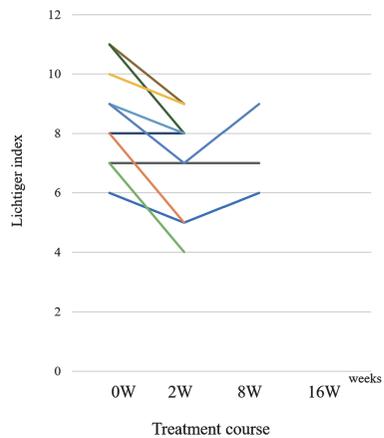
Variable, median (range) or n (%)	n = 18
Sex	
Female	6 (33.3)
Male	12 (66.7)
Age	37 years (19–69)
Body weight	55 kg (40–72)
Disease duration	44 months (12–160)
Disease type	
Extensive	14 (77.7)
Left-sided	4 (22.3)
Severity	
Severe	4 (22.3)
Moderate	14 (77.7)
Mild	0
Admission status	10/18 (55.5)
History of emergency hospitalization	2 times (0–3)
Lichtiger index	8 (6–12)
UCEIS	5 (4–8)
Hemoglobin (g/dL)	11.4 (8.6–15.5)
Albumin (g/dL)	3.4 (2.1–4.2)
C-reactive protein (mg/dL)	1.04 (0.02–5.42)
Corticosteroid	
Refractory	10 (55.5)
Dependent	8 (44.5)
Use of immunomodulator	4 (22.3)
Previous biologics failure	15 (83.3)
1 agent	6 (33.3)
2 agents	7 (38.8)
3 agents	2 (11.1)
Previous calcineurin inhibitor failure	8 (44.5)



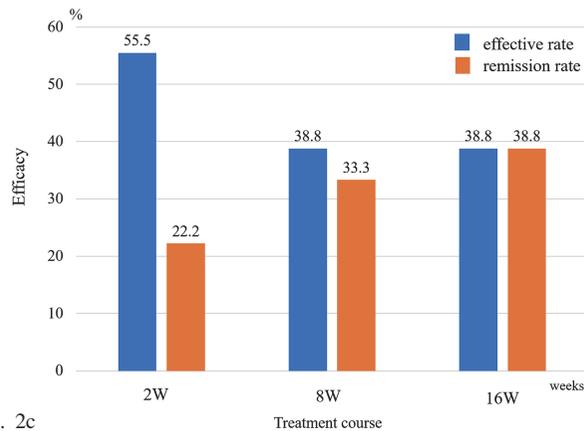
**Fig. 1** Treatment continuation rate of tofacitinib



**Fig. 2a**



**Fig. 2b**



**Fig. 2c**

**Fig. 2** Lichtiger index in clinical course and the efficacy of tofacitinib

**Fig. 2a:** Lichtiger index in 8 patients who had been taking tofacitinib for more than 16 weeks during the induction period.

**Fig. 2b:** Lichtiger index in 10 patients who gave up tofacitinib treatment before 16 weeks during the induction period. Seven and 3 patients stopped tofacitinib administration at the time of 2 weeks and 8 weeks, respectively.

