Journal of Crohn's and Colitis, 2021, 35–42
doi:10.1093/ecco-jcc/jjaa145
Advance Access publication September 24, 2020
Original Article

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Tofacitinib in Ulcerative Colitis: Real-world Evidence From the ENEIDA Registry

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Abstract

Aim: To evaluate the effectiveness and safety of tofacitinib in ulcerative colitis [UC] in real life.
Methods: Patients from the prospectively maintained ENEIDA registry and treated with tofacitinib due to active UC were included. Clinical activity and effectiveness were defined based on Partial Mayo Score [PMS]. Short-term response/remission was assessed at Weeks 4, 8, and 16.
Results: A total of 113 patients were included. They were exposed to tofacitinib for a median time of 44 weeks. Response and remission at Week 8 were 60% and 31%, respectively. In multivariate analysis, higher PMS at Week 4 (odds ratio [OR] = 0].2; 95% confidence interval [CI] = 0].1–0.4) was the only variable associated with lower likelihood of achieving remission at Week 8. Higher PMS at Week 4 [OR = 0.5; 95% CI = 0.3–0.7] and higher PMS at Week 8 [OR = 0.2; 95% CI = 0.1–0.5] were associated with lower probability of achieving remission at Week 16. A total of 45 patients [40%] discontinued tofacitinib over time. Higher PMS at Week 8 was the only factor associated with higher tofacitinib discontinuation [hazard ratio = 1.5; 95% CI = 1.3–1.6]. A total of 34 patients had remission at Week 8; of these, 65% had relapsed 52 weeks after achieving remission; the dose was increased to 10 mg/12 h in nine patients, and five of them reached remission again. Seventeen patients had adverse events.
Conclusions: Tofacitinib is effective and safe in UC patients in real practice, even in a highly refractory cohort. A relevant proportion of patients discontinue the drug over time, mainly due to primary failure.

Key Words: Ttofacitinib; ulcerative colitis.

1. Introduction

Ulcerative colitis [UC] is a chronic inflammatory bowel disease [IBD] with a relapsing-remitting pattern that causes an increased frequency of bowel movements and bloody diarrhoea, leading to organ damage and impaired quality of life.[1,2] The primary goals of therapy in UC are reducing the mucosal inflammation and maintaining symptom remission, though these aims are not achieved in all patients.[1–3]

In the past two decades, the introduction of biologic therapies changed the natural history of UC. Remission and response rates achieved with current biologic treatment (anti-tumour necrosis factor alpha [anti-TNF] and vedolizumab) are around 20–35% and 60–70%, respectively.[4,5] Nevertheless, up to 30% of patients do not respond to anti-TNF drugs [primary non-responders], and about 10–20% per year lose response after an initial improvement [secondary non-responders], thereby requiring a dose escalation or a switch to another drug class.[4–11] In addition to TNF, there are several other cytokine pathways involved in the development of UC, which have led to the development of target-specific drugs.

Tofacitinib is an oral synthetic small-molecule Janus kinase [JAK] inhibitor. The JAKs are downstream signalling molecules of a large number of cytokine pathways involved in IBD.[12,13] The efficacy and safety of tofacitinib have been demonstrated in clinical trials in patients with moderate to severe UC, and this drug has recently been approved by the European Medicines Agency for the treatment of this condition. The results of phase III clinical trials have confirmed the superiority of tofacitinib over placebo in induction treatment and maintenance of clinical remission in patients with moderate to severe UC[14]. However, the experience with tofacitinib in clinical practice, in terms of both effectiveness and safety, is still limited. The use of drugs in clinical trials differs from that in routine clinical practice in several aspects, such as patient characteristics [patients are frequently more refractory to treatments and have more comorbidities in real-life practice], thus limiting the generalisation of clinical trial results. Non-interventional studies, on the other hand, provide information complementary to clinical trials on the effectiveness of treatments in real clinical practice settings.

The ENEIDA project [Spanish Team for Intercultural Studies on Academic Discourse] is a prospectively maintained registry that includes UC patients treated with several therapeutic options in daily practice. This registry offers the opportunity to evaluate the real-life effectiveness and safety of tofacitinib in UC patients. Our aim was to assess the short-term effectiveness of tofacitinib in UC, to evaluate the durability of tofacitinib treatment and the cumulative incidence of relapse over time, to identify predictive factors of short- and long-term response, and to assess the safety profile of tofacitinib in a clinical practice setting. Our results provide data that will be useful for the management of UC patients in real life and will help to position tofacitinib in the therapeutic algorithm of UC.

