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Real-Life Efficacy of Tofacitinib in Various Situations in Ulcerative Colitis: A Retrospective Worldwide Multicenter Collaborative Study

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Background and Aims: Tofacitinib (TFB) appears to be effective in the treatment of ulcerative colitis (UC); however, available real-world studies are limited by cohort size. TFB could be an option in the treatment of acute severe ulcerative colitis (ASUC). We aimed to investigate efficacy and safety of TFB in moderate-to-severe colitis and ASUC.

Methods: This retrospective, international cohort study enrolling UC patients with ≥6-week follow-up period was conducted from February 1 to July 31, 2022. Indications were categorized as ASUC and chronic activity (CA). Baseline demographic and clinical data were obtained. Steroid-free remission (SFR), colectomy, and safety data were analyzed.

Results: A total of 391 UC patients (median age 38 [interquartile range, 28-47] years; follow-up period 26 [interquartile range, 14-52] weeks) were included. A total of 27.1% received TFB in ASUC. SFR rates were 23.7% (ASUC: 26.0%, CA: 22.8%) at week 12 and 41.1% (ASUC: 34.2%, CA: 43.5%) at week 52. The baseline partial Mayo score (odds ratio [OR], 0.850; $P = .006$) was negatively associated with week 12 SFR, while biologic-naïve patients (OR, 2.078; $P = .04$) more likely achieved week 52 SFR. The colectomy rate at week 52 was higher in ASUC group (17.6% vs 5.7%; $P < .001$) and decreased with age (OR, 0.94; $P = .013$). A total of 67 adverse events were reported, and 17.9% resulted in cessation of TFB. One case of thromboembolic event was reported.

Conclusions: TFB is effective in both studied indications. TFB treatment resulted in high rates of SFR in the short and long terms. Higher baseline disease activity and previous biological therapies decreased efficacy. No new adverse event signals were found.

Key Words: tofacitinib, acute severe ulcerative colitis, moderate-to severe ulcerative colitis

Key Messages

What is already known?

In real-life cohorts, data are lacking regarding the efficacy and safety of the orally administered tofacitinib in ulcerative colitis; therefore, we conducted an international, multicenter cohort study. Efficacy is already shown in patients with chronic activity; however, there is a paucity of data on use of tofacitinib in acute severe ulcerative colitis (ASUC). In addition, our data confirm that biologic-naïve patients have better response to the therapy. Based on our data, tofacitinib without other risk factors does not increase thromboembolic events.

What is new here?

Based on our results, tofacitinib is efficacious in ASUC colitis as well. Higher baseline clinical activity, older age, and male sex may decrease efficacy.

How can this study help patient care?

Tofacitinib could be used as a rescue treatment in ASUC. Tofacitinib admission should be considered as a first-line treatment.

Introduction

Advances in therapeutic targets, monitoring tactics, and biologic agents with targeted mechanisms of action have not yet brought the therapeutic breakthrough in the treatment of ulcerative colitis (UC) that we had hoped for. This is partly explained by the lack of predictive markers, and thus inadequate therapeutic choice; partly by the limited use of the multiomic approach, but especially for newer therapies; and partly by the insufficient number of patients, and thus incomplete data.

The orally administered small molecule innovative targeted tofacitinib (TFB) is effective as a monotherapy in biologic-naïve UC patients, but due to its cost and the different funding rules between countries, it is used more frequently in the second line.[1,2] Based on meta-analyses, the pan-JAK inhibitor TFB[3] appears to be effective in UC also in a higher therapeutic line.[2,4,5] TFB is a fast-acting treatment, with short half-life; consequently, in addition to chronic refractory UC, TFB seems to be effective in acute severe UC (ASUC) as well.[6-9] This is supported by previous findings, in which TFB was proved to be effective in steroid-refractory ASUC in biologic-experienced patients.[6,7,10,11] However, safety concerns have been raised,[12] notably the higher incidence of deep vein thrombosis and pulmonary embolism compared with tumor necrosis factor α inhibitors[13]; nonetheless, the higher incidence of thrombotic events in patients with rheumatoid arthritis was not reproduced in UC studies.[14] Both safety and efficacy data are lacking in real-life clinical studies.

For this reason, we organized an international collaboration to conduct the largest-ever retrospective study to collect patient numbers with targeted outcome data. We aimed to study steroid-free remission (SFR), colectomy-free survival, primary nonresponse, and loss of response in different indications of

UC (ASUC and chronic activity [CA]). In addition, we aimed to identify predictive factors of efficacy in different outcomes and to assess the prevalence of adverse events (AEs).

Methods

Study Design and Settings

A retrospective, international, multicenter cohort study was conducted including 23 tertiary referral centers in Europe, Canada, and Israel. Data collection with collaborating centers was performed between February 1 and July 31, 2022. All investigators had to complete the unified database via medical record systems. The treatment protocols differ between the centers due to various funding protocols in different countries; consequently, tofacitinib is not allowed as a rescue treatment in ASUC or as a first-line treatment in UC in some of the involved centers. All centers were tertiary referral centers.

Participants

Consecutive patients with UC ≥18 years of age receiving tofacitinib were enrolled in our cohort. The indication of TFB was classified in to ASUC according to the Truelove-Witts criteria[15] or CA/steroid dependence. Patients with a follow-up duration of <6 weeks were excluded. In addition, patients with previous colectomy + ileal pouch–anal anastomosis or not obvious indication (marked as other) were excluded from further analysis.

Data Collections

The baseline demographic and clinical information comprised gender, age at UC diagnosis, date of UC diagnosis, disease extension, and severity at diagnosis. The disease phenotype was evaluated based on the Montreal classification.[16] Clinical data comprised previous colectomy, extraintestinal manifestations, previous biological treatments (infliximab [IFX], adalimumab, golimumab, vedolizumab, ustekinumab [UST]), concomitant corticosteroid or thiopurine therapy, and indication of tofacitinib induction. Clinical (partial Mayo score [pMayo]), endoscopic (Mayo endoscopic score [eMayo]), and biochemical activity (C-reactive protein [CRP] and fecal calprotectin) and laboratory parameters (hemoglobin, serum iron, ferritin, transferrin saturation, thrombocyte count, cholesterol, triglyceride, and liver enzymes [aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase [GGT], and alkaline phosphatase]) were collected at week 0, weeks 2 to 6, weeks 8 to 14, weeks 22 to 30, and weeks 48 to 56.

