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Real-world evidence of tofacitinib effectiveness and safety in patients with refractory ulcerative colitis

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Abstract

Background: Phase III trials demonstrated effectiveness of tofacitinib, an oral Janus kinase inhibitor, to induce and maintain remission in patients with moderate-to-severe active ulcerative colitis (UC).

Aims: We report the real-world effectiveness and safety of tofacitinib in patients with UC in France.

Methods: From February 2017 to December 2018, we performed a national French cohort study, which included all consecutive patients with an active UC refractory to anti-TNF and vedolizumab, who received tofacitinib. Outcomes were survival without colectomy, survival without tofacitinib discontinuation and steroid-free clinical remission at weeks 14, 24 and 48.

Results: Thirty-eight patients were included, with a median follow-up of 41.5 (18.5–56.8) weeks. Survival without colectomy was 77% [95% confidence interval (95%CI): 59.3–87.9] at week 24 and 70% (95%CI: 50.9–82.8) at week 48. Survival without treatment discontinuation was 70% (95%CI: 52.6–82.3) at week 24. Steroid-free clinical remission was observed in 13 (34%) patients at week 48. Adverse events occurred in 14 (37%) patients, including 6 severe adverse events and three herpes zoster infections.

Conclusion: In a highly refractory UC population, one third of patients treated with tofacitinib achieved steroid-free clinical remission at week 14 and 70% of patients avoided colectomy at one year, with an acceptable safety profile. These data confirm tofacitinib effectiveness in UC, especially after multiple biologic failures.

Keywords: Refractory Ulcerative colitis ; Janus kinase inhibitor

Introduction

Ulcerative colitis (UC) is characterized by chronic inflammation of the colonic mucosa with increased stool frequency, bloody diarrhoea and significant alteration of the quality of life. Its evolution remains variable and unpredictable with a 10-year cumulative relapse and colectomy rates of respectively 67-83% and 15%[1],[2].Treatment armamentarium of UC includes mesalamine, glucocorticoids, immunosuppressive agents and monoclonal antibodies targeting tumor necrosis factor (TNF) alpha or α4β7 integrin. However, approximately 20% of patients are primary non-responders to induction therapy with biologic agents and 50% present secondary loss of response during follow-up[3].

Recently, tofacitinib (CP-690550), an oral, small-molecule Janus kinase inhibitor, demonstrated its effectiveness as induction and maintenance therapy in moderately to severely active UC, with acceptable safety profile[4]. Tofacitinib in one phase 2 and two phases 3 trials induced significantly higher rates of clinical response, clinical remission and mucosal healing at week 8 as compared to placebo[5],[6]. In the maintenance period of the phase 3 studies, significantly more patients receiving tofacitinib had achieved clinical remission and mucosal healing at week 52.

Following these results, a national nominative compassionate early-access program [autorisation temporaire d'utilisation (ATU)] was approved by the French regulatory agency [Agence nationale de sécurité du medicament et des produits de santé (ANSM)] before marketing authorisation in order to provide tofacitinib to patients with moderate to severe disease refractory to other available therapy. We report here the real-world effectiveness and safety of tofacitinib in patients with refractory UC in a multicentre French cohort.

Patients and methods

Study population

All consecutive UC patients who started tofacitinib as part of the French national nominative compassionate early-access program from February 2017 to December 2018 were included in this observational, retrospective, and multicentre cohort study. Patients included were adults with moderate-to-severe active UC diagnosed on usual criteria[7],[8] with prior failure (inadequate response, loss of response or intolerance) of steroids, conventional immunomodulator (thiopurines and/or methotrexate), anti-TNF agents and vedolizumab. Patients with unclassified colitis, pregnancy or lactation and patients treated with tofacitinib in a clinical trial were excluded.

Patient demographic and clinical characteristics were retrospectively retrieved from medical records and included age at diagnosis, gender, smoking habits, familial history of IBD, UC extent according to the Montreal classification[9], extra intestinal manifestation, history of medical and surgical treatment of UC and endoscopic evaluation at baseline if performed[10].

Tofacitinib therapy

Tofacitinib treatment was started at 10 mg twice daily orally for three months. Maintenance therapy could be either maintained at 10 mg twice daily or be alleviated to 5 mg twice daily at the investigator's discretion. Anti-TNF agents and vedolizumab were discontinued before baseline.

