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Original Article

Tofacitinib for Patients with Anti-TNF Refractory Ulcerative Proctitis: A Multicentre Cohort Study from the GETAID

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Abstract

Background: Although ulcerative proctitis [UP] can dramatically impair quality of life, treatment efficacy has been poorly investigated in UP as it was historically excluded from phase 2/3 randomised controlled trials in ulcerative colitis. Our aim was to assess the effectiveness and safety of tofacitinib for the treatment of UP.

Methods: We conducted a retrospective, multicentre study in 17 GETAID centres, including consecutive patients with UP treated with tofacitinib. The primary endpoint was steroid-free remission between Week 8 and Week 14, defined as a partial Mayo score of 2 [and no individual subscore above 1]. Secondary outcomes included clinical response and steroid-free remission after induction and at 1 year.

Results: All the 35 enrolled patients previously received anti-tumour necrosis factor [TNF] therapy and 88.6% were exposed to at least two lines of biologics. At baseline, the median partial Mayo score was 7 (interquartile range [IQR] [5.5-7]). After induction [W8-W14], 42.9% and 60.0% of patients achieved steroid-free remission and clinical response, respectively. At 1 year, the steroid-free clinical remission and clinical response rates were 39.4% and 45.5%, respectively, and 51.2% [17/33] were still receiving tofacitinib treatment. Survival without tofacitinib withdrawal was estimated at 50.4% (95% confidence interval [CI] [35.5-71.6]) at 1 year. Only a lower partial Mayo at baseline was independently associated with remission at induction (Odds ratio [OR] = 0.56 for an increase of 1, (95% CI [0.33-0.95], $p = 0.03$). Five [14.3%] adverse events were reported, with one leading to treatment withdrawal [septic shock secondary to cholecystitis].

Conclusion: Tofacitinib may offer a therapeutic option for patients with refractory UP.

Key Words: Ulcerative proctitis; tofacitinib; refractory proctitis

1. Introduction

Ulcerative proctitis [UP] represents the limited form of ulcerative colitis [UC], with the inflammation confined to the rectum. It leads to distressing symptoms such as increased stool frequency, tenesmus, urgency, and bleeding, which significantly alter the quality of life [QoL].[1] Up to half of the patients diagnosed with UC present with UP at the time of diagnosis.[1] Extension to the proximal part of the colon occurs in up to 30% of patients within 5 years.[1–3] Adequate and early management of flares of UP is crucial to control symptoms and improve QoL as well as to prevent further extension of the disease and progressive fibrotic tissue damage. First- and second-line treatments comprise topical +/- oral aminosalicylates and topical steroids. In case of failure to control symptoms of flare, systemic steroids are required.[4] Level of evidence for immunosuppressive agents as well as biologics for the treatment of refractory UP is low, as patients with UP were historically excluded from randomised controlled trials [RCT] assessing new drugs in UC.[5–7]

Retrospective limited evidence exists regarding the efficacy of thiopurines and awell as vedontiTNF as lizumab in UP.[5,8,9] A small RCT evaluated topical tacrolimus, which showed a better efficacy than placebo to achieve clinical remission.[10] Whereas treatment success rates appear low with thiopurines, vedolizumab and antiTNF may have long-term remission rates around 50% for refractory UP.[5] A significant number of patients will therefore experience treatment failure with anti-TNF therapy and will require further subsequent treatment options. Even though it has a limited nature, refractory UP may lead to total colectomy in selected cases.[11]

Prospective trials evaluating the efficacy of biologics and small molecules in patients with UP are therefore urgently needed. Recently, a phase 3 trial on etrasimod included for the first time a subgroup of patients with UP, showing promising results.[12]

Four classes of biologics and small molecules are now approved for UC. Tofacitinib is a panJAK inhibitor approved in UC, characterised by a rapid mechanism of action that can relieve disabling symptoms quickly.[13] It represents a promising option in UP but needs further clinical evaluation, as currently no data regarding its efficacy and safety have been reported in this clinical setting.