The dose of TFB, the number and the type of AEs, the need of corticosteroid and/or immunomodulator treatment, hospitalization, and colectomy rates were obtained during the follow-up period as well.

Outcomes

The primary outcome was SFR rates at weeks 12 and 52. SFR was defined as a pMayo <2 and CRP <5 mg/L with no rectal bleeding and with no concomitant corticosteroid therapy.

Secondary outcomes were colectomy rates at weeks 12 and 52, primary nonresponse (PNR) rates, loss-of-response (LOR) rates, and persistence of the treatment. PNR was defined as <30% decrease in pMayo or ≥2 bleeding score at week 12, and LOR was defined as need of dose optimization or prolonged induction dose. We compared the secondary outcomes in ASUC and CA. The predictors of SFR, PNR, LOR, and colectomy-free survival rates were analyzed.

The change in the clinical endoscopic activity index (pMayo, eMayo [endoscopic remission was defined as eMayo ≤1]), laboratory parameters monitoring disease activity, iron homeostasis, lipid metabolism, and liver enzymes were compared between visits during the admission of TFB. Liver enzyme elevation was considered as a level at least 1.5 times as high as normal.

The severity of infections was graded by the need of antibiotic or antiviral therapy. Severity of an AE was classified by the need of cessation of the treatment or dose reduction of therapy. AEs were also analyzed in the relation with concomitant steroid therapy. Definitions are shown in the Supplementary Appendix.

Statistical Methods

Statistical tests were performed using R statistical software version 4.1.1 (R Foundation for Statistical Computing) and SPSS software version 24 (IBM Corporation). Descriptive statistics are interpreted as median and interquartile range (IQR) or mean ± SD for continuous variables or numbers with percentage for categorical variables. Handling missing variables, the outcomes were analyzed with the intention-to treat viewpoint. Change in continuous variables during the follow-up period was assessed with repeated-measures analysis of variance. Pearson's chi-square tests were performed to determine difference in frequency of categorical data. After identification of possible predictive factors of primary outcomes and secondary outcomes (colectomy, and PNR and LOR rates), multivariate logistic regression models were constructed (overall model fit was assessed by the Nagelkerke R^2 and goodness of fit was determined by performing the Hosmer-Lemeshow test). Kaplan-Meyer analysis was performed to describe persistence on therapy and to compare the week 52 colectomy-free survival rate between ASUC and CA groups. Patients with incomplete follow-ups were included in the analysis as censored data. Values of $P < .05$ were considered statistically significant.

Ethical Approval

Ethical approval for the study was obtained from the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged (39/2022-SZTE RKEB; 5153). The research was carried out according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Results

Baseline Characteristics

In total, 391 UC patients (male-to-female ratio of 208:183; median follow-up period of 26 [IQR, 14-52] weeks) were included. A total of 47 (12.0%) patients were from Israel, 24 (6.1%) were from Canada, and 320 (81.8%) were from Europe. The median age was 38 (IQR, 28-47) years and the median duration of disease was 7 (IQR, 4-12) years. The flowchart of included patients is presented in Figure 1.

Almost two-thirds of the patients had pancolitis (64.7%). The main indications of TFB were CA (70.1%) and ASUC (27.1%). Further 2.8% of patients received TFB marked as