2. Methods

2.1. Study design

This was an observational, prospective and multicentre study carried out with data from the ENEIDA registry, a large prospectively maintained Spanish database promoted by the Spanish Working Group on Crohn's and Ulcerative Colitis [GETECU], initiated in 2007, which in December 2019 included approximately 60 000 patients from 82 centres. Patients aged 18 years or older, diagnosed with UC, who received at least one dose of tofacitinib due to active disease (Partial Mayo Score [PMS] ≥2) were included.[15] Patients who had received tofacitinib for an indication different from UC, those with colonic resection, and those who started the treatment less than 8 weeks before data analysis, were excluded. The ENEIDA registry was approved by research ethics committees in all participating centres. Written informed consent to participating in the ENEIDA project was obtained from all patients.

2.2. Data collection

Patient demographic and clinical characteristics were collected and included: sex, age, colitis extent, extraintestinal manifestations, previous surgery for UC, concurrent use of immunomodulators and steroids, previous treatments for UC, and biological markers (C-reactive protein [CRP] or faecal calprotectin). Start of treatment and change of tofacitinib dose were also registered. Endoscopic assessment information was recorded when available and graded as quiescent, mild, moderate, or severe according to the endoscopic subscore of the Mayo index. In addition, all adverse events during the follow-up period were recorded. Patients were followed up until latest administration of tofacitinib or lastest visit, whichever came first. Data were remotely monitored to assess data quality.

2.3. Evaluation of effectiveness

Short-term effectiveness was assessed at Weeks 4, 8, and 16. Long-term effectiveness was evaluated every time the patients came to the clinic for disease monitoring until latest administration of tofacitinib or latest visit, whichever came first. Clinical activity and effectiveness were assessed based on PMS [including stool frequency, rectal bleeding, and physician's global assessment], ranging from 0 to 9.

2.4. Definitions

2.4.1. Active disease

Active disease was defined as a score ≥2 points in PMS. When endoscopy was available, the severity was graded by local investigators as quiescent, mild, moderate, or severe.

2.4.2. Severity of clinical activity

The severity of clinical activity was rated based on the PMS: <2 remission, 2–4 mild, 5–7 moderate, and >7 severe.

2.4.3. Evaluation of response

Clinical remission or response was determined by PMS calculated at baseline and at Weeks 4, 8, and 16. Clinical remission was defined as a PMS <2. Clinical response was defined as a reduction in PMS ≥3 points and at least 30% from baseline, with a decrease ≥1 point in the rectal bleeding subscale.

2.4.4. Relapse

Relapse was defined as worsening of patient's symptoms coupled with endoscopic, radiographic, or serological [CRP or faecal calprotectin] evidence of inflammation that led the physician to escalate the dose of treatment, add another medication, change to other drug, or change treatment to surgery.

2.5. Statistical analysis

For categorical variables, percentages were calculated [with their 95% confidence intervals]. The descriptive analysis of quantitative variables calculated the mean and standard deviation [SD], or the median and interquartile range [IQR], depending on whether they were normally distributed or not. In the univariate analysis, categorical variables were compared using the chi square [χ^2] test and quantitative variables using the appropriate test. Shor-term effectiveness was evaluated at Week 8; clinical remission at Week 8 was the main variable. Nevertheless, the proportions of patients with clinical remission or clinical response at Weeks 4 and 16 were also evaluated. Variables associated with the likelihood of treatment response after the induction were identified using a logistic regression model. The latest observation carried forward method was used to impute missing data for the short-term evaluation [Weeks 4, 8, and 16].