**Fig. 2c:** Effective and remission rates by tofacitinib treatment.

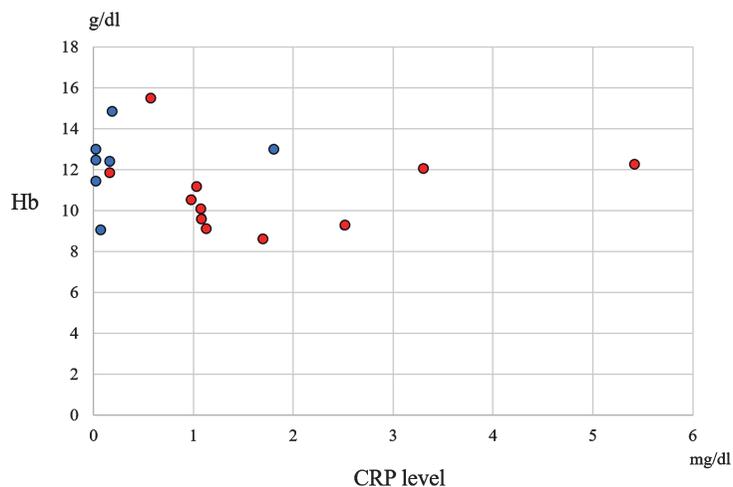
Because about half of the patients ceased TOF treatment within 8 weeks (Figure 1), we tried to find the patients who can continue TOF treatment for more than 8 weeks. Background characteristics of 2-week and 8-week responders and non-responders were compared using the Mann–Whitney *U* test or Fisher’s exact test (Table 2, 3). History of emergency hospitalization in 2-week responders was significantly less than that in 2-week non-responders (Table 2). The C-reactive protein (CRP) level in 8-week responders was significantly lower than that in 8-week non-responders, and the hemoglobin level in 8-week responders was significantly higher than that in 8-week non-responders (Table 3). A scatter plot of baseline laboratory data showed that TOF was effective, especially in 5 patients with a hemoglobin level  $\geq 12$  g/dL and a CRP level  $< 1.0$  mg/dL (Figure 3) (effective rate with 80% (4/5) vs that of the others with 23% (3/13),  $P=0.047$ , Fisher’s exact test). At the result, the only difference between the two groups was that the CRP was significantly lower and the Hb level was higher in the effective group, which only meant that the inflammatory response was subdued and there was less bleeding in the effective group. That was the limitation of this small group analysis.

**Table 2** Background characteristics of 2-week responders and non-responders

Variable	Responder	Non-responder	<i>P</i> -value
N	10	8	
Male/ Female	6/4	6/2	0.63
Age, median $\pm$ range	38 $\pm$ 14	34 $\pm$ 16	0.59
Body weight, kg, median $\pm$ range	57 $\pm$ 7	53 $\pm$ 12	0.32
Disease duration (month), median $\pm$ range	51 $\pm$ 43	58 $\pm$ 59	0.82
Disease type: Extensive/ left-sided	7/3	7/1	0.58
In-patient/ out-patient	4/6	6/2	0.18
History of emergency hospitalization, mean times	1.1	2.0	0.02
Lichtiger index $\pm$ SD	8.2 $\pm$ 1.8	8.6 $\pm$ 1.5	0.44
UCEIS	5.3 $\pm$ 1.2	5.5 $\pm$ 0.9	0.68
Hemoglobin (g/dL)	12.2 $\pm$ 1.2	10.5 $\pm$ 1.1	0.05
Albumin (g/dL)	3.5 $\pm$ 0.6	3.1 $\pm$ 0.7	0.34
C-reactive protein (mg/dL)	1.0 $\pm$ 1.7	1.4 $\pm$ 1.0	0.13
Corticosteroid: Dependent/ refractory	5/5	3/5	0.99
Use of immunomodulator/ non-use	2/8	2/6	0.99
Previous biologics failure/ naïve	8/2	7/1	0.99
Previous biologics double or triple failure/ single failure or naïve	3/7	6/2	0.15
Previous calcineurin inhibitor failure/ naïve	2/8	6/2	0.05

**Table 3** Background characteristics of 8-week responders and non-responders

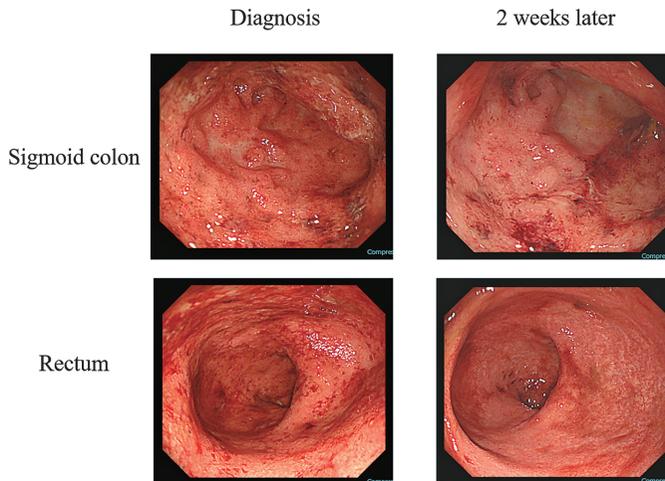
Variable	Responder	Non-responder	P-value
N	8	10	
Male/ Female	4/4	8/2	0.32
Age, median $\pm$ range	39 $\pm$ 15	33 $\pm$ 15	0.35
Body weight, kg, median $\pm$ range	54 $\pm$ 11	56 $\pm$ 7	0.62
Disease duration (month), median $\pm$ range	60 $\pm$ 48	54 $\pm$ 54	0.43
Disease type: Extensive/ left-sided	5/3	9/1	0.27
In-patient/ out-patient	2/6	8/2	0.05
History of emergency hospitalization, mean times	1.9	1.1	0.05
Lichtiger index $\pm$ SD	8.4 $\pm$ 1.4	8.1 $\pm$ 2.1	0.55
UCEIS	5.5 $\pm$ 0.8	5.4 $\pm$ 1.3	0.68
Hemoglobin (g/dL)	12.7 $\pm$ 2.0	10.3 $\pm$ 1.5	0.01
Albumin (g/dL)	3.6 $\pm$ 0.6	3.1 $\pm$ 0.7	0.09
C-reactive protein (mg/dL)	0.3 $\pm$ 0.6	1.8 $\pm$ 1.5	<0.01
Corticosteroid: Dependent/ refractory	3/5	5/5	0.99
Use of immunomodulator/ non-use	2/6	2/8	0.99
Previous biologics failure/ naïve	6/2	9/1	0.55
Previous biologics double or triple failure/ single failure or naïve	2/6	7/3	0.15
Previous calcineurin inhibitor failure/ naïve	1/7	7/3	0.02



