Real-World Evidence of Tofacinitib in Ulcerative Colitis: Short-Term and Long-Term Effectiveness and Safety

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INTRODUCTION: **The objective of this study was to assess the durability, short-term and long-term effectiveness, and safety of tofacitinib in ulcerative colitis (UC) in clinical practice.**

METHODS: **This is a retrospective multicenter study including patients with UC who had received the first tofacitinib dose at least 8 weeks before the inclusion. Clinical effectiveness was based on partial Mayo score.**

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RESULTS: **A total of 408 patients were included. Of them, 184 (45%) withdrew tofacitinib during follow-up (mean = 18 months). The probability of maintaining tofacitinib was 67% at 6 m, 58% at 12 m, and 49% at 24 m. The main reason for tofacitinib withdrawal was primary nonresponse (44%). Older age at the start of tofacitinib and a higher severity of clinical activity were associated with tofacitinib withdrawal. The proportion of patients in remission was 38% at week 4, 45% at week 8, and 47% at week 16. Having moderate-to-severe vs mild disease activity at baseline and older age at tofacitinib start were associated with a lower and higher likelihood of remission at week 8, respectively. Of 171 patients in remission at week 8, 83 (49%) relapsed. The probability of maintaining response was 66% at 6 m and 54% at 12 m. There were 93 adverse events related to tofacitinib treatment (including 2 pulmonary thromboembolisms [in patients with risk factors] and 2 peripheral vascular thrombosis), and 29 led to tofacitinib discontinuation.**

DISCUSSION: **Tofacitinib is effective in both short-term and long-term in patients with UC. The safety profile is similar to that previously reported.**

KEY WORDS: ulcerative colitis; tofacitinib; real-world evidence

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C840

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with a relapsing-remitting pattern that causes bloody diarrhea, leading to organ damage and impaired quality of life. 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 (1,2).

In the last 2 decades, the introduction of targeted and biological therapies has changed the natural history of UC. Nevertheless, up to 30% of patients do not respond to a first-line treatment (primary nonresponders), and approximately 20% per year lose response after an initial improvement (secondary nonresponders), thereby requiring a dose escalation or a switch to another drug class (3–10). In addition to the initially described tumor necrosis factor (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 inhibitor. Janus kinase are downstream signaling molecules of many cytokine pathways involved in inflammatory bowel disease (11). Tofacitinib was approved for the treatment of moderate-to-severe UC based on the efficacy and safety data shown in the UC clinical development program. The results of phase 3 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 (12).

The use of drugs in clinical trials differs from that of the routine clinical practice in several aspects such as patient characteristics (patients are frequently more refractory to treatments and with more comorbidities in real-life practice), thus limiting the generalization of clinical trial results. Noninterventional studies, on the contrary, provide complementary information to clinical trials on the effectiveness and the way of use of treatments in real clinical practice settings. However, the experience with tofacitinib in clinical practice, both for effectiveness and safety, is still quite limited (13). Studies published so far include a limited number of patients with a limited follow-up (below 1 year), which makes it difficult to get robust conclusions and to examine certain aspects of the use of this drug.

Our objective was to understand in depth the role of tofacitinib in the treatment of UC in clinical practice and to provide useful data to know its real benefit. To reach our goal, we aimed to describe the durability of tofacitinib treatment and factors conditioning drug interruption in clinical practice, the short-term and long-term effectiveness, the dose adjustments, and the safety profile in a real-life, large, multicenter nationwide study. We anticipate that our results will provide useful data for the management of patients with UC in real life and will help to position tofacitinib in the therapeutic algorithm of UC.

METHODS

Study design

This is a retrospective, multicenter, noninterventional study to assess the retention of tofacitinib treatment in patients with UC. Every patient who met the criteria in each participating center was included. Patients were followed up until the last tofacitinib dose or the last visit, whichever came first. Data were remotely monitored to assess data quality. Because this is an observational study, the schedule of tofacitinib administration was not predefined and was decided by the clinician responsible for patients' treatment. The project was approved by the Ethics Committee of Hospital Universitario de La Princesa.

Patient population

The study population consisted of adult patients who had received at least 1 dose of tofacitinib due to UC at least 8 weeks before the start date of recruitment. Patients treated with tofacitinib for any indication other than UC, with previous colectomy, and/or those who had been involved in a clinical trial with tofacitinib were excluded.