Follow-up

During the follow-up period, data recorded at weeks 14, 24, 36, 48 were: disease activity, assessed according to partial Mayo Clinic score[11] (including stool

frequency, rectal bleeding and physician's global assessment, ranging from 0 to 9), steroids intake, haemoglobin (g/dL), platelet count (/mm^3), CRP (mg/L), leukocyte count (/mm^3), UC-related hospitalizations, surgery, tofacitinib discontinuation, and endoscopic evaluation[12]. Adverse events were collected in all patients receiving at least one dose of tofacitinib.

Outcomes

Study outcomes were survival without colectomy, survival without tofacitinib discontinuation, steroid-free clinical remission and clinical response. Clinical remission was defined as a partial Mayo score < 3 with a combined stool frequency and rectal bleeding subscore ≤ 1[13],[14]. Clinical response was defined as a reduction in the partial Mayo score from baseline of at least three points and a decrease > 30%, with a decrease ≥ 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 from the baseline score at week 0. Relapse was defined as recurrence of symptoms, including rectal bleeding in a patient in clinical remission, requiring systemic therapeutic change. Failure was defined as the interruption of tofacitinib before the end of follow-up for colectomy or serious adverse events and non-response as the absence of the objective response criteria mentioned above despite the continuation of tofacitinib. Mucosal healing was defined as a Mayo endoscopic subscore of 0-1.

Safety was assessed prospectively by the physician in charge and retrospectively collected from patient records. Adverse events were classified as severe when they lead to hospitalization, disability or persistent damage and death.

Statistical analysis

Qualitative data are expressed as number (%), quantitative data as median [interquartile deviation] or mean ± standard deviation (SD). All patients included were evaluated and analysed on an intent-to-treat basis in the present study. The study period started at first treatment administration and ended at colectomy or in December 2018 in non-operated patients.

Survival without colectomy and survival without tofacitinib discontinuation were analysed using the Kaplan-Meier method.

The proportions of patients who met the criteria for the latter end points during the present follow-up of maintenance therapy were computed relative to the whole population included at week 0.

All of the analyses were two-tailed, and p-values less than 0.05 were considered significant. All of the statistical evaluations were performed using Prism 6 statistical software. All of the authors had access to the study data and reviewed and approved the final manuscript.

Results

Patient characteristics

Thirty-eight patients received tofacitinib within the nominative compassionate early-access program in 14 tertiary care centres.

Patients' baseline characteristics are reported in Table 1. Fifteen (39%) were women; median age was 41 (28–52) years old with a median disease duration of 7 (interquartile range – IQR: 5–11.8) years. According to the Montreal classification, 22 (58%) patients had pancolitis (E3), 13 (34%) left-sided colitis (E2), and 3 (8%) proctitis (E1). Regarding prior exposure to conventional immunomodulator, 35 (92%) patients had received thiopurines, 9 (24%) methotrexate and 1 (3%) tacrolimus.

All patients previously received at least one anti-TNF agent and vedolizumab, 4 (11%) received also ustekinumab and 1 (2.6%) cyclosporine before inclusion. In total, 31 (81.6%) patients were primary non-responders to an anti-TNF and 27 (71%) failed at least 2 different anti-TNF molecules.

In patients receiving steroids and/or immunomodulator at inclusion, no standardized tapering regimen was mandatory and treatments were continued at the investigator's discretion. All patients received tofacitinib as a monotherapy, except one who was receiving concomitant immunomodulator.

At baseline, 20 (53%) patients were taking steroids. The median partial Mayo score was 6 (5–8) and the median CRP was 11 (5.5–19.3). Regarding endoscopic disease activity, available in 32 (84%) patients, median Mayo endoscopic subscore and ulcerative colitis endoscopic index of severity (UCEIS) were 3 (2–3) and 5 (4–6) respectively.

Survival without colectomy or tofacitinib discontinuation

With a median follow-up duration of 41.5 weeks (18.5–56.8), 16 (42%) patients discontinued tofacitinib: 7 (18%) underwent colectomy for worsening UC under treatment, 4 (10%) for non-response and 5 (13%) for severe adverse event (among which 3 were underwent colectomy after treatment discontinuation). Altogether, 10 patients (26%) underwent colectomy throughout the study. No death was observed.