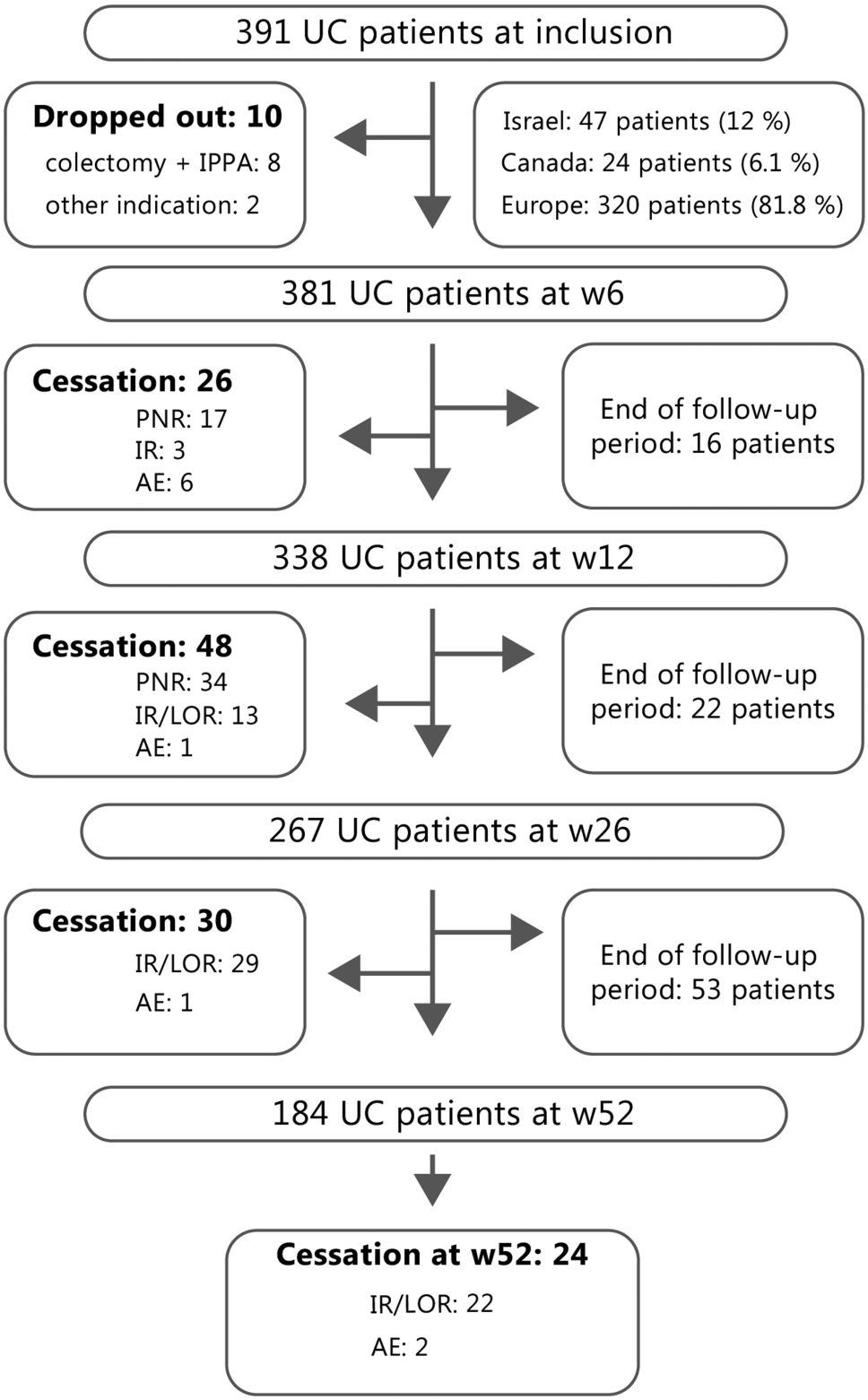

Figure 1. Study flowchart of included patients. AE, adverse event; IPAA, ileal pouch–anal anastomosis; IR, ineffective response; LOR, loss of response; PNR, primary nonresponse; UC, ulcerative colitis; w, week.

other indication, specified as colectomy + ileal pouch–anal anastomosis surgeries in 2.6% of the patients; thus, they received TFB due to pouchitis, and a further 0.2% was not specified. All patients received an induction dose of 20 mg/d. The vast majority of the cohort had received anti-tumor necrosis factor treatment previously (83.6%; IFX: 74.9%, adalimumab: 39.1%, and golimumab: 0.8%), and two-thirds of the patients had received vedolizumab (64.2%). TFB was used in biologic-naïve patients in 11.8% of patients. Baseline demographic characteristics by groups are summarized in Table 1.

Table 1. Baseline demographic and clinical data of the cohort.

Characteristics	Total number of patients (n = 391)	ASUC (n = 106)	Chronic activity (n = 274)
Age, y	38 (28-47)	38 (29-48)	37 (28-46)
Male	208 (53.2)	45 (42.5)	156 (56.9)
pMayo	7 (5-8)	7 (5-8)	6 (5-8)
eMayo	3 (2-3)	3 (3-3)	3 (2-5)
CRP, mg/L	19.3 ± 26.6	35.3 ± 36.82	13.5 ± 18.72
Fecal calprotectin, µg/g	1559.7 ± 1345.9	2046.5 ± 1282.7	1361.9 ± 1351.8
Disease duration, y	7 (4-12)	8 (5-12)	7 (3-12)
Follow-up period, wk	26 (14-52)	26 (14-52)	39 (14-52)
Disease extension[a]			
Proctitis	10 (2.6)	3 (2.8)	7 (2.6)
Left-sided colitis	125 (32.7)	34 (32.1)	90 (32.8)
Pancolitis	247 (64.7)	69 (65.1)	177 (64.6)
Previous colectomy + IPAA	9 (2.3)	—	—
Follow-up period, wk	26 (14-52)	26 (14-52)	39 (17-52)
Baseline concomitant treatment			
5-ASA	206 (52.6)	55 (51.9)	148 (54.0)
Budesonide-MMX	58 (14.8)	20 (18.9)	36 (13.1)
Azathioprine	17 (4.3)	5 (4.7)	11 (4.0)
Methotrexate	7 (1.8)	2 (1.9)	5 (1.8)
Cyclosporine	6 (1.5)	1 (0.9)	5 (1.8)
Prednisolone/methylprednisolone	179 (45.7)	52 (49.1)	123 (44.9)
Previous biologic treatments			
IFX	293 (74.9)	74 (69.8)	209 (76.3)
ADA	153 (39.1)	37 (34.9)	109 (39.8)
GOL	3 (0.8)	1 (0.9)	2 (0.7)
VDZ	251 (64.2)	64 (60.4)	179 (65.3)
UST	25 (6.4)	9 (8.5)	13 (4.7)
Therapeutic line			
Biologic naive	46 (11.8)	21 (19.8)	25 (9.1)
Second line	89 (22.8)	22 (20.8)	65 (23.7)
Third line	147 (37.6)	31 (29.2)	113 (41.2)
Fourth line	97 (24.8)	28 (26.4)	65 (23.7)
Fifth line	12 (3.1)	4 (3.8)	6 (2.2)
Extraintestinal manifestation	85 (21.7)	22 (20.8)	63 (23.0)
Arthritis	57 (14.6)	15 (14.2)	40 (14.6)
Erythema nodosum/pyoderma gangrenosum	7 (1.8)	1 (0.9)	4 (1.5)
Uveitis	2 (0.5)	1 (0.9)	1 (0.4)
PSC	16 (4.1)	1 (0.9)	13 (4.7)

Values are median (interquartile range), n (%), or mean ± SD.
Abbreviations: ADA, adalimumab; ASUC, acute severe ulcerative colitis; CRP, C-reactive protein; eMayo, Mayo endoscopic score; GOL, golimumab; IFX, infliximab; IPAA, ileal pouch–anal anastomosis; pMayo, partial Mayo score; PSC, primary sclerosing cholangitis; UST, ustekinumab; VDZ, vedolizumab; 5-ASA, 5-acetylsalicylic acid.
[a]Montreal classification.