The Kaplan-Meier method, where patients who discontinued tofacitinib for any reason were right censored at the time of discontinuation, was used to evaluate the long-term durability of tofacitinib treatment. In addition, we analysed the cumulative incidence of relapse among patients who reached remission at Week 8. Any differences between survival curves were evaluated with the log-rank test. Stepwise multivariate analysis using the Cox model was performed to identify factors associated with tofacitinib discontinuation or relapse over time. In the log-rank test and in the multivariate analysis, statistical significance was considered when $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 113 patients were included. The main characteristics of the study population are summarised in Table 1. The majority of patients [70%] had extensive colitis. All patients had been previously exposed to anti-TNF agents, 89% to vedolizumab, and 4% to ustekinumab; 95 [84%] patients had received only anti-TNF agents, 13 [11.5%] anti-TNF agents and vedolizumab, and five [4.5%] patients anti-TNF agents, vedolizumab and ustekinumab, before tofacitinib treatment. At baseline, 11% of patients were under immunomodulators [nine patients under thiopurines and four under methotrexate] and 48% under steroids. A total of 18 patients were under steroids at Week 4, 14 at Week 8, and nine patients at Week 16 [of them, only three were in clinical remission at Week 16].

The median Partial Mayo Score at the start of tofacitinib treatment was 6 [IQR = 6–8]; 67% of patients had endoscopic assessment of disease activity before starting tofacitinib treatment: 65% had severe, and 29% moderate activity. In addition, one-third of patients had anaemia, two-thirds had CRP levels over the normal limit, and median faecal calprotectin at baseline was 1 499 µg/g.

A patient flow chart, including tofacitinib dose adjustments, discontinuations and reasons for discontinuations; is shown in Figure 1. In all, 94 of patients started tofacitinib treatment with 10 mg/12 h; two of these had to interrupt the treatment before Week 4 due to primary non-response. A total of 101 patients reached Week 8 under tofacitinib treatment; 92% of these with the 10 mg/12 h dose and 27 patients changed to the maintenance dose [5 mg/12 h]. A total of 77 patients reached Week 16 under tofacitinib treatment, 28 of these receiving under 10 mg/12 h. Four patients were changed to the maintenance dose at Week 16.

Table 1. Characteristics of the study population [A] among patients with or without remission at Week 8 [B].

[A] Characteristics	
Median age [SD] [years]	46 [1.3]
Median time of follow-up [IQR] [weeks]	44 [30-66]
Male gender [%]	53
UC extent	
Proctitis [%]	4
Left-sided colitis [%]	26
Extensive colitis [%]	70
Median Partial Mayo Score at baseline [IQR]	6 [6-8]
Endoscopic assessment at baseline [%]	67
Moderate activity [%]	29
Severe activity [%]	65
CRP above the normal limit at baseline [%]	68
Anaemia at baseline [%]	32
Median faecal calprotectin at baseline [µg/g]	1499
Previous biologic treatment [%]	100
Anti-TNF [%]	100
Vedolizumab [%]	89
Ustekinumab [%]	4
Number of previous biologic agents	
1-=-2 previous biologics [%]	31
>3 previous biologics [%]	69
Concomitant immunosuppresants [%]	11
Steroids during induction, [%]	48

[B] Remission	No remission at Week 8	Remission at Week 8	*p*
Severe endoscopic activity at baseline [%]	74	46	0.02
Median CRP at baseline [mg/dL]	1.3	0.6	0.03

SD, standard deviation; UC, ulcerative colitis,; IQR, interquartile range; CRP, C-reactive protein; TNF, tumour necrosis factor.

3.2. Short-term effectiveness

In the short term, 18 [16%] patients reached clinical remission at Week 4, 34 [31%] at Week 8, and 33 [32%] at Week 16. With respect to clinical response [including both patients with response and those with remission], 45 [40%] had response at Week 4, 66 [60%] at Week 8, and 59 [57%] at Week 16 [Figure 2].

Patients who achieved remission at Week 8 had, at baseline, a lower proportion of severe endoscopic activity [46% vs 74%, p <0.05] and lower CRP [0.6 mg/dL vs 1.3 mg/dL, p <0.05] than patients who did not achieve remission. Other characteristics, such as disease extension, treatment with steroids at baseline, or number of previous biologics, were similarly distributed in both groups. In addition, patients who achieved remission at Week 8 had lower CRP at Week 4 [0.13 mg/dL vs 1.2 mg/dL, p <0.05] and lower PMS [1 vs 5, p <0.05] than patients who did not achieve remission. In the multivariate analysis, higher PMS at Week 4 [OR = 0.2; 95% CI = 0.1–0.4] was the only variable associated with the likelihood of achieving remission at Week 8 [the higher the PMS, the lower probability of achieving remission].