Data collection

Patient demographic and clinical characteristics were collected: sex, age, smoking, age at diagnosis, disease extent, extraintestinal manifestations (EIM) and immune-mediated inflammatory diseases (IMID), previous surgery for UC, concomitant use of steroids and immunomodulators at the beginning of and during

follow-up, previous treatments for UC, reasons for discontinuation of previous treatments for UC (immunomodulators and biologic agents), start date of tofacitinib therapy, response to tofacitinib, clinical activity at baseline and during follow-up, concomitant medication for UC, date of discontinuation (when it occurred), reason for discontinuation (lack of primary response, relapse, patient choice, adverse event, surgery for UC worsening, others, unknown reason), dosing regimen during maintenance, treatment after loss of response to tofacitinib (if any), dose increase (if any), dose decrease (if any), response after dose optimization, evolution of EIM and IMID, surgery for UC, hospitalizations (due to UC or for other reasons), and adverse events. In addition, information about endoscopic activity (endoscopic subscore of the Mayo index) or biological markers (such as C-reactive protein [CRP] or fecal calprotectin concentration) was requested from clinicians responsible for patients' treatment, when available.

Data were collected and managed using REDCap electronic data capture tools hosted at (www.aegastro.es). Asociación Española de Gastroenterología is a nonprofit Scientific and Medical Society focused on Gastroenterology, which provides this service free of charge, with the sole aim of promoting independent investigator-driven research.

Tofacitinib durability and effectiveness measurements

The durability of tofacitinib treatment was calculated considering the entire period under tofacitinib treatment: from the first dose to the last dose with this drug. Patients included in this study had to have received tofacitinib for clinical indication. Some patients might have received the treatment being in remission due to intolerance to or contraindication of other drugs. Only patients with active disease (partial Mayo score [PMS] $>$ 2) were considered in the short-term effectiveness analysis.

Active disease was defined as a PMS $>$2. When endoscopy was available, the severity was graded by local investigators as quiescent, mild, moderate, or severe. The severity of clinical activity was rated based on the PMS.

Clinical remission was defined as a PMS $\leq$2. Clinical response was defined as a reduction in the PMS $\geq$3 points and a decrease of at least 30% from baseline, with a decrease of $\geq$1 point on the rectal bleeding subscale (absolute score 0–1). Relapse was defined as a worsening in the patient's symptoms leading the doctor to intensify the treatment dose, add another medication for the control of UC, or switch to another treatment or surgery.

Evolution of EIM and IMID

The evolution of previous EIM and IMID was evaluated based on clinicians' judgment. The onset of new EIM and IMID under tofacitinib treatment was recorded.

Safety assessments

All adverse events occurring during tofacitinib treatment were registered and their relationship with tofacitinib administration, based on clinicians' criteria, were recorded. Serious adverse events were defined according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and European Union guidelines on pharmacovigilance of medicinal products for human use. Major cardiovascular adverse events were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Statistical analysis

For categorical variables, percentages were calculated (with their 95% confidence intervals [CI]). The descriptive analysis of quantitative variables calculated the mean and SD, or the median and interquartile range (IQR), depending on whether the variables were normally distributed or not. In the univariate analysis, categorical variables were compared using the χ^2 test and quantitative variables using the appropriate test. For short-term effectiveness evaluation, only patients with PMS $>$2 at baseline were considered. Short-term effectiveness was evaluated at weeks 4, 8, and 16. Variables associated with the likelihood of treatment response after induction were identified using a logistic regression model. In patients who discontinued tofacitinib owing to lack of therapeutic effect, an adverse event, or worsening of UC before their last visit, the last observation carried forward method was used to impute missing values at subsequent time points for both short-term and long-term evaluation.

The Kaplan-Meier method, where patients who discontinued tofacitinib for any reason were censored during discontinuation, was used to evaluate the long-term durability of tofacitinib treatment (main outcome). In addition, we analyzed 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 multivariate analysis, statistical significance was considered when $P < 0.05$. The cumulative incidence of adverse events was calculated; in addition, for the most relevant adverse events, the incidence rates were calculated and expressed as patients with first events per 100 patient-years.

RESULTS

A total of 408 patients were included. The main characteristics of the study population are summarized in Table 1. A total of 234 patients (57%) had extensive colitis, and 151 (37%) had left-sided colitis. Almost all patients, but 26 (6.4%), had clinically active disease defined as a PMS $>$2 at tofacitinib start; 69 (17%) had mild activity and 313 (77%) moderate-to-severe activity. The mean age was 44 years, the median time from UC diagnosis was 7.5 years, 45% had comorbidities (see Supplementary Table 1, http://links.lww.com/AJG/C840), and 30% had cardiovascular and thrombotic risk factors (see Supplementary Table 2, http://links.lww.com/AJG/C840). Regarding previous treatment for UC, 97% had been exposed to biologics and more than 70% to 2 or more biologics before tofacitinib treatment (see Supplementary Table 3, http://links.lww.com/AJG/C840).