We therefore aimed to assess the effectiveness and safety of tofacitinib for the treatment of anti-TNF refractory UP, through a multicentre GETAID cohort study.

2. Methods

2.1. Study design and patients

We conducted an observational, multicentre study with retrospective collection from 17 GETAID centres. The cohort was built from a centralised GETAID registry from French and Belgian inflammatory bowel disease [IBD] centres in which consecutive patients were enrolled using an online registry. Data were retrospectively collected from medical records. Inclusion period ranged from August 2017 to May 2022. Patients were followed from tofacitinib initiation until last news or May 2023. Inclusion criteria were as follows: [1] age >16 years; [2] diagnosis of ulcerative colitis based on ECCO criteria[14]; [3] history of UC limited to the rectum [inflammation extending up to the rectosigmoid hinge or below] without any previous history of extent to the sigmoid and above; and [4] exposure to at least one line of anti-TNF [as stated in the French marketing authorisation approval.[15]] Patients with Crohn's disease or not willing to participate were excluded. The study was made in accordance with local ethical regulatory rules [MR004—health data hub F20221018150341].

2.2. Outcome measures

The primary outcome measure was steroid-free clinical remission after induction [assessed between Week 8 and Week 14], defined as a partial [clinical only] Mayo score of 2 or less with no individual clinical subscore above 1. Secondary outcomes included clinical response [decrease of at least 30% of the partial Mayo score from baseline] at induction and steroid-free clinical remission and clinical response at 1 year.

Secondary outcomes also included persistence rate of tofacitinib and endoscopic response and remission at induction. Endoscopic response was defined as a decrease of 2 or more of the Ulcerative Colitis Endoscopic Index of Severity [UCEIS] and endoscopic remission was defined as a UCEIS of 0.

In case of withdrawal of tofacitinib for any reason, it was considered as a failure. Adverse effects were classified as severe when they led to treatment interruption and/or hospital admission.

2.3. Statistical analysis

Quantitative variables were expressed as median (interquartile range [IQR]). Qualitative variables were given as numbers [percentages]. Quantitative variables were compared using [paired] Student's t test. Tofacitinib persistence was assessed using a Kaplan-Meier analysis. Univariate and multivariate logistic regression with backward selection was performed to identify factors associated with steroid-free clinical remission at induction. Calculations were performed using R software [The R Project for Statistical Computing: https://www.r-project.org/].

3. Results

3.1. Baseline characteristics

A total of 35 patients recruited from 17 GETAID centres were included. Baseline characteristics are displayed in Table 1; 57% were female, median age at tofacitinib initiation was 45.9 years [IQR 35-52.3], including 12 [34.3%] patients older than 50 and two [8%] aged over 60 years. The median UC duration at inclusion was 14.7 years [IQR 8.3-25.6]. At inclusion, all patients had a partial Mayo score of at least 3.

In terms of prior drug exposure, patients had a median exposure to two [IQR 2-3] distinct lines of biologics. All patients had received previous treatment with anti-TNF agents, including 21 [60%] patients who were treated with infliximab. Vedolizumab had been administered to 26 [74.3%] patients in the past, and ustekinumab had been used by nine [25.7%] patients. At the time of inclusion, among the eight [22.9%] patients who were treated with oral steroids, three had a dose of 20 mg or more of equivalent prednisone.

Baseline endoscopic evaluation was available in 26 patients, with all patients presenting a Mayo endoscopic subscore of 2 or 3. Twelve patients [46.2%] had an endoscopic subscore of 2 and 14 [53.8%] had a subscore of 3. Median UCEIS at baseline was at 5 [IQR 4-6]. The median C-reactive protein

Table 1. Baseline characteristics.