Baseline clinical activity indexes were the following: median pMayo was 7 (IQR, 5-8) and median eMayo was 3 (IQR, 2-3). Biochemical markers showed elevated CRP (19.3 ± 26.6 mg/L) and fecal calprotectin (measured in 189 [48.3%] patients; mean 1559.7 ± 1356.0 µg/g). At the initiation of TFB, 45.7% of patients were on systemic corticosteroids. The change in clinical indexes and laboratory parameters are summarized in the Supplementary Appendix.

Corticosteroid-Free Remission Rates

In total, 81 (23.7%) patients achieved SFR at week 12 and 117 (41.1%) patients achieved SFR at week 52. The SFR rates at week 12 were 26.0% in the ASUC group and 22.8% in the CA group, and no difference was observed between groups ($P = .522$). The SFR rates at week 52 were 34.2% in the ASUC group and 43.5% in the CA group, and no difference was observed between groups ($P = .352$). The sustained steroid-free clinical remission rate was 17.9% (Figure 2).

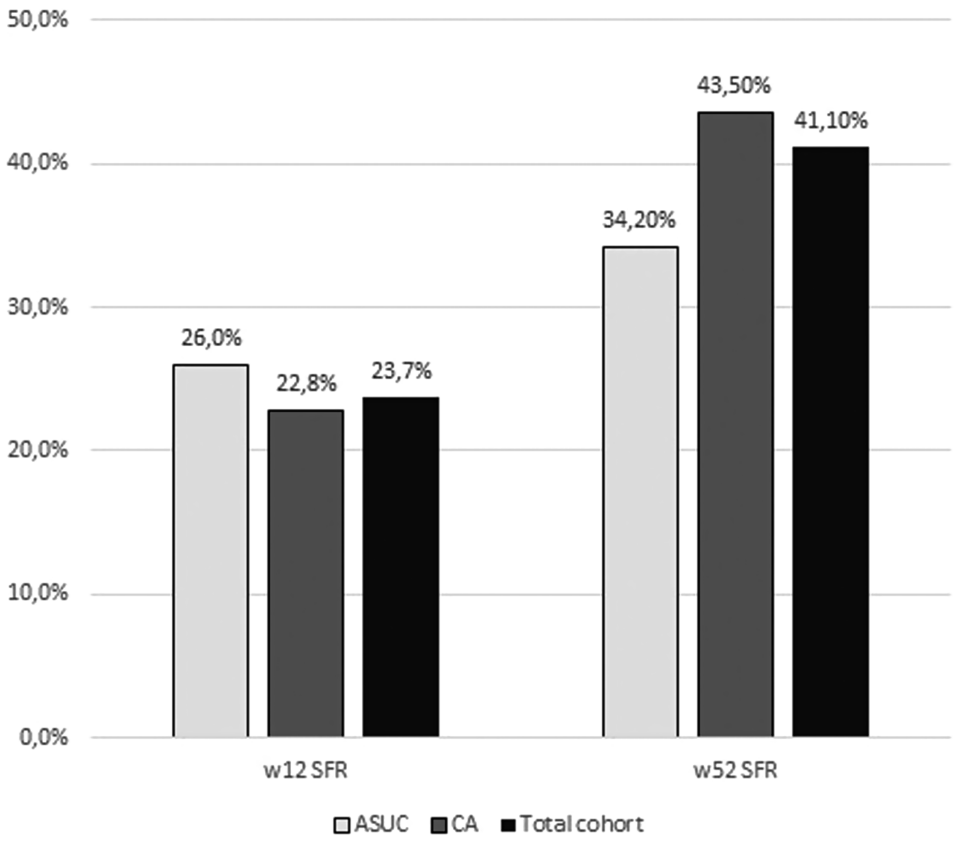

Figure 2. Week 12 (w12) and w52 steroid-free remission (SFR) rates in our cohort. ASUC, acute severe ulcerative colitis; CA, chronic activity.

In the total cohort, a higher pMayo at baseline was negatively associated with the week 12 SFR (odds ratio [OR], 0.850; $P = .006$), such as in the ASUC group (OR, 0.765; $P = .012$). In the CA group, male sex (OR, 0.503; $P = .04$) and baseline CRP (OR, 0.962; $P = .031$) decreased the week 12 SFR rates (Table 2).

Both in the ASUC group (OR, 5.378; $P = .004$) and in the total cohort (OR, 2.078; $P = .04$), biologic-naïve patients more likely achieved week 52 SFR, while in the CA group older age (OR, 1.026; $P = .016$) seemed to be beneficial (Table 2). A higher proportion of patients achieved 52-week SFR who received TFB in lower therapeutic line, close to the significance level ($P = .061$) (Supplementary Appendix).

Colectomy Rates, PNR, LOR, and Persistence of Therapy

In total, the colectomy rate was 4.6% at week 12, and no predictive factor was identified. In the ASUC group, the colectomy rate was higher (7.5% compared with 3.5% in the CA group); however, the difference was not significant ($P = .115$). No factor was found to be associated with the colectomy rate either in the ASUC or in the CA group.

The week 52 colectomy rate was 8.0% in total, and the colectomy rate was significantly higher in the ASUC group compared with the CA group (17.6% vs 5.7%; $P = .005$). Based on the survival analysis (Figure 3), more patients had colectomy during the follow-up period in the ASUC group ($P = .008$). In the total cohort, ASUC indication (OR, 4.829; $P < .001$) increased the colectomy rate at week 52, whereas older age decreased it (OR, 0.946; $P = .013$). No specific predictive factors were identified in the CA and ASUC groups (Table 2).

The PNR rate was 21.5% in the total cohort. The frequency of PNR was higher in the ASUC group (36.5% compared with 24.5%); however, it was not significant ($P = .175$). No marker was found to be associated with higher a PNR rate.