Durability of tofacitinib treatment in patients with UC

A total of 184 patients (45%) withdrew tofacitinib treatment during follow-up (median = 18 months, IQR = 10–29 months). The median time of exposure to tofacitinib was 8.5 months (IQR = 4–18 months). The incidence rate of tofacitinib discontinuation was 41% per patient-year of follow-up (95% CI = 36%–48%). The survival curve of tofacitinib treatment is shown in Figure 1. The probability of maintaining tofacitinib treatment was 91% at 1 month, 67% at 6 months, 58% at 12 months, 53% at 18 months, 49% at 24 months, 46% at 30 months, and 45% at 36 months. Reasons for tofacitinib withdrawal were as follows: 81 (44%) primary nonresponse, 48 (26%) loss of response, 29 (16%) adverse events, 19 (10%) partial response, and 7 (3.8%) medical decision (Figure 2). After tofacitinib withdrawal, 74 patients

Table 1. Characteristics of the study population

Variables	N = 408
Age (yr), mean (SD)	44 (15)
Median time of follow-up (mo) (IQR)	18 (10–29)
Median time from UC diagnosis (yr) (IQR)	7.5 (4–13)
Male sex, n (%)	232 (57)
Comorbidities, n (%)	182 (45)
Cardiovascular and thrombotic risk factors, n (%)	124 (30)
Family history of IBD, n (%)	61 (15)
Ulcerative colitis extension	
Extensive colitis, n (%)	234 (57)
Left-sided colitis, n (%)	151 (37)
Proctitis, n (%)	23 (6)
Extraintestinal manifestations, n (%)	115 (28)
Previous biologic agents, n (%)	397 (97)
Anti-TNF, n (%)	377 (92)
Vedolizumab, n (%)	298 (73)
Ustekinumab, n (%)	24 (5.9)
Mean no. of previous biologic agents (SD)	2 (0.9)
Median partial mayo score at baseline (IQR)	6 (5–7)
Severe endoscopic activity, n (%)	140 (55)
Anemia at baseline, n (%)	132 (32)
Concomitant mesalazine, n (%)	163 (40)

IBD, inflammatory bowel disease; IQR, interquartile range; TNF, tumor necrosis factor.

(40%) were treated with ustekinumab, 36 (20%) underwent surgery, 29 (16%) received vedolizumab, 21 (11%) an anti-TNF agent, and 24 (13%) other therapeutic options.

In the univariate analysis, the mean age of patients who withdrew the treatment was significantly lower than that of those who maintained tofacitinib (41 vs 47 years, $P < 0.05$). The severity of clinical activity of UC at baseline was associated with a lower probability of tofacitinib survival: stool frequency ($P < 0.001$), bloody stools ($P < 0.001$), and severity based on the PMS

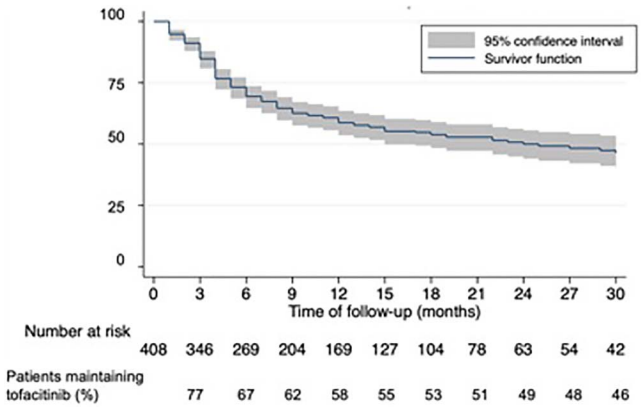

Figure 1. Survival curve of tofacitinib treatment in ulcerative colitis.