Characteristics at baseline		*N* = 35
Sex [female], *n* [%]		20 [57.1%]
Age at UC diagnosis [years], median [IQR]		36.8 [25.3-45]
Age at tofacitinib initiation [years]		45.9 [35-52.3]
Duration of UC at tofacitinib initiation [years]		14.7 [8.3-25.6]
Extraintestinal manifestations		9 [25.7%]
Primary sclerosing cholangitis		0 [0%]
Active smoking at inclusion		1 [2.9%]
Previous treatment exposure		
	Topical 5-ASA	34 [97.1%]
	Oral 5-ASA	31 [88.6%]
	Topical steroids	29 [82.9%]
	Systemic steroids	28 [80%]
	Thiopurines	19 [54.3%]
	Methotrexate	8 [22.9%]
	Anti-TNF	35 [100%]
	Infliximab	21 [60%]
	Golimumab	15 [42.9%]
	Adalimumab	14 [40%]
	Vedolizumab	26 [74.3%]
	Ustekinumab	9 [25.7%]
Number of biologic treatment lines[a]		
	1	4 [11.4%]
	2	17 [48.6%]
	3+	14 [40%]
Concomitant medication at tofacitinib initiation, *n* [%]		
	Topical 5-ASA	5 [14.3%]
	Oral 5-ASA	4 [11.4%]
	Topical steroids	6 [17.1%]
	Steroids [prednisone eq >= 20mg]	3 [8.6%]
	Steroids [prednisone eq <20 mg]	5 [14.3%]
	Immunosuppressant	1 [2.9%]
	None	17 [48.6%]
Partial MAYO		7 [5.5-7]
Endoscopic evaluation [*n* = 26]	Mayo subscore = 2	12 [46.2%]
	Mayo subscore = 3	14 [53.8%]
	UCEIS	5 [4-6]
CRP [mg/l] [*n* = 26]		3.9 [2.7-6.8]
Faecal calprotectin [µg/g] [*n* = 8]		1180 [773-1650]

CRP, C-reactive protein; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; IQR, interquartile range; 5-ASA, 5-aminosalicylates; TNF, tumour necrosis factor; eq, equivalent.
[a]One line for each mechanism of action.

[CRP] level [*n* = 28] stood at 3.9 mg/L [IQR 2.7-6.8]. Baseline faecal calprotectin measurements were available only for eight patients [Table 1].

3.2. Clinical remission and response at induction and at 1 year

All patients started at a 10 mg twice daily dose for at least 8 weeks. At induction, steroid-free clinical remission was reached in 15 out of 35 patients [42.9%] and 21 patients [60%] had a clinical response. Partial Mayo score was 3 [IQR 1-5] at Week 8-Week 12 as compared with 7 [IQR 5.5-7] at baseline [p <0.001].

At induction, four of 10 patients with endoscopy assessment available both at baseline and at Week 8-Week 14 were in endoscopic response [decrease of UCEIS of 2 or more] and one patient [10%] was in endoscopic remission [UCEIS at 0]. Among these 10 patients with paired assessment, median UCEIS at baseline was at 6 [IQR 5-6] versus 4 [IQR 1.25-5] at the induction time point [p = 0.02, paired t test].

At 1 year, 22 patients were still on tofacitinib with 11 receiving 10 mg twice daily, and the remaining 11 patients where on a 5-mg twice daily regimen. At 1 year, 13 of 33 patients [39.4%] were in steroid-free clinical remission and 15 patients [45.5%] were in clinical response. Response and remission rates are displayed in Figure 1.

CRP was available in 26 patients at baseline, in 22 at induction, and in 18 patients at 1 year. The median CRP was at 3.9 [IQR 2.7-6.8] mg/L at baseline, at 2.1 mg/L [IQR 0.8-5, p = 0.14] vs baseline, Student's t test] at the induction time point, and at 2.9 [IQR 0.6-4.8] at 1 year [p = 0.57 vs baseline].