Survival without colectomy at week 24, at week 48 and at the end of follow-up were 77.1% [95% confidence interval (95%CI): 59.3–87.9], 70% (95%CI: 50.9–82.8) and 70% (95%CI: 50.9–82.8), respectively (Figure 1). Survival without tofacitinib discontinuation at week 24, at week 48 and at the end of follow-up were 70.2% (95%CI: 52.6–82.3), 58.8% (95%CI: 41.1–72.8), and 58.8% (95%CI: 41.1–72.8), respectively (Figure 2). None of the patients who discontinued tofacitinib have restarted the drug.

Overall, 16 (42%) patients discontinued tofacitinib during the follow-up period, including 7 patients with disease worsening and colectomy, 5 for severe adverse events and 4 for non-response. Most treatment discontinuations occurred within 24 weeks (n = 13). All colectomies were due to disease worsening and none were due for the indication of dysplasia or neoplasia.

Steroid-free clinical remission

At week 14, steroid-free clinical remission was achieved in 12/38 (32%) patients and clinical response in 18/38 (45%) (Figure 3). At week 24 and 48, steroid-free clinical remission was achieved in 12/38 (32%) and 13/38 (34.2%) respectively and clinical response was obtained in 14/38 (37%) at week 24 and 48. Concerning the 20 patients taking steroids at inclusion, 5 (25%) were in steroid-free clinical remission and 9 (45%) have weaned steroids at week 14. At week 24, 11 (55%) patients had stopped steroids,

2 (10%) continued steroids and 6 (30%) stopped tofacitinib. At week 24, 8 (40%) patients were in steroid-free clinical remission until week 48.

During the follow-up period, 9 (24%) patients experienced disease relapse, including two subjects in remission who relapsed after tofacitinib discontinuation for adverse events. Figure 4 illustrates response and remission from baseline to the end of follow-up for each patient included.

Endoscopic evaluation

During follow-up, 24 (63%) patients had at least one endoscopic assessment by flexible sigmoidoscopy. Mucosal healing ,defined by a Mayo endoscopic subscore of 0-1, was observed in 1 (2.6%) patient among 11 who had an endoscopy at week 14, in 5 (13.2%) patients among 12 at week 24, in 2 (5.3%) patients among 5 at week 36 and in 3 (7.9%) patients among 8 at week 48[15].

Safety

Twenty-two adverse events have been observed in 14 (37%) patients during the follow-up period (Table 2), including 6 serious adverse events: 5 severe infections (one ophthalmic zoster infection, two viral pulmonary infections, one pyelonephritis, one rectal abscess) and one case of toxic thyroid adenoma after one year of treatment. Overall, three patients treated with tofacitinib 10 mg twice daily developed a zoster infection, all before week 14, including one requiring tofacitinib discontinuation. Within the 11 other infections, upper respiratory tract infections (n = 3) and dental infections (n = 3) were the most commonly observed. Hypercholesterolemia has been observed in 3 (7.9%) patients and none required anticholesterol drug. No major adverse cardiovascular events (MACE) have been reported.

Two (5%) patients underwent tofacitinib dose reduction to 5 mg twice daily during follow-up (one due to a herpes zoster infection and the other because of clinical remission at week 24); these two dose reductions were followed by an interruption of treatment for adverse event. All other patients continued tofacitinib 10mg twice daily until the end of follow-up.

Discussion

We report here one of the first real-life cohort studies exploring tofacitinib effectiveness and safety in UC. When given as rescue therapy in a highly refractory UC population, survival without colectomy was 70% at one year, with an acceptable safety profile. About one third of these patients had a steroid-free clinical remission as early as 24 weeks with tofacitinib and had a maintained clinical remission in steroid free condition until the end of follow-up with a safety profile consistent with those reported in the pivotal tofacitinib studies.

Notably, patients included in our study presented several characteristics of high risk of colectomy. Of these, 76.3% had an age at diagnosis of less than 40 years, with moderate to severe disease activity according to the Mayo score and severe endoscopic lesions (median UCEIS score of 5). In addition, 60% had pancolitis (E3), compared to 24-28% in population-based study[1] and disease extension is known to be associated with a significant increased risk of colectomy[1],[16]. Second, all patients were refractory to all usual therapies (including anti-TNF agents and vedolizumab). Tofacitinib has been prescribed as last-chance drug before surgery for all patients, highlighting that remission in one third of them and survival without colectomy in the other two thirds at one year are very hopeful results.