**Fig. 3** Relation between baseline hemoglobin (Hb) and C-reactive protein (CRP) levels  
 Blue dots: 2-week responders, Red dots: non-responders

There were no serious adverse events during the observation period except for two patients. During the observation period, one patient stopped taking TOF because of severe vomiting on the sixth day of treatment. One patient developed a small abscess in the left ear with pain, which healed after antibiotic treatment; this patient continued taking TOF.

We experienced one patient whom TOF was effective, despite tumor necrosis factor (TNF) antibody and tacrolimus failure status. A 24-year-old female patient was admitted for the treatment of refractory UC. She developed watery diarrhea and bloody stool more than ten times. Her CRP and hemoglobin levels were 0.08 mg/dL and 9.0 g/dL, respectively. Her LI was 9 points and the endoscopic score was 8 points on the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) on the day of admission (Figure 4). She received infliximab and tacrolimus, which were partially effective, but did not achieve clinical remission. Then, TOF was administered, and her symptoms improved dramatically. Two weeks later, her LI was 6 points and the UCEIS score was 5 points (Figure 4). The admission duration was 61 days in total, with discharge occurring 15 days after TOF administration. The other 5 patients who failed with TNF antibody and tacrolimus also failed TOF before 16 weeks.



**Fig. 4** Endoscopic photographs in a tofacitinib effective case  
The Ulcerative Colitis Endoscopic Index of Severity score improved from 8 to 5 points in 2 weeks.

## DISCUSSION

The pathogenesis of UC is very complex, including genetic and environmental factors that can affect the outcome of medical treatment. Certainly, a wide array of cytokines is involved in the mucosal inflammatory reactions of UC. JAKs represent a family of intracellular, non-receptor tyrosine kinases that transfer cytokine-mediated signals via the JAK-STAT pathway.<sup>10</sup> TOF is a pan-JAK inhibitor lacking specificity for any JAK but is partially selective for multiple cytokines. Thus, TOF blocks JAK-1 and JAK-3 and, at high concentrations, tyrosine kinase 2 and JAK-2 pathways. Interestingly, TOF is rapidly absorbed after oral intake with a time to peak concentration of 30 min, thus allowing a more comfortable route of administration for the patient and a quicker onset than most other drugs used to treat inflammatory bowel diseases.<sup>11</sup>

Given the overlap between JAKs and interactions with STATs, and the association with more than one cytokine, it is certain that TOF is likely to affect several immunological pathways. Furthermore, a JAK inhibitor can block mediators of cytokines not dependent on the JAK-STAT signaling pathway; for example, indirectly affecting TNF by obstructing interferons. Because not all cytokines are pro-inflammatory (eg, some interleukins, such as IL-2 and IL-10, have anti-inflammatory functions), the wider impact of their inhibition may be complex. Based on such complicated effects involving the molecular mechanism of TOF in the human body, we reviewed the patients who were treated by TOF and clarified its characteristics and side effects.