In total, the prevalence of LOR was 54.1%, and it was more common in the CA group (58.5%) compared with the ASUC group (41.0%) ($P = .006$). In the LOR group, dose optimization was effective in 69 (37.5%) patients. No predictive factor was identified. At week 52, the dosage was distributed as follows: 5 mg/d in 7 (3.9%) patients, 10 mg/d in 94 (52.8%) patients, 20 mg/d in 75 (42.1%) patients, 25 mg/d in 1 (0.6%) patient, and 30 mg/d 1 in (0.6%) patient.

Patients with a CA indication seemed to remain on TFB for a longer period of time (35.3 ± 17.7 weeks) compared with patients with ASUC (29.6 ± 18.8 weeks) ($P = .07$) (Figure 4).

Change in Clinical and Biochemical Activity

The clinical activity index decreased significantly ($P < .001$) from a baseline level of 6.2 ± 2.2 to 3.5 ± 2.7 at week 12 and 1.8 ± 2.1 at week 52. Changes in pMayo are presented in the Supplementary Appendix.

Markers of biochemical activity decreased significantly during the treatment period. Baseline CRP was 19.34 ± 26.59 µg/mL, and it decreased to 10.15 ± 18.86 µg/mL at week 12 and 6.42 ± 11.46 µg/mL at week 52 ($P < .001$). Fecal calprotectin decreased from a baseline level of 1559.7 ± 1355.96 mg/g to 663.73 ± 654.08 mg/g at week 12 and 313.76 ± 401.47 mg/g at week 52 ($P < .001$).

Table 2. Logistic regression to predict week 12 and 52 SFR, and week 52 colectomy rate in the cohort[a].

			OR	SE	z	*P* value	95% CI
SFR predictive factors							
Week 12	ASUC	Constant	1.658	0.682	0.741	.459	0.426-6.394
		Baseline pMayo	0.765	0.107	-2.502	.012[b]	0.616-0.940
	CA	Constant	0.589	0.300	-1.763	.078	0.324-1.058
		Male	0.503	0.334	-2.058	.040[b]	0.260-0.967
		Baseline CRP	0.962	0.018	-2.163	.031[b]	0.926-0.992
	Total cohort	Constant	0.785	0.367	-0.658	.510	0.377-1.602
		Baseline pMayo	0.850	0.059	-2.764	.006[b]	0.756-0.954
Week 52	ASUC	Constant	0.341	0.299	-3.599	<.001[b]	0.190-0.613
		Biologic naive	5.378	0.589	2.856	.004[b]	1.695-17.061
	CA	Constant	0.290	0.434	-2.855	.004[b]	0.124-0.678
		Age	1.026	0.011	2.415	.016[b]	1.005-1.047
	Total cohort	Constant	0.632	0.130	-3.525	<.001[b]	0.489-0.815
		Biologic naive	2.078	0.357	2.052	.040[b]	1.033-4.180
Colectomy rate predictive factors							
Week 52	Total cohort	Constant	0.374	0.763	-1.288	.198	0.084-1.670
		ASUC	4.829	0.501	3.144	.002[b]	1.810-12.886
		Age	0.946	0.022	-2.482	.013[b]	0.906-0.988

Abbreviations: ASUC, acute severe ulcerative colitis; CA, chronic activity; CI, confidence interval; eMayo, Mayo endoscopic score; OR, odds ratio; pMayo, partial Mayo score; SFR, steroid-free remission.
[a]After identification of possible predictive factors, multivariate logistic regression models were constructed.
[b]$P < .05$ was considered as statistically significant result.

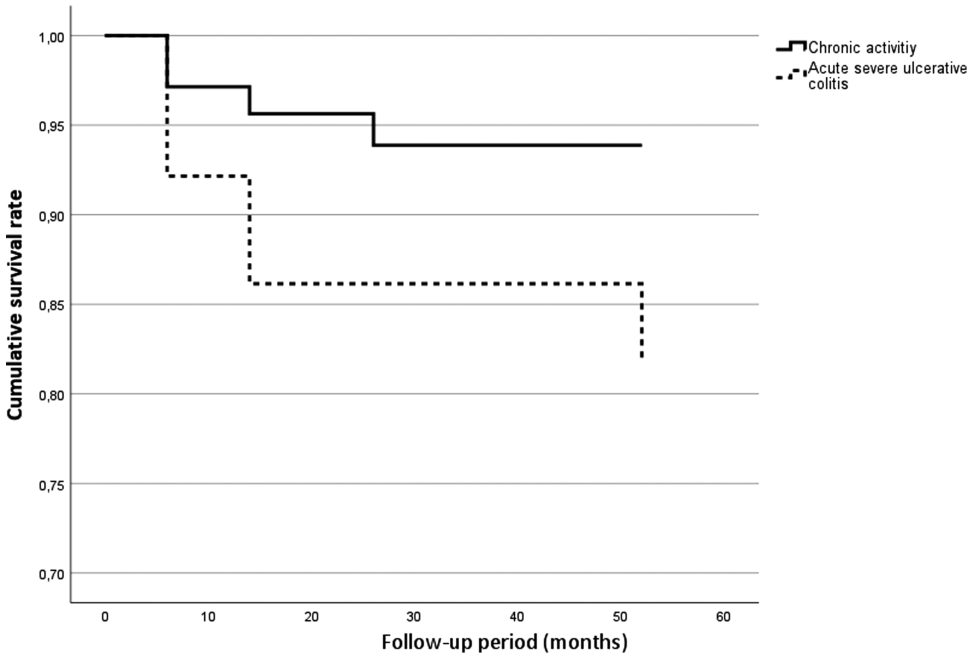

Figure 3. Survival analysis regarding week 52 colectomy rates between the chronic activity and acute severe ulcerative colitis groups ($P = .06$).

The level of serum albumin increased ($P < .001$) as well during the treatment, from a baseline level of 38.6 ± 8.7 g/L to 43.1 ± 6.1 g/L at week 52. An increase was already observed after 6 weeks ($P < .001$), as albumin was 41.2 ± 5.4 g/L. Furthermore, the platelet level altered during the treatment ($P = .002$), as it decreased from a baseline level of 372.9 ± 136.0 g/L to 311.2 ± 109.8 g/L at week 52. The changes in laboratory parameters are presented in Supplementary Appendix.