Effectiveness of tofacitinib in refractory IBD have also been reported in a recent retrospective real-life study conducted in an American tertiary centre[17]. The effectiveness results in terms of clinical response and steroid-free clinical remission were encouraging and close to our own results. However, 38% of the patients received 5 mg bid instead of 10 mg bid, 19% of them never received vedolizumab and 7% of the patients had Crohn's disease. In addition, 14% of patients were treated concomitantly with immunomodulator or vedolizumab in association with tofacitinib. In

our cohort, all patients except one received tofacitinib as a monotherapy, without any other immunosuppressant or biologic therapy, which makes it easier to interpret the effectiveness results.

Beyond the effectiveness of the treatment, its safety is an integral part of the therapeutic decision guided by the benefit-risk balance. The most frequently occurring adverse events in our cohort were asthenia, hypercholesterolemia, infectious diseases such as upper respiratory tract infection and herpes zoster. Serious adverse events occurred in 15.8% (n = 6) in our population versus 5.6% with tofacitinib 10 mg bid in a recent study on the safety of tofacitinib[4]. This discrepancy result could be explained by the severity of UC in our cohort. Infection was the reason of tofacitinib discontinuation for adverse events (n = 5, 13.2%) in all cases, and all infections resolved after that withdrawal. A case of toxic thyroid adenoma requiring a thyroidectomy at week 48 has been reported and had never previously been described to our knowledge. The unusual distribution of side effects such as infections (23.7%) versus myalgia, asthenia or paraesthesia (18.4% in total) is probably due to the underestimation of mild adverse events as frequently found in retrospective study. It is important to note that an FDA communication in February 2019 alerted to the increased risks of pulmonary embolism in patients with rheumatoid arthritis, aged 50 years or older and having at least one cardiovascular risk factor, taking tofacitinib 10mgx2/day in combination with methotrexate versus anti-TNF. However, this risk has not been reported in UC at this time and no cases were described in our study. In a recent review, the safety profile of tofacitinib was considered similar to that observed in UC clinical trials with vedolizumab or anti-TNF, except for herpes zoster, more common with tofacitinib[4].

This study presents some limitations: 1) its retrospective design, but all data have been collected in IBD centres; 2) the population was composed of a small group of patients but this is the totality of patients treated with tofacitinib in France thanks to an early-access program; 3) a relative heterogeneous follow up with limited number of endoscopic data for mucosal healing evaluation. Of note, endoscopic evaluations were not systematically scheduled (as can be the case in clinical trials) and were generally performed more frequently on non-responders. This bias prevents us from drawing any conclusion on the effectiveness on mucosal healing under tofacitinib in this population. Still, this study remains the first European real-world cohort concerning the effectiveness and safety of tofacitinib, in a highly refractory and severe UC population.

The decision on the ideal positioning of tofacitinib within the current algorithm is crucial and will depend, among other things, on the price of its refunding not currently fixed. In a meta-analysis comparing first and second line treatments in moderate to severe UC[18], tofacitinib was the best second-line treatment, after failure of anti-TNF agents, for remission induction and mucosal healing, but currently no direct comparison data with vedolizumab in patients who failed conventional treatment and anti-TNF agents are available to justify the therapeutic decision. In March 2019, the Transparency Commission of the French High Authority for Health gave tofacitinib a place in the 3rd treatment line for patients who fail conventional treatment and anti-TNF drugs, representing an alternative to vedolizumab depending on the patient's choice of administration methods and their tolerance profile.

In our study, several patients were in response, or even achieved clinical remission, late in the course of tofacitinib (up to W36) which was continued beyond week 16 as recommended because despite the severe activity of their UC, patients were stabilized on treatment without clinical aggravation (Figure 4). This should

therefore be taken into account in patients for whom tofacitinib is used as rescue therapy so that it is not interrupted early if the patient's clinical course is favourable.

In this highly refractory population with moderate-to-severe UC, tofacitinib achieved steroid-free clinical remission in one third of patients at 6 months. Survival without colectomy was observed in three quarters of the patients at 6 months, and maintained in the large majority of cases at one year. Safety profiles were consistent with those reported in the pivotal tofacitinib studies. Along this, tofacitinib represents a treatment of choice for UC patients who are refractory to conventional therapies and further studies are expected to determine the best position of tofacitinib in the therapeutic strategy of UC[19],[20].

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Table legends

Table 1: Population characteristics in the tofacitinib cohort (*n* = 38)

Table 2: Adverse events in the tofacitinib group (*n* = 38).