At Week 16, 27% of patients without remission at Week 4, and 12% of those without remission at Week 8, had achieved remission. Clinical characteristics at baseline, including PMS, CRP concentration, haemaglobin, faecal calprotectin, number of previous biologic treatments, endoscopic activity, or concomitant treatment with immunomodulators or steroids were similar in patients with or without remission at Week 16. Patients who achieved remission at Week 16 had lower proportion of elevated CRP both at Week 4 [37% vs 67%, p <0.05] and at Week 8 [24% vs 51%, p <0.02] than those who did not achieve remission at Week 16. In addition, patients in clinical remission at Week 16 had lower PMS both at Week 4 [2 vs 4, p <0.01] and at Week 8 [1 vs 4, p <0.01] than those without remission at Week 16. In the multivariate analysis, higher PMS at Week 4 [OR = 0.5; 95% CI = 0.3–0.7] and higher PMS at Week 8 [OR = 0.2; 95% CI = 0.1–0.5] were associated with lower probability of achieving remission at Week 16.

3.3 Tofacitinib survival

A total of 45 patients [40%] discontinued tofacitinib over time [median of exposure to tofacitinib was 44 weeks; IQR = 30–66 weeks]. Cumulative discontinuation rate was 34% and 46% at 24 and 52 weeks, respectively [Figure 3]. The reasons for tofacitinib discontinuation were: primary non-response in 29 patients [26%], adverse events in seven patients [6%], relapse in six patients [5%], partial response in two patients [2%], and pregnancy wish in one patient [1%]. PMS at Week 8 was the only factor associated with tofacitinib discontinuation [hazard ratio = 1.5; 95% CI = 1.3–1.6].

3.4 Long-term effectiveness

A total of 34 patients were in remission at Week 8; 13 [38%] relapsed during follow-up [Figure 4]; the dose was increased to 10 mg/12 h in nine patients, and five of these reached remission again. No factors associated with relapse over time were identified.

3.5. Adverse events

Seventeen patients [15%] had adverse events during follow-up, some of them more than one adverse event: four patients had hypercholesterolaemia, one herpes zoster [single dermatome involvement and resolved without postherpetic neuralgia], one herpes simplex, three infections, two dyspnoea, one neoplasia, one lymphopenia, one headache, one hypertriglyceridaemia, and four others. With respect to infections, two patients had salmonella gastrointestinal infections [leading to tofacitinib discontinuation] and the third patient a cryptoglandular anorectal abscess [treated with drainage and antibiotics; tofacitinib was maintained]. No thromboembolic events were reported. Seven patients [6%] presented adverse events that led to treatment discontinuation. The first patient developed high fever and headache with doubtful meningeal signs and was empirically treated with antiviral drugs, although microbiological tests were always negative. The suspicion was a serious viral infection but the agent was not identified. After withdrawing treatment and completing valganciclovir treatment, all symptoms disappeared. Two patients presented with severe salmonella gastrointestinal infections and recovered without sequelae. Another patient had severe abdominal pain without identifying the cause. The fifth patient presented dyspnoea clearly associated with the drug intake. The sixth patient presented herpes zoster infection, dyspnoea and dizziness. Finally, a patient developed a metastatic breast cancer probably related to a high immunosuppressive load before being treated with tofacitinib.

4. Discussion

To our knowledge, this is the largest cohort among the few published real-life studies of UC patients treated with tofacitinib. Our results provide new information about the effectiveness of tofacitinib in real life, which is of great value to position this treatment in clinical practice.