Endoscopic Response

Colonoscopy was performed in 312 (79.8%) cases before and in 242 cases after the admission of TFB (mean 22.5 ± 16.1 weeks). In total, 12 (3.9%) patients were in endoscopic

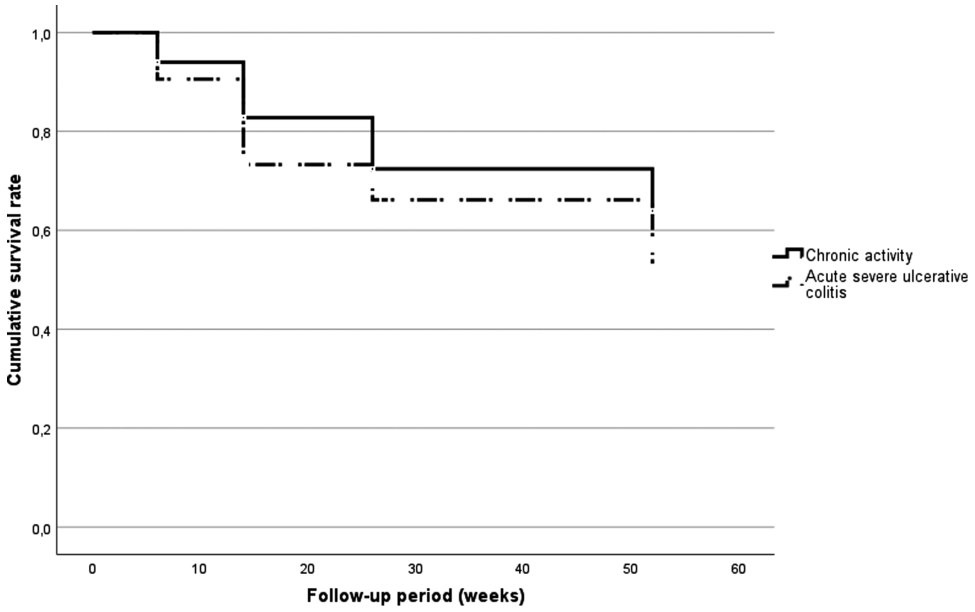

Figure 4. Drug persistence between various indications of tofacitinib ($P = .056$).

remission before TFB treatment, whereas 92 (43.0%) patients were in remission at the follow-up endoscopy, based on eMayo ($P < .001$). Changes in eMayo are presented in the Supplementary Appendix.

Adverse Events

In total, 67 (17.1%) AEs were reported during the study. Based on our definition, 17.9% of them (12 cases) were severe AEs (3.1% of the total cohort). In 6 (50.0%) cases, the cessation of TFB was due to severe infection (2 herpes zoster, 1 pneumonia, 1 perianal abscess, 1 carbuncle, and 1 *Clostridioides difficile* infection), while in the other half of the cases, it was dyspnea (with no evidence of thromboembolic complications), vertigo, nausea, gastric pain, and skin rash (not specified as urticaria).

A total of 25 (6.4%) patients had an infection during TFB. The 3 most common infectious diseases were herpes zoster (24.0%), pneumonia (16.0%), and *Clostridioides difficile* infection (16.0%). The infection rate was not influenced by concomitant steroid therapy ($P = .847$).

Two (0.5%) patients were reported to have malignant diseases (melanoma and cholangiohepatic adenocarcinoma) during the administration of TFB therapy. Only 1 (0.25%) patient had a pulmonary venous thromboembolic event; however, this patient had cholangiohepatic adenocarcinoma as well besides primary sclerosing cholangitis, which was diagnosed nearly after 1 year of treatment. This patient ultimately passed away due to the carcinoma. No more fatal events were reported.

The level of serum cholesterol was altered during the treatment ($P = .006$), as baseline 4.8 ± 1.2 mmol/L increased to 5.5 ± 3.6 mmol/L. However, no similar change was observed in the triglyceride level (baseline 1.26-1.30 mmol/L at week 52; $P = .229$).

In addition, abnormal liver functions were also observed in a few cases, as 12 (3.1%) patients had novum glutamate oxaloacetate transaminase/glutamate pyruvate transaminase liver enzyme elevation, while 6 (1.5%) patients had novum GGT elevation. There was no overlap between these patients. Liver enzyme elevation was above 1.5-fold in 16 (88.9%) cases, and in 2 cases it was above 3-fold (in 1 patient, the dose of TFB was reduced, while in the other case, statin therapy was initiated). Concomitant corticosteroid administration was not associated with elevated liver enzymes ($P = .621$). In total, no significant change was observed regarding the level of liver enzymes during the treatment period.

The AEs were mostly self-limiting, although in some cases, certain interventions were needed. We wish to highlight that all AEs were reversible. Moderate AEs resulting in dose reduction or admission of specific therapeutic agent occurred in 6 (14.3%) cases and moderate infections occurred in 13 (52.0%) cases. Cessation of the TFB treatment was needed in 12.0% and dose reduction was needed in 8.0%, or with specific treatment for the AE (Table 3).

Discussion

Our international, retrospective, multicenter study has the largest study population so far: it is comparable to the Global Clinical Programme with 1157 patients[17] and to a real-life meta-analysis with 1162 patients.[2] To our knowledge, our study is the first to compare the efficacy of TFB in different indications of UC (CA, rescue therapy); furthermore, it investigated predictive factors for SFR, colectomy, PNR, and LOR as well. So far, only few adult and pediatric patients have been reported to receive TFB treatment with rescue therapy indication.[18-20]

In our study, the week 12 SFR rate was 23.7%, in accordance with the week 16 to 26 SFR rate of 25.0% in the meta-analysis conducted by Lucaciu et al,[21] which was lower than the real-life meta-analysis of 44.3% conducted by Taxonera et al[2] but exceeded the week 8 remission result of the OCTAVE 1 and 2 trials of 18.5% and 16.6%, respectively.[22] In our study, early efficacy did not differ between the CA and ASUC groups. Higher clinical activity reduced the chance of achieving week 12 SFR, whereas in CA group, higher CRP and male sex were negative predictors, in addition, older age was associated with increased chance of achieving week 52 SFR in CA. Male sex has previously been associated with

Table 3. All adverse events in the cohort.