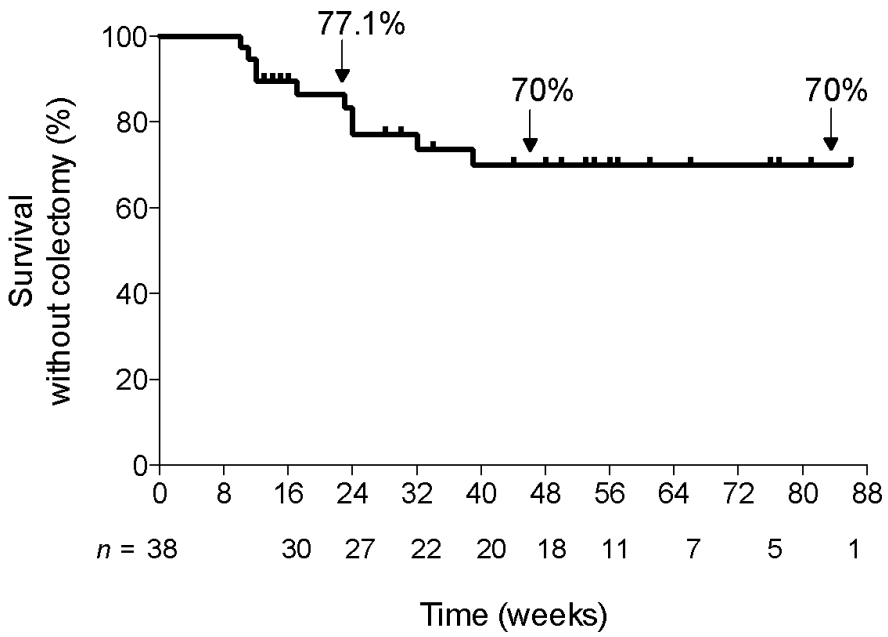
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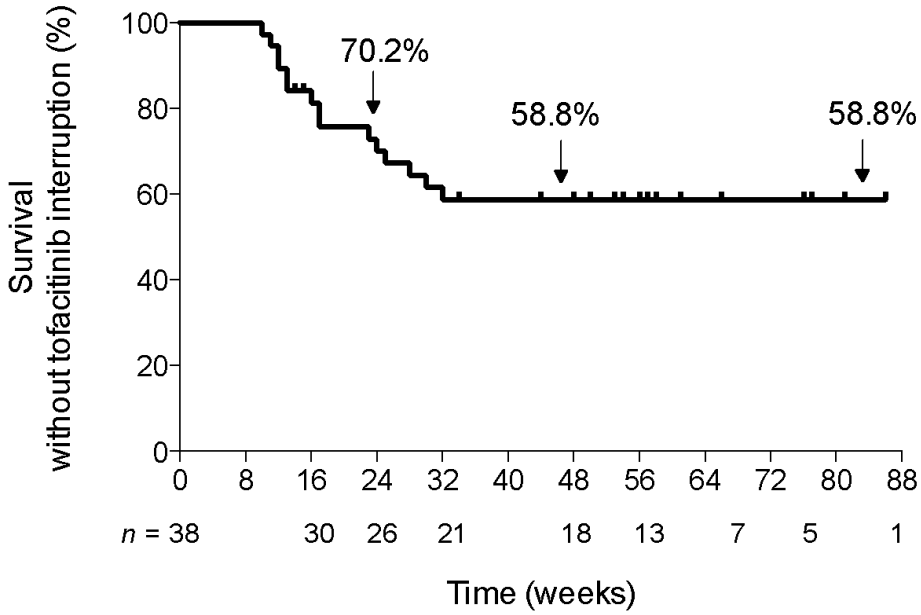
Figure 1: Survival without colectomy from week 0 to the end of follow-up among 38 patients with refractory ulcerative colitis treated by tofacitinib.