3.3. Factors associated with steroid-free clinical remission at induction

We further evaluated factors associated with steroid-free clinical remission at the induction time point [between Week 8 and Week 14] using a univariate and multivariate logistic regression with backward selection. In univariate analysis, the only factor significantly associated with the absence or steroid-free clinical remission at induction was a lower partial Mayo at baseline: (odds ratio [OR] = 0.56 for an increase of 1 [95% CI 0.33-0.95], p = 0.03). In multivariate analysis, only a lower partial Mayo score at baseline remained independently and significantly associated with the remission at the induction time point (OR = 0.56 for an increase of 1, [95% CI 0.33-0.95], p = 0.03) [Table 2].

3.4. Tofacitinib persistence

At the end of follow-up (median of 14.7 months [IQR 8.3-25.6]), 17 [48.6%] patients had stopped tofacitinib treatment. Survival without tofacitinib withdrawal was estimated at 85.7% [95% CI 74.9-98.1] at 3 months, at 68% [95% CI 54.1-85.6], at 6 months and at 50.4% [95% CI 35.5-71.6] at 1 year [Figure 2]. Eight patients encountered primary treatment failure, leading to their discontinuation of treatment within 3 months of initiation. Seven [41.1%] patients encountered secondary treatment failure. Additionally, one patient discontinued treatment due to a serious infection, and another patient ceased treatment due to pregnancy. Colectomy occurred in one patient, 5 months after tofacitinib initiation for refractory UP after the previous failure of three biologics [infliximab, golimumab, vedolizumab].

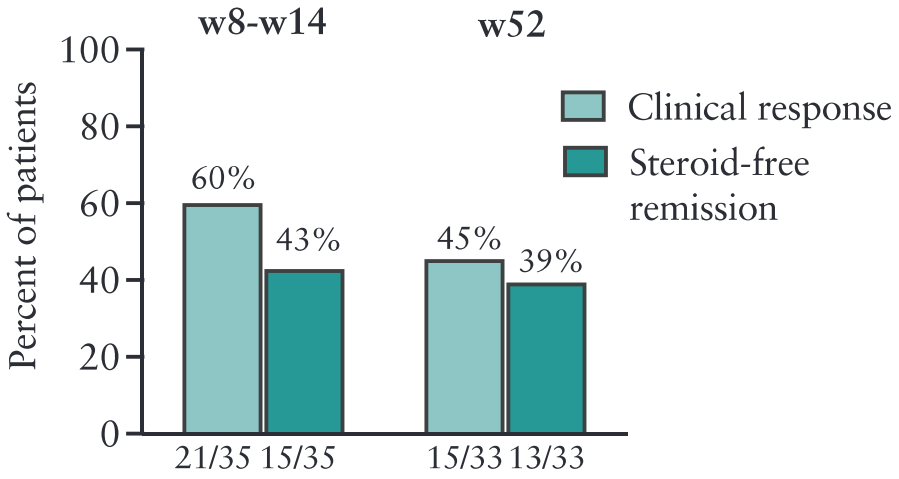

Figure 1. Histograms representing percentages of response and remission: 33 patients of the 35 studied patients had at least 1 year of follow-up.

Table 2. Factors associated with steroid-free clinical remission at induction.

		Odds ratio [95% confidence interval]	*p*	Adjusted odds ratio	*p*
Sex	Female	1.23 [0.32-4.77]	0.77		
Steroids at induction		0.75 [0.15-3.79]	0.73		
UC duration	For increase of 1 year	1.03 [0.93-1.15]	0.56		
partial MAYO	For increase of 1	0.56 [0.33-0.95]	0.03	0.56 [0.33-0.95]	0.03
Age at initiation	For increase of 1 year	0.97 [0.92-1.03]	0.28		
Number of lines of biologics	For increase of 1	0.48 [0.20-1.19]	0.11		

UC, ulcerative colitis.

3.5. Safety

Adverse events occurred in five patients [14.3%] with five infectious events. Only one led to treatment discontinuation, a 52-year old woman who had septic shock secondary to cholecystitis. The four remaining infectious events did not lead to permanent treatment withdrawal and included one symptomatic but non-serious episode of COVID-19, one herpes zoster, one bronchitis, and one bartholinitis. No death, cancer, venous thrombotic or major adverse cardiovascular event occurred in the cohort.