	Adverse events	Severe	Moderate
Infectious diseases			
Total	25 (6.4)	—	—
Pneumonia	4 (1.0)	1 (25.0)	3 (75.0)
Herpes zoster	6 (1.5)	2 (33.3)	4 (66.7)
Herpes labialis	2 (0.5)	—	—
Clostridioides difficile	4 (1.0)	1 (25.0)	3 (75.0)
COVID-19	1 (0.26)	—	—
Perianal abscess	3 (0.8)	1 (33.3)	2 (66.7)
Acne	2 (0.5)	1 (50.0)	1 (50.0)
Gastroenteritis	3 (0.8)	-	-
Malignant disorder			
Total	2 (0.5)	—	—
Melanoma	1 (0.26)	—	—
Cholangiohepatic adenocarcinoma	1 (0.26)	—	1 (100.0)
Cardiovascular/hemorheology			
Total	2 (0.5)	—	—
Hypertension	1 (0.26)	—	1 (100.0)
Pulmonary embolism	1 (0.26)	—	1 (100.0)
Liver functions			
Total	18 (4.9)	—	—
Elevated GOT/GPT	12 (3.1)	—	2 (16.7)
Elevated GGT	6 (1.5)	—	—
Other			
Total	20 (5.1)	—	—
Dyspnea	1 (0.26)	1 (100.0)	—
Arthralgia	8 (2.0)	—	1 (12.5)
Skin rash	5 (1.3)	2 (40.0)	—
Headache	1 (0.26)	—	—
Gastric pain/dyspepsia	3 (0.8)	1 (33.3)	—
Nausea	1 (0.26)	1 (100.0)	—
Vertigo	1 (0.26)	1 (100.0)	—

Values are n (%).
Abbreviations: GGT, γ-glutamyl transferase; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase.

reduced SFR rates in a meta-analysis.[21] The ENEIDA registry (Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales) has identified baseline pMayo as the only short-term predictor.[23]

Based on our findings, TFB is remarkably efficient as a rescue therapy in ASUC, as the week 12 colectomy rate was 7.5%, and the week 52 was 17.6%. Compared with international data, both IFX and cyclosporine had poorer short and long term outcome. Based on the study conducted by Laharie et al,[24] the 98-day colectomy rates were 17% in the cyclosporine and 21% in the IFX group, while Williams et al[25] found the 3-month colectomy rates to be 29% in IFX and 30% in cyclosporine. In this study, the 12-month outcome was also higher than experienced in our cohort, as in IFX it was 35%, and in cyclosporine it was 41%. These findings can be confirmed as well by a South Korean cohort,[26] in which the 3-month colectomy rate was 26.1% in cyclosporine and 13.3% in IFX. However, the 12-month colectomy rate was comparable to our study in the case of IFX (18.4%). Nevertheless, we emphasize the favorable effect of TFB knowing that the majority of the patients (almost 90%) did not receive it as a first-line treatment. In addition, our study found that biologic-naïve patients more likely achieved SFR in the total cohort, especially in patients with ASUC, and TFB admission in lower therapeutic line seemed to be more effective in achieving week 52 SFR. These results are confirmed by a meta-analysis[2] in which biologically naive patients had better response to therapy. Our findings did not confirm previous findings that low albumin level and higher eMayo may be associated with higher colectomy rate. Furthermore, we found that the chance of colectomy is 4.8 times higher in ASUC. In accordance with the meta-analyses conducted by Steenholdt et al,[27] TFB could be a promising therapeutic agent in ASUC to prevent colectomy.

In the total cohort, the 8.0% week 52 colectomy rate is almost the same as in the meta-analysis.[2] Our study confirmed the findings of Sandborn et al[28] that older age increases the chance of remission, as we found it to be a protective factor both in colectomy and SFR (in the CA group); however, we would like to highlight the observations of Lichtenstein et al[29] that serious AEs, opportunistic infections, herpes zoster, malignancies, and major cardiovascular events are more frequent in elderly patients. We suggest further investigations to clarify the role of age as a protective factor, as previous studies have shown similar or worse outcomes in case of other biological therapies.[30-32]

Primary nonresponse rates were slightly lower (21.5%) compared with previous data (26.0%).[33] No predictive factor was identified, in contrast with the retrospective observational cohort study conducted by Honap et al[33] in which higher baseline CRP and younger age were associated with increased PNR rates. We found no link between the number of previous biologic therapies and PNR, in accordance with existing data.[33,34]

Almost 1 in 2 patients had LOR, and it was more common in cases of CA, which is probably due to the fact that PNR was more frequent and that the follow-up time was shorter in case of ASUC. However, an extended induction dose and an increase in dose were effective in one-third of the patients. We wish to highlight that LOR is the least studied outcome of TFB admission in UC. All patients received TFB as 20-mg/d induction dose, and the maintenance dose was 10 mg/d, while the treatment escalation was mostly identical to the induction dose; however, in selected cases, a higher dosage was used at the decision of the physician as well (25 and 30 mg/d, respectively).