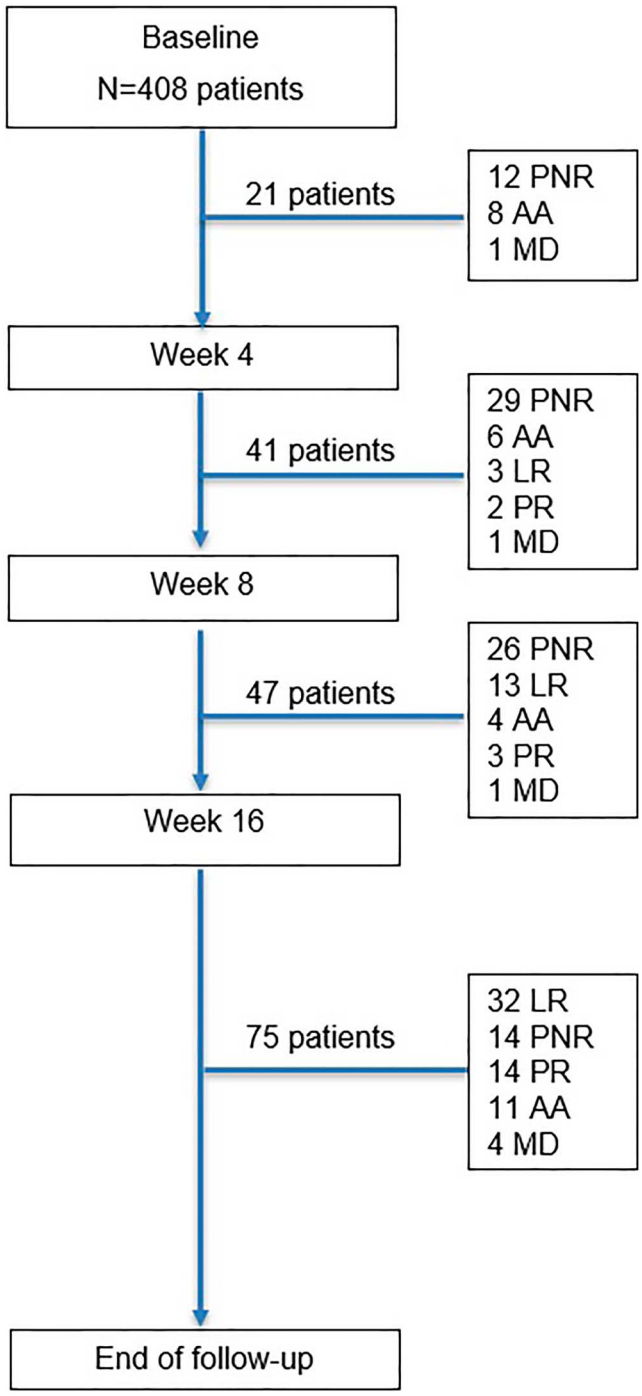

Figure 2. Timing and reasons for tofacitinib withdrawal. AA, adverse events; LR, loss of response; MD, medical decision; PNR, primary nonresponse; PR, partial response.

($P < 0.001$). Other variables such as sex, smoking habits, thromboembolic risk factors, family history of the disease, UC extension, EIM, type of previous treatments for UC, number and type of previous biologics, anemia at baseline, severity of endoscopic activity, or concomitant treatment with mesalamine were not associated with tofacitinib survival.

In the multivariate analysis, older age at the start of tofacitinib was associated with a lower likelihood of tofacitinib withdrawal