The JAK-STAT signaling pathway is important for cytokines that regulate cellular immune and antibody-mediated responses. However, some other cytokines with a major role in the inflammatory network do not directly use the JAK-STAT pathway; examples include TNF, IL-1, and IL-17. Even if the inflammation profile of the patient is not dominated by TNF and not improved by treatment with a TNF- $\alpha$  antibody, TOF administration may be effective because of its different mechanism of action. For example, based on prior biologic use in patients with refractory rheumatoid arthritis, a good response to baricitinib, a JAK inhibitor, was reported.<sup>12</sup> In moderate and severe active UC, patients with prior exposure to the TNF antagonists, ustekinumab and TOF, were ranked highest for induction of clinical remission and were superior to vedolizumab and adalimumab (ustekinumab vs vedolizumab: odds ratio (OR), 5.99; 95% confidence interval (CI), 1.13–31.76; TOF vs vedolizumab: OR, 6.18; 95% CI, 1.003–8.00; ustekinumab vs adalimumab: OR, 10.71; 95% CI, 2.01–57.20; TOF vs adalimumab: OR, 11.05; 95% CI, 1.79–68.41; moderate confidence in all estimates).<sup>13</sup> In our study, the majority of patients (83.3%) were in the status of biologic failure. The British Society of Gastroenterology consensus guideline recommends that TOF can be used in induction and maintenance therapy of UC in patients where anti-TNF antibody treatment has failed (GRADE: strong recommendation, high-quality evidence; agreement: 91.1%).<sup>4</sup>

In our report of patients, TOF was effective when the CRP level was low and the hemoglobin level was > 12 g/dL. Our report included 55.5% of TOF-effective patients in 2 weeks; however, half of the patients stopped taking TOF within 8 weeks. The treatment continuation rate was inferior to that reported in previous studies. We considered that this may have been because our report included patients with acute, moderate, and severe UC, and with high CRP levels. Thus, when choosing TOF for the treatment of acute, moderate, and severe UC, a lower CRP level should be considered. Alternatively, steroid treatment, fasting, or some anti-inflammation strategy may be tried prior to TOF.

Real-world data for effectiveness of TOF have been demonstrating by several articles<sup>14–17</sup> and our case reports were comparable with them (Table 4), however, current results are preliminary and should be confirmed by larger cohort studies. In addition, any biologic antibody drug is usually introduced at the same time as TOF. Global clinical trials have shown the efficacy of biologics for introduction therapy of UC.<sup>18</sup> However, those studies involving Japanese patients sometimes had a gap in the results.<sup>8,9</sup> A network meta-analysis in Japanese patients showed that infliximab and vedolizumab had the highest odds for inducing a clinical response, remission, and mucosal healing. Golimumab and vedolizumab had numerically higher odds of achieving efficacy in the maintenance phase.<sup>19</sup> Overall, few randomized controlled trials on UC treatments have been published. Thus, clinicians must select the best medicine for treating refractory UC with reference to global trials, real-world data, meta-analyses, and their own experience.

TOF can induce serious side effects, namely severe anemia, herpes zoster infection, increased serum lipid levels, and thrombosis. Although patients in our report did not have any serious adverse events, the safety of TOF should be evaluated by long-term observation.

**Table 4** Tofacitinib effective and remission rates for moderate to severe ulcerative colitis in real-world data

Country	year	N	2 weeks (%)		4 weeks (%)		8 weeks (%)		12 weeks (%)		14 weeks (%)		16 weeks (%)		24 weeks (%)	
			Effective	Remission	Effective	Remission	Effective	Remission	Effective	Remission	Effective	Remission	Effective	Remission	Effective	Remission
Germany <sup>14</sup>	2020	38			47.4	28.9									36.1	19.4
Japan <sup>15</sup>	2021	30			40	20	47	40	50	43					45	41
France <sup>16</sup>	2020	38									44.8	31.6			36.9	31.6
Spain <sup>17</sup>	2021	113			40	16	60	31					57	32		
This study	2021	18	55.5	22.2	38.8	33.3							38.8	38.8		

This report has several limitations. Mayo score is most often used to assess UC disease activity. On the other hand, our unit usually uses LI instead of Mayo score because medical chart software provides us LI only. Therefore, this study used LI.