4. Discussion

In the present study, we report the largest cohort of patients treated with tofacitinib for refractory UP. Our findings suggest that even after experiencing multiple failures with biologics, a noteworthy proportion of patients can still derive significant benefits from tofacitinib. So far, a low level of evidence exists for all classes of biologics and small molecules in UP. Controlled and randomised trials were only performed for topical treatments. As an example, historical data show that as a first-line induction treatment, topical 5-aminosalicylates [5-ASA] are more efficient than topical steroids to induce clinical remission, as shown in a meta-analysis.[16] More recently,two randomised, controlled trials were performed, involving topical treatment with tacrolimus.[10,17] Lie *et al.* showed a trend toward a greater endoscopic remission with topical tacrolimus at Week 4 as compared with topical beclomethasone [29.7% vs 14.5%, $p = 0.09$]. Interestingly in this randomised controlled trial, which included 85 patients, a significant proportion of patients were receiving concomitant immunomodulators.

Regarding systemic immunosuppressant and biologic treatments, only observational and limited studies were reported so far.[18] The largest number of patients with UP treated with a biologic is reported with anti-TNF, with long-term remission rates ranging from 50% to 69%.[5,8,9] Additionally, a single-centre study reported the use of vedolizumab in 15 patients with UP. Dubois *et al.* described long-term remission in 10 of 15 [67%] patients treated with vedolizumab, with a median follow-up of 11 months.[5] Interestingly, the persistence rate was significantly higher in patients with UP treated with biologics [$n = 33$] as compared with patients treated with thiopurines [$n = 19$].[5]

In a more recent development, the ELEVATE UC trial introduced etrasimod as an advanced therapy for UC.[19] Notably, unlike previous phase 3 trials in UC, this study included patients with disease confined to the rectum, marking a significant step forward in the field. Importantly, crude rates of response and remission were numerically higher in the subgroup of patients with UP.[12] This suggests that previous results for other biologics and small molecules generated in phase 3 randomised, controlled trials conducted in patients with UC and excluding patients with proctitis, may be extended to patients with UP. This includes tofacitinib, which showed efficacy to treat patients with UC [excluding UP] in the landmark OCTAVE phase 3 trial.[20] Our cohort presents retrospective data in a specific population of highly refractory UP, and it suggests that tofacitinib may be effective to treat such patients, with a long-term remission rate close to 40%.