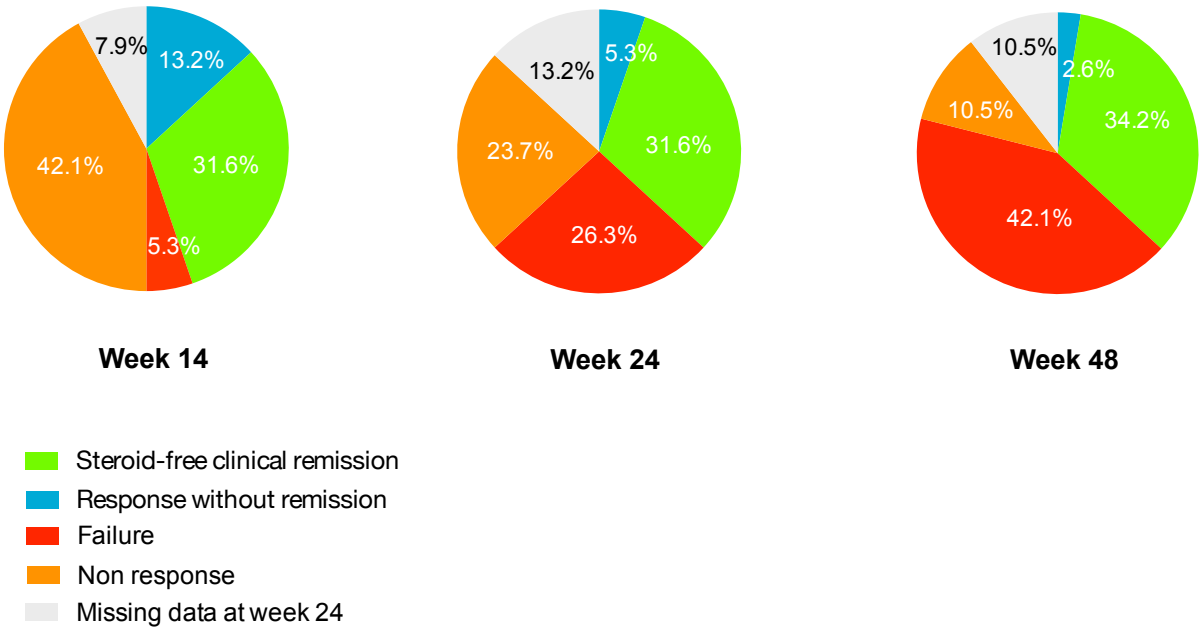
Figure 2: Survival without treatment discontinuation from week 0 to the end of follow-up among 38 patients with refractory ulcerative colitis treated by tofacitinib.

Figure 3: Outcomes of UC patients treated with tofacitinib at weeks 14, 24 and 48. Patients in remission are in green, patients who responded without steroid-free clinical remission are in blue, patients who did not respond tofacitinib are in orange and those who stopped treatment for colectomy or adverse events are in red.

Figure 4: Clinical course of UC patients treated with tofacitinib during follow-up. Each line represents one patient over time. In red are represented non-responders, in blue are responders who have relapsed and in green are remission patients. The black dots correspond to the occurrence of a colectomy.


77.1%
70%
70%
100
80
60
40
20
0
Survival without colectomy (%)
0 8 16 24 32 40 48 56 64 72 80 88
n = 38 30 27 22 20 18 11 7 5 1
Time (weeks)


Survival without tofacitinib interruption (%)
100
80
60
40
20
0
70.2%
58.8%
58.8%
0
8
16
24
32
40
48
56
64
72
80
88
n = 38
30
26
21
18
13
7
5
1
Time (weeks)


7.9%
13.2%
42.1%
31.6%
5.3%
13.2%
5.3%
23.7%
31.6%
26.3%
10.5%
2.6%
10.5%
34.2%
42.1%
Week 14
Week 24
Week 48
Steroid-free clinical remission
Response without remission
Failure
Non response
Missing data at week 24