Both AE and serious AE rates were comparable with international data.[2] In our cohort, herpes zoster was the most common infection in addition to pneumonia, *C. difficile*, and perianal abscess. In 1 in 4 patients, the infection was severe, and the affected patients made up half of the cases of cessation of TFB, and 1 patient passed away due to it. A thromboembolic event occurred in only 1 case; additionally, this patient had concurrent pancreas carcinoma. In accordance with our results, patients in the OCTAVE induction 1 and 2 trials and in the OCTAVE-Sustain trails have had thromboembolic events.[35,36] Five thromboembolic events were reported (1 deep vein thrombosis and 4 pulmonary embolisms) and they had concomitant risk factors as well (eg, anamnestic deep venous thrombosis/pulmonary embolisms or thrombophlebitis, oral contraceptive, traumatic event, or concomitant metastatic cholangiocarcinoma).[36] In addition to pancreas

tumor, in 1 case, melanoma was reported. Furthermore, we experienced both aminotransferase[37] and GGT[38] elevation as well in a few cases, but these results were mild, temporary, and reversible. Furthermore, in accordance with previous data,[39] cholesterol level was increased in our study as well without the elevation of triglyceride level. Based on our previous results, similar changes in lipid metabolism were also observed in 2 other rescue therapeutic agents, cyclosporine[40] and systemic steroids,[41] as a significant increase was observed in the level of cholesterol but not in the level of triglyceride. In summary, it can be concluded that AEs were predominantly mild and ceased spontaneously or with a reduction in dose or providing specific treatment.

The major strengths of the study are the large number of patients included, the nationwide setup, and that there are no previous data and comparisons of TFB in different indications. The limitations of this study were retrospective data collection and analysis and that the 52-week follow-up period was reached by only 184 of a total of 391 patients, and thus the extrapolation of the data could be narrowed. In addition, due to the multicenter setting, the analysis was impacted by data collection bias.

Conclusions

Our results in a larger cohort proved that TFB may be effective in both moderate-to-severe UC and in patients with ASUC as a rescue therapy. In addition, our observations suggest better colectomy rates in ASUC compared with IFX or cyclosporine. TFB treatment resulted in high rates of SFR and mucosal healing in both short and long terms even after anti-tumor necrosis factor and vedolizumab failure. Higher baseline disease activity and the number of previous biological therapies negatively influenced efficacy. TFB admission could be more effective as a first-line treatment in biologic-naïve patients as a rescue therapy or in a lower therapeutic line in CA due to its outstanding efficacy among available therapeutic options and its reassuring safety profile. Serious AEs were rare, and our results seem to support the assumption that thromboembolic events are associated with other risk factors.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

Author Contribution

T.R.: Original Draft Preparation, Review & Editing, Data Curation, Investigation, Methodology, Formal Analysis. **P.B.**: Review & Editing, Data Curation, Conceptualization, Project Administration. **C.K.**: Supervision, Review & Editing. **A.B., R.B., A.F., B.F., K.K., G.M., D.G.R., M.A., M.Z., H.A.B., H.Y., C.B., A.R., F.C., A.B.-G.S., D.P., A.A., E.V.S., M.K., M.L., E.C., R.F., A.R., S.N., Ž.K., E.S., T.S., P.S., M.F., D.D., O.V.K., A.V.K., J.K., N.M., L.B.:** Review & Editing, Supervision, Data Curation. **T.N.**: Software, Formal analysis, Visualisation. **P.W., P.L.L., Z.S., K.F.:** Review & Editing, Supervision, Data Curation, Conceptualization, Project Administration, Methodology. **T.M.**: Conceptualization, Investigation, Methodology, Project Administration, Resources, Supervision, Original Draft Preparation, Review & Editing.

The TFB Study Group comprises Simone Saibeni, Kristyna Kastylova, Jakob Benedict Seidelin, Johan Burisch, and Helga Hajdú.

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Conflicts of Interest

G.M. has received speaker fees from AbbVie, Takeda, Janssen, and Pfizer. N.M. has received speaking and/or consulting fees from Pfizer, Takeda, Janssen, Ferring, BiomX, BMS, Nestlé, and Trobix; and grant support from Takeda, Janssen, Abbott, AbbVie, Pfizer, BMS, Corundum Innovation Ltd, and Nestlé. L.M. has served as a speaker for AbbVie, Takeda, Celltrion, Biogen, and Janssen Cilag. C.B. has received lecture fees and served as a consultant for Takeda, MSD, Ferring, Galapagos, and Janssen. S.S. has received lecture fees and served as a consultant and advisory board member for AbbVie, Arena, Ferring, Gilead, Janssen, MSD, and Takeda. D.D. has served as a speaker, consultant, and an advisory board member for MSD, AbbVie, Takeda, Pfizer, Janssen, Amgen, Biogen, and Krka. E.V.S. has served as a speaker for AbbVie, AGPharma, Alfasigma, Dr Falk, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Unifarco; served as a consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr Falk, Fresenius Kabi, Janssen, Merck & Co, Reckitt Benckiser, Regeneron, Sanofi, Shire, SILA, Sofar, Synformulas GmbH, Takeda, and Unifarco; and received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, and Unifarco. D.P. has received speaker fees from MSD, Takeda, Galapagos, and Janssen, Pfizer; advisory board fees from Pfizer. A.A. has received consulting and/or advisory board fees from AbbVie, Allergan, Amgen, Arena, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Eli Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mylan, Pfizer, Protagonist Therapeutics, Roche, Samsung Bioepis, Sandoz, Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Arena, Biogen, Ferring, Galapagos, Gilead, Janssen, MSD, Mitsubishi-Tanabe, Nikkiso, Novartis, Pfizer, Sandoz, Samsung Bioepis, Takeda; and research grants from MSD, Pfizer, Takeda and Biogen. P.L.L. has served as a speaker and/or advisory board member for AbbVie, Amgen, BioJamp, Bristol Myers Squibb, Fresenius Kabi, Genetech, Gilead, Janssen, Merck, Mylan, Organon, Pendopharm, Pfizer, Roche, Sandoz, Takeda, Tillots, and Viatris; and received unrestricted research grant support from AbbVie, Gilead, Takeda, and Pfizer. K.F. has received speaker honoraria from AbbVie, Janssen, Ferring, Takeda, and Goodwill Pharma. T.M. has received speaker's honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer, Janssen, Sandoz, MundiPharma, Phytotec, Roche, Fresenius, and Teva.

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