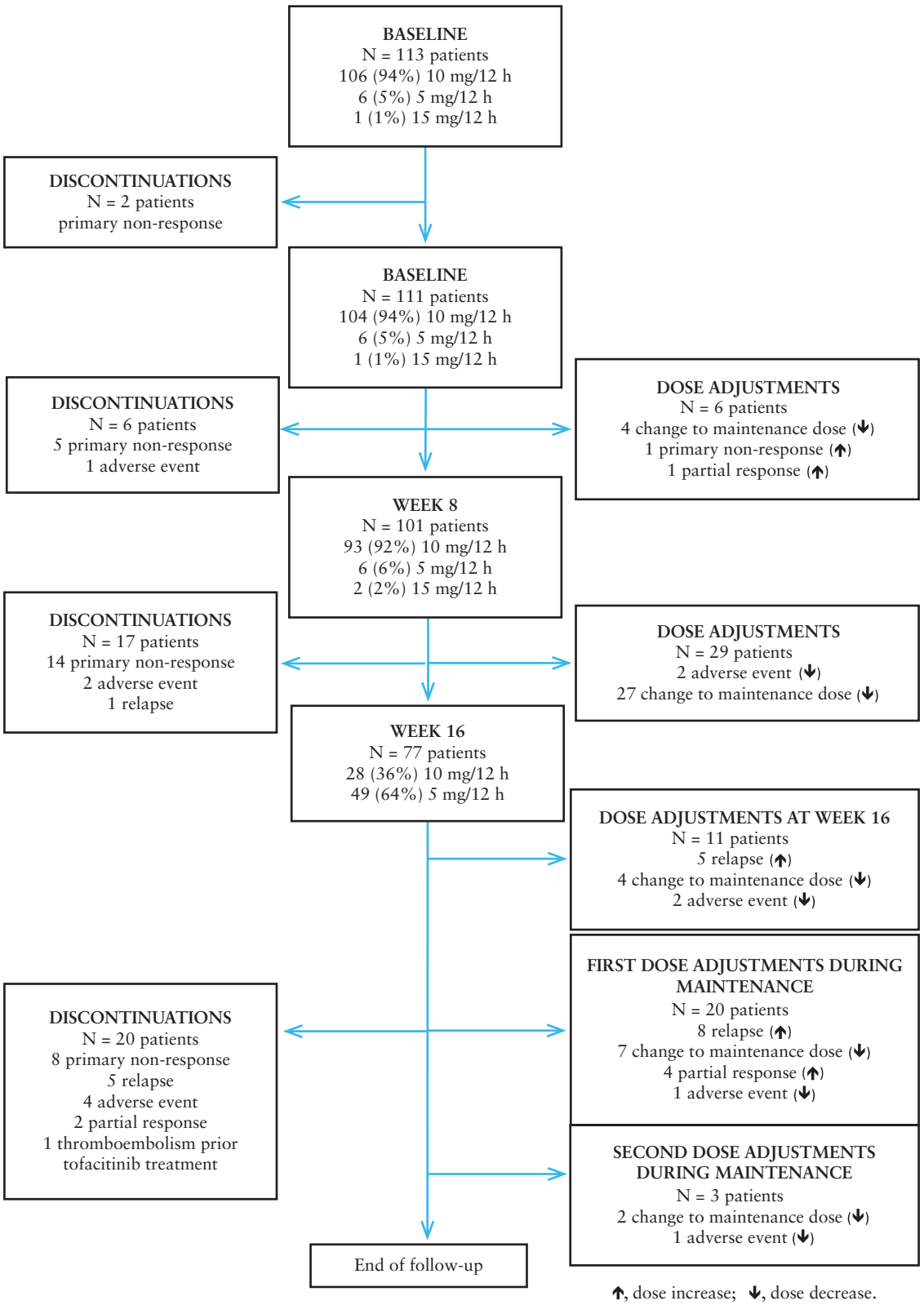

Figure 1. Flow chart of patients, including tofacitinib dose adjustment, discontinuations and reasons for discontinuation. Not all patients reached all the evaluation moments because, even if they maintained the treatment, they may not have had time since the beginning of the treatment.

First, our results support that tofacitinib is effective in clinical practice in a refractory UC population [all patients had previously failed treatment with biologic therapies such as anti-TNF drugs or vedolizumab]. Thus, at Week 8, approximately one-third of patients achieved remission and two-thirds had response. In addition, after the first 4 weeks, almost 20% of patients achieved clinical remission

and 40% of patients responded to treatment, confirming the early response to tofacitinib which was previously observed in the OCTAVE trials.[16] However, despite the fast mechanism of action of tofacitinib, some patients need longer to reach remission. In this respect, in our study, patients without remission at Week 4 did benefit from continuing the treatment: 20% of patients without remission at Week 4, and 12% of those without remission at Week 8, achieved remission at Week 16. Similarly to our results, previous studies showed that a substantial proportion of non-responders to an initial 8-week course of tofacitinib with a twice-daily dose of 10 mg respond to an additional extended induction course of 8 weeks.[17,18]