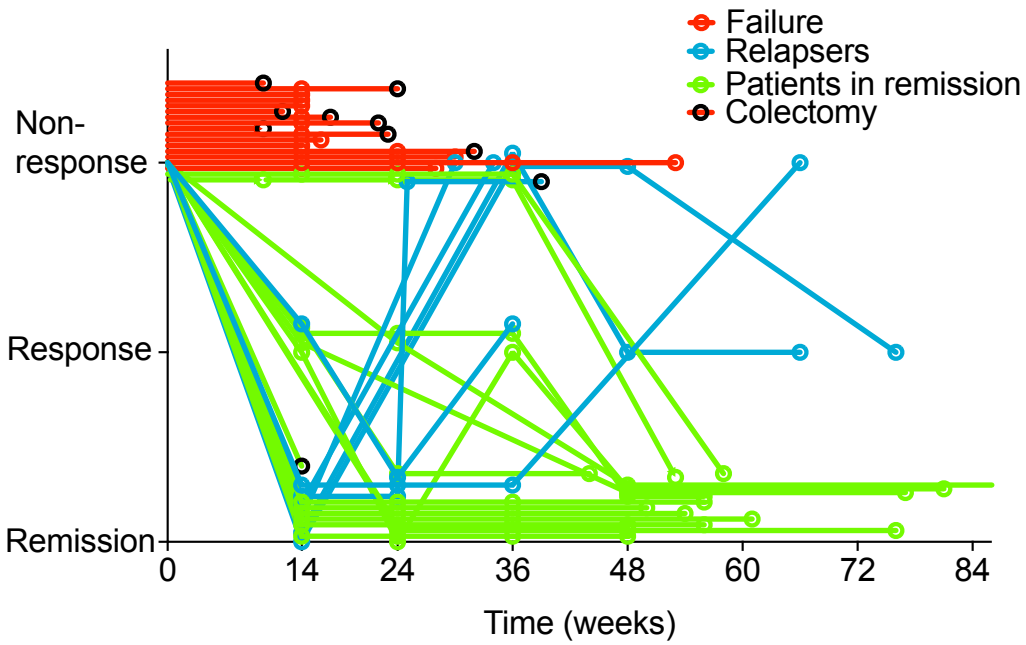

Failure
Relapsers
Patients in remission
Colectomy
Non-
response
Response
Remission
0
14
24
36
48
60
72
84
Time (weeks)

Table 1: Population characteristics in the tofacitinib cohort (*n* = 38)

	Tofacitinib
	***n* = 38**
Baseline demographics and medical history:	
Age, yr.	41 (28–52)
Women, No. (%)	15 (39.5%)
Medical History: No. (%)	
Appendectomy	4 (10.5%)
Abdominal surgery	1 (2,6%)
Current smoking	3 (7.9%)
Smoking cessation	8 (21%)
Family history of IBD	9 (23.7%)
Baseline characteristics of UC:	
Duration of disease, median, yr.	7 (5–11.8)
Age at diagnostic, median, yr.	29.5 (13–73)
Extent of disease, No. (%)	
Proctitis	3 (7.9%)
Left-sided colitis	13 (34.2%)
Extensive colitis/ pancolitis	22 (57.9%)
Total Mayo score	9 (7–10)
Partial Mayo score	6 (5–8)
UCEIS score	5 (4–6)
C-reactive protein–mg/liter, median	11 (5.5–19.3)
Hemoglobin–g/dL, median	12.8 (11.7–14)

History of treatment at baseline	
Oral steroids, No. (%)	20 (52.6%)
Previous treatment with TNF antagonist	38 (100%)
Previous treatment with vedolizumab	38 (100%)
Previous treatment with ustekinumab	4 (10.5%)
Previous treatment with cyclosporine	1 (2.6%)
Previous treatment failure	
Immunosuppressant	36 (94.7%)
Non-response to anti-TNF	31 (81.6%)
Loss of response to anti-TNF	19 (50%)
≥ 2 anti-TNF	27 (71%)
Number of previous treatment lines	
3	11 (28.9%)
4	19 (50%)
5	8 (21.1%)

Abbreviations: IQR, interquartile range; yr, year; IBD, inflammatory bowel disease; UC, ulcerative colitis; UCEIS, ulcerative colitis endoscopic index of severity; TNF, tumor necrosis factor. Variables are presented as n (%) mean ±standard deviation (SD) or median (IQR range).

Table 2: Adverse events in the tofacitinib group (*n* = 38).

	Tofacitinib ***n* = 38**
Adverse event, No. (%)	14 (36.8%)
Asthenia, No. (%)	4 (10.5%)
Myalgia, No. (%)	2 (5.3%)
Hypercholesterolemia	3 (7.9%)
Paresthesia, No. (%)	1 (2.6%)
Infectious adverse event, No. (%)	9 (23.7%)
Dental infection	3 (7.9%)
Upper respiratory tract infection	3 (7.9%)
Pyelonephritis	1 (2.6%)
Herpes zoster	3 (7.9%)
Anastomotic rectal abscess	1 (2.6%)
Toxic thyroid adenoma	1 (2.6%)
Serious infection, No. (%)	5 (13.2%)
Any serious adverse event, No. (%)	6 (15.8%)
Colectomy, No. (%)	10 (26.3%)

A serious adverse event is defined as an adverse event leading to hospitalisation, disability or persistent damage or death.