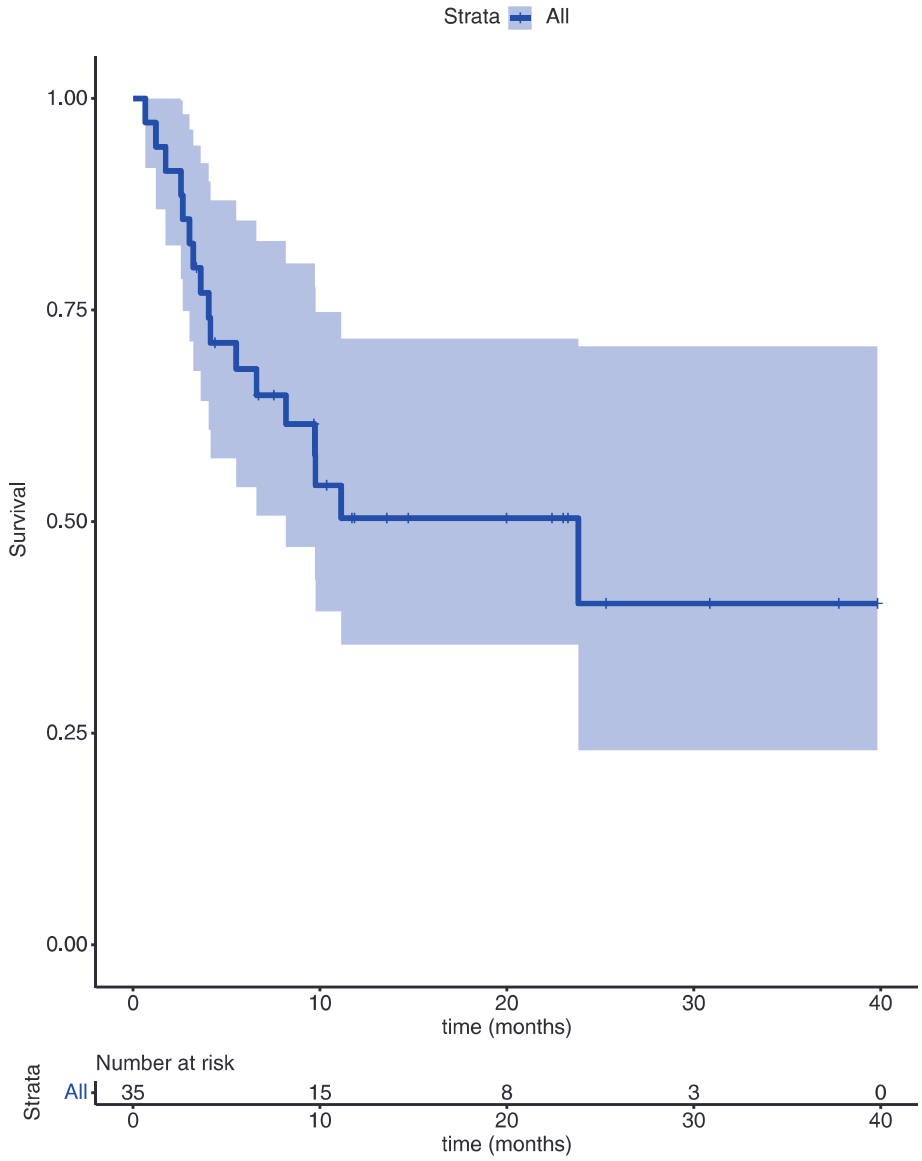

Figure 2. Kaplan-Meier survival estimates for discontinuation in patients receiving tofacitinib. The coloured area shows 95% confident intervals.

It is also noteworthy that at 1 year, half of the patients maintained a high-dose regimen of 10 mg twice daily.

To date, there have been no reported observations or case reports regarding the use of tofacitinib specifically in UP. The safety profile was found to be acceptable, with only one adverse event leading to the discontinuation of treatment. Moreover, this serious infection [septic shock secondary to cholecystitis] did not appear to be directly linked to the use of tofacitinib. In addition, one episode of mild herpes zoster has been reported, which did not force permanent discontinuation of the treatment. Even though not designed for that purpose, our study did not reveal any thromboembolic event in patients with refractory UP.

In the biologic era, refractory UP remains a highly challenging clinical situation with induced disability, especially for patients with multiple therapeutic failures. Topical treatment is often not accepted by patients as a long-term treatment option. Therefore tofacitinib, already approved for the treatment of UC, emerges as an additional option that is now available in the physician's armamentarium to treat UP.

The strengths of our study include a real-life setting and a relatively large number of patients included for UP. Our study is inherently limited by its retrospective nature, by the absence of systematic endoscopic evaluation, and by a limited sample size. There is also a lack of extensive calprotectin evaluation.

In conclusion, tofacitinib offers a promising therapeutic option for patients with UP, even in cases of multiple biologic exposure. Other small molecules may also be offered to patients with UP, as recently suggested by the ELEVATE UC trial. These findings, along with our study, support the idea of including patients with UP in phase 2/3 UC trials.

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Conflict of interest

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Author contributions

MU: study design and data analysis, patient recruitment, data collection, and writing up of the first draft of the manuscript. MN, AN, AA, BC, Abe, Abu, GB, CLB, CR, GLC, GS, MC, MV, LG, MF, LPB, JK: patient recruitment, data collection, reviewing and editing the manuscript. YB: study design, reviewing and editing the manuscript. All authors approved the final version of the manuscript.

Data Availability

Individual anonymised data will be provided upon request to the corresponding author.

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