Our results are consistent with those from pivotal studies. In this respect, in a phase II trial with patients who received 10 mg twice-daily, at Week 8 clinical response and remission occurred in 61% and 48% of the patients, respectively.[12] In the OCTAVE induction 1 and 2 trials, remission at Week 8 was achieved by 18% and 17% of the patients, respectively.[14,19]

With respect to real-life studies, short-term effectiveness of tofacitinib in refractory UC was evaluated in a retrospective study conducted by Lair-Mehiri *et al.* in 38 refractory UC patients, previously treated with anti-TNF [100%] and vedolizumab [97%].[20] At Week 14, steroid-free remission was achieved in 32% and clinical response in 45% of patients. Similarly, the other published cohort on the effectiveness of tofacitinib in real life included 58 UC patients who previously failed anti-TNF [93%] and anti-integrin [81%]; this study showed that remission at Week 8 [defined as complete resolution of clinical symptoms] was achieved in 33% of the patients, and clinical response [defined as symptomatic improvement from baseline] in 36%.[21]

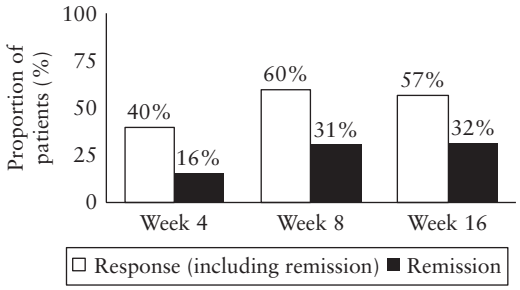

Figure 2. Short-term effectiveness of tofacitinib in ulcerative colitis [last-observation-carried-forward method].

Furthermore, we detected predictive factors of remission that would allow us to identify the subset of patients who will benefit the most from the treatment. In this regard, we observed that early response at Weeks 4 and 8 indicated higher probability of remission at Week 16; thus, patients with more severe disease as measured by PMS at Week 4 and Week 8 were less likely to achieve remission at Week 16. The other two published cohorts of patients with UC treated with tofacitinib did not identify predictive factors of response to the treatment, probably due to their limited sample size.[20,21] In our cohort, patient characteristics at baseline, such as PMS, CRP concentration, faecal calprotectin concentration, or number of previous biologics, were not associated with the likelihood of remission at Week 8. In line with our results, in the OCTAVE 1 and 2 trials, tofacitinib efficacy was consistent regardless of CRP levels at baseline, baseline steroid use, or previous exposure to anti-TNF.[14] Based on these results, tofacitinib might be a good therapeutic option also in patients with previous failure to anti-TNF.

On the other hand, a significant proportion of patients [40%] discontinued the drug over time [cumulative discontinuation rate was 34% and 46% at 24 and 52 weeks, respectively], mainly due to primary failure [26%] followed by adverse events [6%], relapse [5%], and partial response [2%]. In line with our results, Weisshof *et al.* reported discontinuation of tofacitinib in 26/58 [45%] patients during a median follow-up period of 10 months, due to poor response or adverse events.[21] Lair-Mehiri *et al.* reported a discontinuation rate of 42% [16/38] in a follow-up period of 41 weeks, mostly occurring within 24 weeks and due to lack of effectiveness [seven disease worsenings and four non-responses].[20]