In conclusion, TOF may provide an early response to refractory UC. This case report shows preliminary results of the introduction ability of TOF, even for TNF antibody and tacrolimus failure patients.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

- 1 Fukuda T, Naganuma M, Kanai T. Current new challenges in the management of ulcerative colitis. *Intest Res.* 2019;17(1):36–44. doi:10.5217/ir.2018.00126.
- 2 Singh S, Allegretti JR, Siddique SM, Terdiman JP. AGA technical review on the management of moderate to severe ulcerative colitis. *Gastroenterology.* 2020;158(5):1465–1496.e17. doi:10.1053/j.gastro.2020.01.007.
- 3 Amiot A, Serrero M, Peyrin-Biroulet L, et al. One-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multicentre cohort study. *Aliment Pharmacol Ther.* 2017;46(3):310–321. doi:10.1111/apt.14167.
- 4 Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut.* 2019;68(Suppl 3):s1–s106. doi:10.1136/gutjnl-2019-318484.
- 5 Meyer DM, Jesson MI, Li X, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. *J Inflamm(Lond).* 2010;7:41. doi:10.1186/1476-9255-7-41.
- 6 Vong C, Martin SW, Deng C, et al. Population Pharmacokinetics of Tofacitinib in Patients With Moderate to Severe Ulcerative Colitis. *Clin Pharmacol Drug Dev.* 2021;10(3):229–240. doi:10.1002/cpdd.899.
- 7 Suzuki Y, Watanabe M, Matsui T, et al. Tofacitinib as induction and maintenance therapy in Japanese patients with active ulcerative colitis. *Inflamm Intest Dis.* 2019;4(4):131–143. doi:10.1159/000502144.
- 8 Pfizer Inc. [Internet]. XELJANZ prescribing information. Available from: <http://labeling.pfizer.com/ShowLabeling.aspx?id=959>. Accessed January 10, 2021.
- 9 Pfizer Inc. [Internet]. XELJANZ summary of product characteristics. uk/emc/product/2500/smpc. Available from: <https://www.medicines.org>. Accessed January 10, 2021.
- 10 Kisseleva T, Bhattacharya S, Braunstein J, Schindler CW. Signaling through the JAK/STAT pathway, recent advances and future challenges. *Gene.* 2002;285(1–2):1–24. doi:10.1016/s0378-1119(02)00398-0.
- 11 D'Amico F, Parigi TL, Fiorino G, Peyrin-Biroulet L, Danese S. Tofacitinib in the treatment of ulcerative colitis: efficacy and safety from clinical trials to real-world experience. *Ther Adv Gastroenterol.* 2019;12:1756284819848631. doi:10.1177/1756284819848631.
- 12 Genovese MC, Kremer JM, Kartman CE, et al. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. *Rheumatology(Oxford).* 2018;57(5):900–908. doi:10.1093/rheumatology/kex489.
- 13 Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. *Clin Gastroenterol Hepatol.* 2020;18(10):2179–2191.e6. doi:10.1016/j.cgh.2020.01.008.
- 14 Hoffmann P, Globig AM, Thomann AK, et al. Tofacitinib in Treatment-Refractory Moderate to Severe Ulcerative Colitis: Real-World Experience from a Retrospective Multicenter Observational Study. *J Clin Med.* 2020;9(7):2177. doi:10.3390/jcm9072177.
- 15 Shimizu H, Fujii T, Hibiya S, et al. Rapid prediction of 1-year efficacy of tofacitinib for treating refractory ulcerative colitis. *Intest Res.* 2021;19(1):115–118. doi:10.5217/ir.2020.00030.
- 16 Lair-Mehiri L, Stefanescu C, Vaysse T, et al. Real-world evidence of tofacitinib effectiveness and safety in patients with refractory ulcerative colitis. *Dig Liver Dis.* 2020;52(3):268–273. doi:10.1093/ecco-jcc/jjaa145.
- 17 Chaparro M, Garre A, Mesonero F, et al. Tofacitinib in Ulcerative Colitis: Real-world Evidence From the

- ENEIDA Registry. *J Crohns Colitis*. 2021;15(1):35–42. doi:10.1093/ecco-jcc/jjaa145.
- 18 Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019;381(13):1201–1214. doi:10.1056/NEJMoa1900750.
- 19 Hibi T, Kamae I, Pinton P, et al. Efficacy of biologic therapies for biologic-naïve Japanese patients with moderately to severely active ulcerative colitis: a network meta-analysis. *Intest Res*. 2021;19(1):53–61. doi:10.5217/ir.2019.09146.