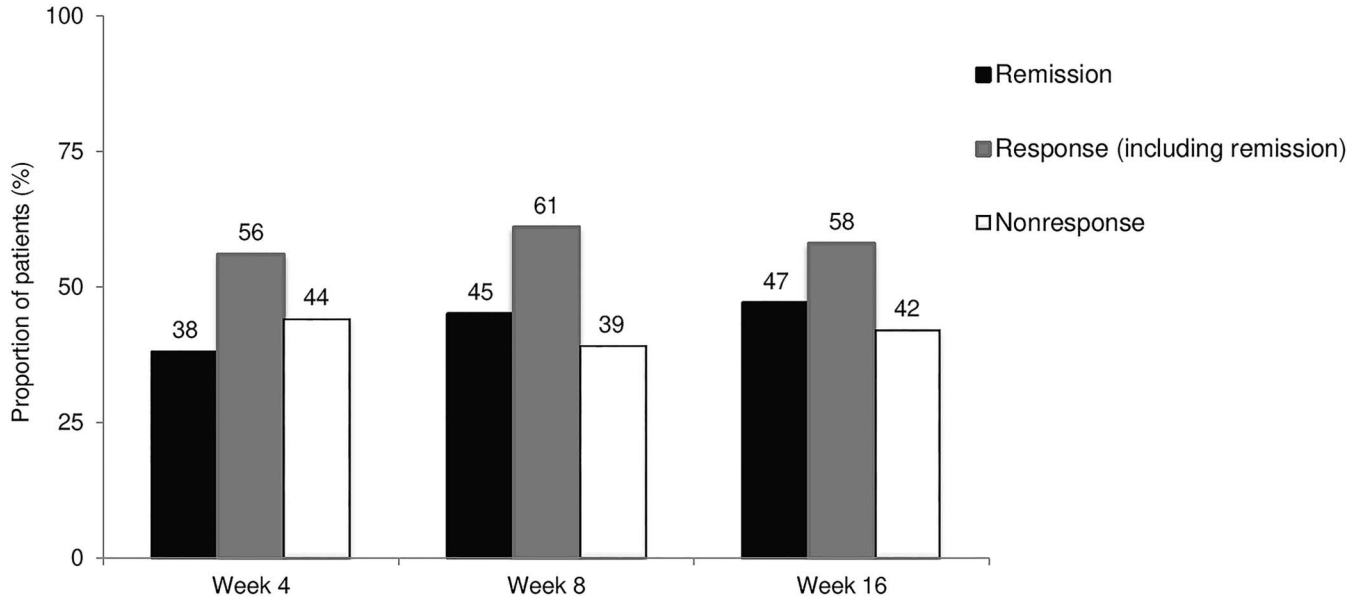

Figure 3. Short-term effectiveness of tofacitinib in ulcerative colitis.

(hazard ratio [HR] = 0.98, 95% CI = 0.97–0.99), while the severity of clinical activity at baseline based on the PMS was associated with a higher likelihood of tofacitinib withdrawal (mild vs remission: HR = 1.5, 95% CI = 0.5–4, and moderate-to-severe vs remission: HR = 3, 95% CI = 1.2–7.4).

Short-term effectiveness

A total of 382 patients had clinical activity of the disease at baseline (PMS >2) and were included in the effectiveness analysis. Short-term effectiveness is shown in Figure 3; of note, 38% of patients were in remission at week 4, 45% at week 8, and 47% at

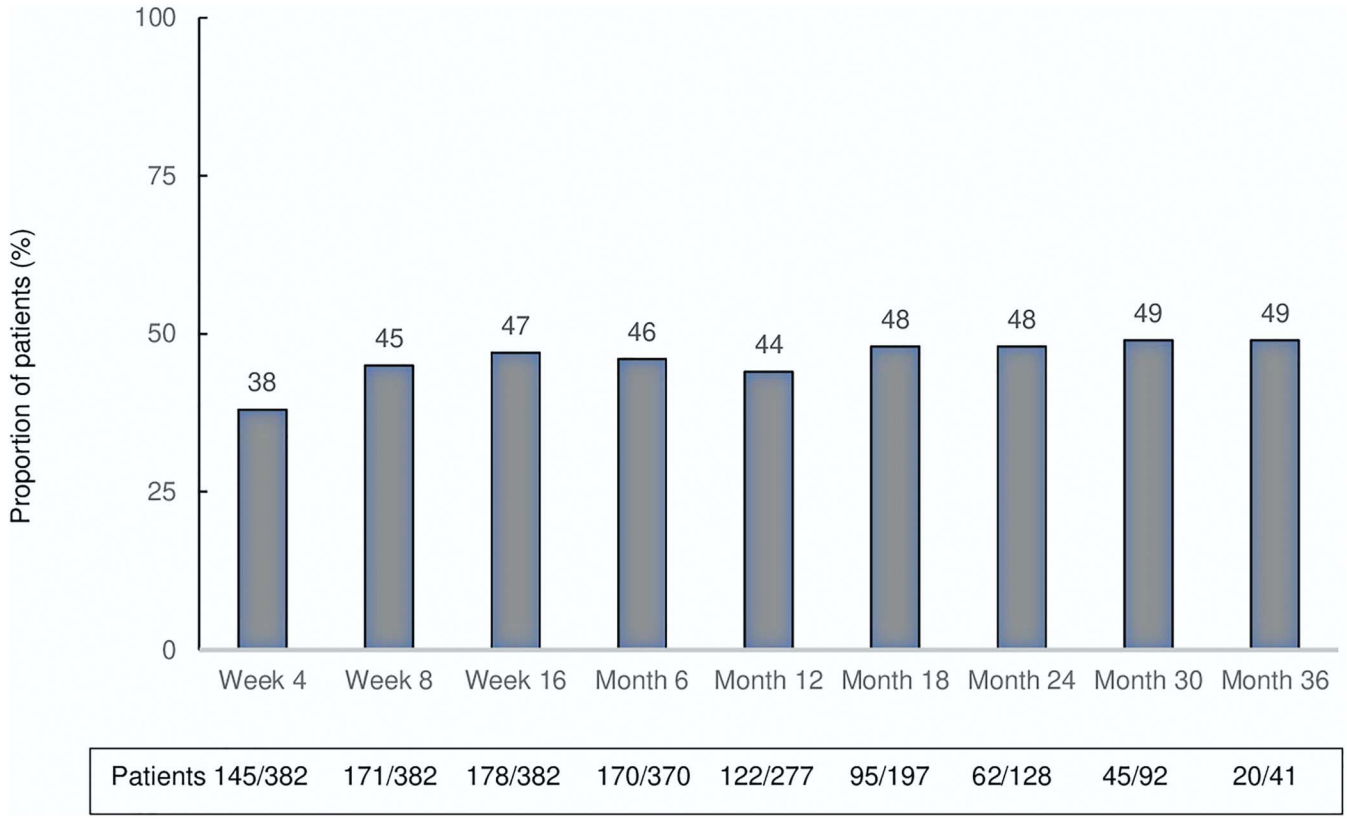

Figure 4. Proportion of patients with ulcerative colitis in remission under tofacitinib treatment.