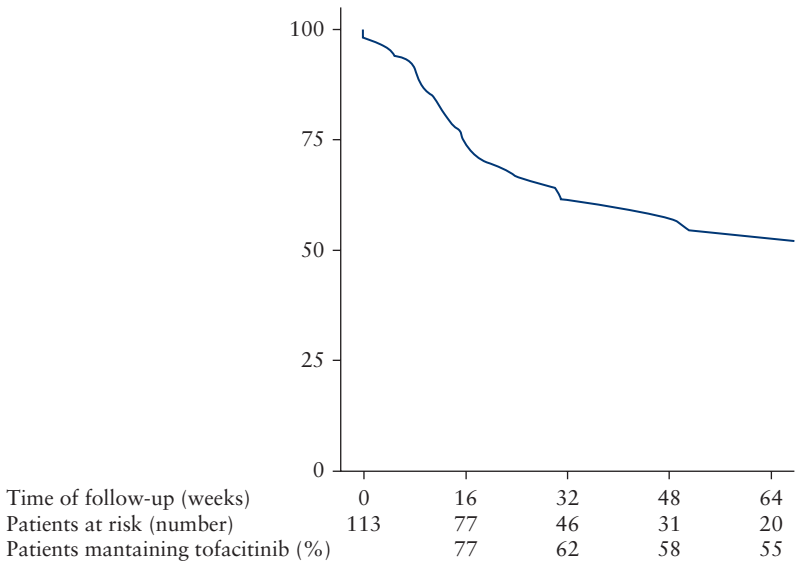

Figure 3. Survival curve of patients maintaining tofacitinib treatment over time.

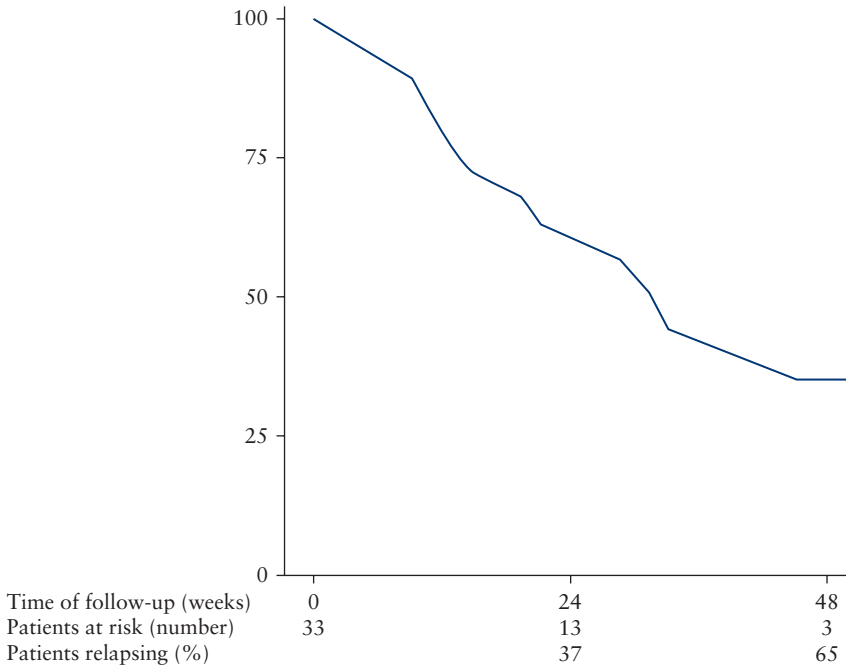

Figure 4. Survival curve of patients relapsing over time [from Week 8 and including only patients in remission at that time].

Tofacitinib is a small molecule with lack of immunogenicity as opposed to biologic agents, which are large protein-based molecules. It is known that the formation of antibodies against biologic drugs could affect their long-term efficacy.[22] It is still unclear whether the response to tofacitinib is lasting or long-term response could be lost in patients treated with this drug. We observed that 38% of patients who achieved remission at Week 8 relapsed over time [median of exposure to tofacitinib, 44 weeks]. The durability of remission under tofacitinib treatment was also evaluated in the OCTAVE Sustain trial, where patients were included to assess whether tofacitinib could be used to maintain remission.[14] For patients already in remission at maintenance trial entry, sustained remission at Week 52 occurred in 35% of patients in the 5-mg group and 47% in the 10-mg group. In our study, after relapsing, tofacitinib dose was escalated from 5 mg/12 h to 10 mg/12 h in nine patients; five of these reached remission again after increased tofacitinib dose. Sands *et al.* analysed the efficacy of dose escalation of tofacitinib [to 10 mg/12 h] in patients who lost response while being treated with tofacitinib 5 mg/12 h as maintenance therapy in the OCTAVE open trial; at Month 12, 75% of patients maintained remission.[23] After dose escalation, 35% and 49% recaptured remission at Months 2 and 12, respectively. Thus, dose escalation might be an option in patients relapsing under the maintenance dose.

Of note, the European Medicines Agency advised that maintenance doses of 10 mg twice daily should not be used in patients with UC who are at high risk of blood clots unless there is no suitable alternative treatment, due to the dose-dependent increased risk of blood clots in the lungs and deep veins of patients who are already at high risk.[24] This recommendation should be taken into consideration when deciding the treatment schedule with tofacitinib. Nevertheless, data about the dose-dependent increased risk of thromboembolic events come from studies in rheumatoid arthritis patients, and particularly in patients over 50 years of age, whereas the abovementioned risk has not been confirmed in UC patients yet.[25] In this respect, in a *post-hoc* analysis of the OCTAVE trials, only five patients developed thromboembolic events [one deep venous thrombosis and four pulmonary embolisms]; all of them had risk factors for venous thromboembolism and were predominantly under the 10-mg/12 h dose.[26] In our study, the safety profile of tofacitinib was in line with previous data,[27] and no thromboembolic events were reported. However, it should be acknowledged that the analysis is limited by small sample size and limited drug exposure, and therefore more data are needed.

Our study has some limitations. First of all, although the ENEIDA registry is prospectively completed, efficacy outcomes are rated on the basis of clinical subjective assessment. To overcome the potential heterogeneity in clinical assessment, clinicians were asked to provide PMS score values at every visit. In addition, we could not evaluate mucosal healing. However, this reflects what happens in clinical practice, where endoscopy studies are generally not carried out if patients have good response after induction. Information about concomitant steroids is not easy to understand in real-world evidence studies where the follow-up is not pre-established per protocol [follow-up time was different in each patient]. Unfortunately, there is no available information on the precise dose of steroids during tofacitinib treatment. Finally, all of our patients had previously failed treatment with biologic agents, and therefore we could not assess the impact of biologic exposure on tofacitinib effectiveness.

On the other hand, our study has several strengths. First of all, this is the largest study published up to now on the effectiveness of tofacitinib on UC in real-life. Clinical activity was categorised based on PMS, which has acceptable correlation with the presence of inflammation,[28] and we also included other objective parameters such as CRP levels or faecal calprotectin concentrations. Finally, we could assess durability of tofacitinib treatment, relapse rate, and response to dose escalation.

In conclusion, tofacitinib is relatively effective, providing a rapid therapeutic effect in UC patients in real practice, even in a highly

refractory cohort. A relevant proportion of patients discontinue the drug over time, mainly due to primary failure. A relevant proportion of the patients who achieve remission after induction relapse over time, although dose escalation is able to recapture remission in over 50% of them. Finally, safety was consistent with the known profile of tofacitinib.

Funding

The ENEIDA registry of GETECCU is supported by Biogen, Jannsen, Takeda, and Pfizer.

Conflict of Interest

MC has served as a speaker, or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma. MBdeA has served as a speaker, a consultant, and advisory member for or has received research funding from MSD, Abbvie, Hospira, Takeda, Janssen, Kern, Ferring, FaesFarma, ShirePharmaceuticals, Dr FalkPharma, Chiesi, GebroPharma, OtsukaPharmaceuticals, and TillottsPharma. IV-M has served as speaker, consultant, and advisory member for and has received funding from MSD, Abbvie, Pfizer, Ferring, Shire Pharmaceuticals, Takeda, Jannsen. TM has served as speaker, consultant, and advisory member for and has received funding from Janssen, Abbvie, Pfizer, Amgen, Takeda, Tillotts Pharma, Shire. JPG has served as a speaker, a consultant, and advisory member for or has received research funding from MSD, Abbvie, Hospira, Pfizer, Kern Pharma, Biogen, Takeda, Janssen, Roche, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Vifor Pharma. ED has served as a speaker, or has received research or education funding or advisory fees from MSD, AbbVie, Takeda, Kern Pharma, Pfizer, Janssen, Celgene, Adacyte Therapeutics, Otsuka Pharmaceuticals, Ferring, Shire Pharmaceuticals, Tillots, Thermofisher, Grifols, Gebro. PN has served as a speaker, or has received research or education funding from MSD, AbbVie, Takeda, Kern Pharma, Pfizer, Janssen, Biogen, Sandoz, Adacyte Therapeutics, Faes, Ferring and Tillots. The rest of authors have nothing to declare.

Author Contributions

MCh and JPG: study design, data collection, data analysis, data interpretation, writing the manuscript. AG: data monitoring. The rest of the authors: patient inclusion. All authors approved the final version of the manuscript.

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