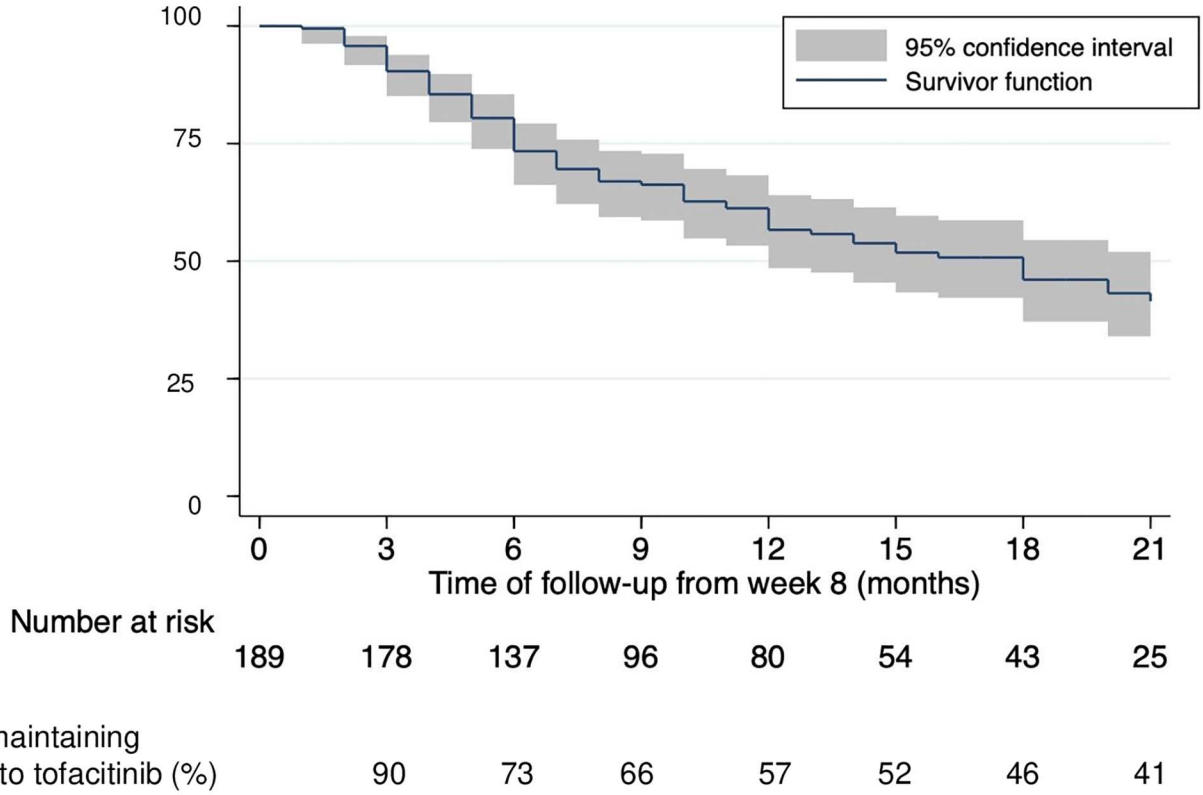

Figure 5. Survival curve of maintenance of tofacitinib effectiveness in patients with ulcerative colitis.

week 16. Of the patients with no response at week 4, 18% reached remission at week 8, and 26% at week 16. Of the patients with nonresponse at week 8, 19% reached remission at week 16.

Week 4

In the univariate analysis, the severity of clinical activity at baseline was the only variable associated with remission at week 4, and this finding was confirmed in the multivariate analysis, where the severity of the disease at baseline (moderate-to-severe vs mild) was the only variable associated with the likelihood of achieving remission at week 4 (odds ratio [OR] = 0.2, 95% CI = 0.1–0.4).

Week 8

In the univariate analysis, only the age at the start of tofacitinib treatment and the severity of clinical activity at baseline were associated with remission at week 8. In the multivariate analysis, having moderate-to-severe vs mild disease activity at baseline (OR = 0.2, 95% CI = 0.1–0.4) and older age at tofacitinib start (OR = 1.01, 95% CI = 1.002–1.03) were the only variables associated with the likelihood of achieving remission at week 8.

Week 16

In the univariate analysis, the presence of EIM, the age at the start of tofacitinib treatment, and the severity of clinical activity at baseline were associated with remission at week 16. In the multivariate analysis, having moderate-to-severe vs mild disease activity at baseline (OR = 0.4, 95% CI = 0.2–0.6) was the only variable associated with the likelihood of achieving remission at week 16.

Remission during follow-up

The proportion of patients in remission at each time point is represented in Figure 4. The proportion of patients in remission was above 40% during follow-up.

Relapse

Patients with active disease (PMS >2) at baseline who achieved remission at week 8 were included in the relapsing analysis. A total of 171 patients met these criteria; of them, 83 (48.5%) relapsed. The probability of maintaining remission was 90% at 3 months, 73% at 6 months, 57% at 12 months, 46% at 18 months, and 41% at 21 months (Figure 5). The incidence rate of relapse was 56% (95% CI = 44%–70%) per patient-year of follow-up. Neither in the univariate nor in the multivariate analysis, factors associated with relapse could be identified. In fact, the cumulative incidence of relapse was similar in patients who deescalated the dose after the induction than in those who maintained the initial dose. Tofacitinib dose was escalated in 55 (66%) of those patients who relapsed; 33 (60%) reached remission, 12 (22%) had response, and 10 (18%) did not respond.

Dose adjustments

A total of 261 patients (64%) had at least 1 dose change during tofacitinib treatment. The incidence rate of relapse was similar in patients with active disease at baseline who started with 10 mg bid dose, reached remission at week 8, and maintained the same dose over time than in those who were changed to the maintenance dose (5 mg bid). A total of 144 patients (35%) had 1 change, 80 (20%) 2 changes, 31 (7.6%) 3 changes, 4 (1%) 4 changes, and 2 (0.5%) 5 changes. Tofacitinib doses over time are summarized in

Table 2. Extraintestinal manifestations and immune-mediated inflammatory diseases in the study population

Previous nonactive at tofacitinib start	n (%)	Worsening attributable to tofacitinib treatment
Juvenile idiopathic arthritis	1 (0.2)	None
Peripheral arthropathy	15 (3.7)	3 (20%) worsened
Rheumatoid arthritis	1 (0.2)	None
Primary sclerosing cholangitis	4 (1)	None
Autoimmune thyroid disease	2 (0.5)	None
Episcleritis	4 (1)	1 (25%) worsened
Erythema nodosum	12 (2.9)	None
Scleritis	1 (0.2)	None
Multiple sclerosis	1 (0.2)	None
Axial spondiloarthropathy	11 (2.7)	None
Aphthous stomatitis	3 (0.7)	None
Systemic lupus erythematosus	1 (0.2)	None
Pyoderma gangrenosum	2 (0.5)	None
Psoriasis	13 (3.2)	None
Uveitis	1 (0.2)	None
Vasculitis	1 (0.2)	None
Others	5 (1)	None
Previous active at tofacitinib start	**n (%)**	**Outcome attributable to tofacitinib treatment**
Juvenile idiopathic arthritis	1 (0.2)	No change
Peripheral arthropathy	32 (7.8)	8 (25%) remission, 13 (40.6%) improvement, 11 (34.4) no change
Rheumatoid arthritis	4 (1)	1 (25%) remission, 1 (25%) improvement, 1 (25%) no change, 1 (25%) worsening
Primary sclerosing cholangitis	1 (0.2)	No change
Autoimmune thyroid disease	1 (0.2)	No change
Erythema nodosum	2 (0.5)	2 (100%) remission
Axial spondiloarthropathy	15 (3)	3 (23%) remission, 7 (54%) improvement, 5 (33%) no change, 1 (7%) worsen
Systemic lupus erythematosus	1 (0.2)	No change
Pyoderma gangrenosum	1 (0.2)	1 (100%) improvement
Psoriasis	1 (0.2)	No change
Uveitis	1 (0.2)	No change
Others	2 (0.5)	No change
New onset under tofacitinib treatment	**N (%)**	**Attitude toward tofacitinib**	**Outcome**
Peripheral arthropathy	4 (1)	No change	2 no change 2 remission
Erythema nodosum	1 (0.2)	No change	1 remission
Aphthous stomatitis	1 (0.2)	No change	1 remission
Vasculitis	1 (0.2)	Withdrawal	1 improvement
IgA pemphigus	1 (0.2)	No change	1 no change

Supplementary Digital Content (see Supplementary Table 4, http://links.lww.com/AJG/C840); of note, the proportion of patients on 10 mg bid was more than 40% in all time points during follow-up.

EIM and IMID

In our study, approximately one-third of patients had EIM and/or IMID (active or not) at the start of tofacitinib treatment (prevalence and outcomes of previous nonactive EIM or IMID,

Table 3. Adverse events under tofacitinib treatment

Adverse event	n (% of the overall cohort)	Severe	Serious adverse event	Attributed to tofacitinib	Tofacitinib discontinuation	Resolved without sequelae
Anemia, n (%)	15 (3.7)	1 (6.7)	1 (6.7)	6 (40)	1(6.7)	10 (67)
Nonmelanoma skin cancer, n (%)	2 (0.5)	1 (50)	1 (50)	0 (0)	0 (0)	2 (100)
Cardiovascular events, n (%)	3 (0.5)	3 (100)	3 (100)	0 (0)	1 (50)	2 (66)
Herpes zoster, n (%)	11 (2.6)	0 (0)	0 (0)	7 (64)	1 (9)	9 (82)
Herpes (other than herpes zoster), n (%)	10 (2.5)	0 (0)	0 (0)	8 (80)	0 (0)	10 (100)
Hypercholesterolemia, n (%)	27 (6.6)	0 (0)	0 (0)	24 (89)	0 (0)	14 (52)
Hypertriglyceridemia, n (%)	5 (1.2)	1 (20)	0 (0)	3 (60)	0 (0)	4 (80)
Infections, n (%)	46 (11)	7 (15)	18 (39)	18 (39)	9 (20)	40 (87)
Lymphopenia, n (%)	7 (1.7)	0 (0)	0 (0)	6 (86)	1 (14)	3 (43)
Neoplasias, n (%)	1 (0.2)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Pulmonary thromboembolisms, n (%)	2 (0.5)	1 (50)	2 (100)	2 (100)	2 (100)	1 (50)
Peripheral venous thromboembolisms, n (%)	2 (0.5)	0 (0)	0 (0)	2 (100)	1 (33)	2 (100)
Others, n (%)	59 (15)	8 (14)	9 (15)	27 (46)	13 (22)	38 (64)

3 exitus (heart stroke, complications from COVID-19, breast cancer) considered nonrelated to tofacitinib by the clinicians responsible for patients' care.

prevalence and outcomes of active EIM and IMD, and attitude toward tofacitinib treatment and outcomes are summarized in Table 2). The most frequent EIM at tofacitinib start was peripheral arthropathy. A total of 15 patients had nonactive peripheral arthropathy during tofacitinib initiation, and 3 of them had a worsening that was attributed to treatment. One patient with a history of episcleritis also worsened, but all other EIM inactive at baseline remained inactive. Among the active EIM tofacitinib initiation, the most frequent one was peripheral arthropathy (32 patients): of them, 8 remitted and 13 improved with tofacitinib. A total of 15 patients had active axial arthropathy, of which 10 patients achieved remission of symptoms or improved. The occurrence of *de novo* EIM or IMID was rare and led to withdrawal of tofacitinib in only 1 case (vasculitis), with resolution of symptoms after treatment discontinuation.

Table 4. Incidence rates of the most relevant adverse events during tofacitinib treatment

Type of adverse event	N	Incidence rate (95% confidence interval) (cases per 100 patient-yr)
Major cardiovascular adverse events		
All	1	0.23 (0.03–1.66)
Attributable to tofacitinib	0	—
Cardiac adverse events		
All	3	0.70 (0.22–2.18)
Attributable to tofacitinib	0	—
Herpes zoster		
All	11	2.64 (1.46–4.77)
Attributable to tofacitinib	7	1.67 (0.79–3.50)
Pulmonary thromboembolism		
All[a]	2	0.46 (0.11–1.87)
Attributable to tofacitinib	2	0.46 (0.11–1.87)
Peripheral venous thrombosis		
All[a]	2	0.46 (0.11–1.87)
Attributable to tofacitinib	2	0.46 (0.11–1.87)
Serious infections		
All	18	4.35 (2.74–6.91)
Attributable to tofacitinib	7	1.67 (0.79–3.5)
Nonmelanoma skin cancer		
All	2	0.47 (0.11–1.87)
Attributable to tofacitinib	0	—

[a]All of them had been considered attributable to tofacitinib.

Hospitalizations

A total of 91 patients (22%) were hospitalized during the study period; 63 patients (69%) due to UC.

Safety

A total of 152 patients (37%) had at least 1 adverse event during follow-up. The severity, the relation to tofacitinib, the attitude toward the drug, and the outcomes are summarized in Table 3, while the incidence rate of the main adverse events is summarized in Table 4.

There were 35 patients (8%) who had serious adverse events under tofacitinib treatment, infections and cardiovascular events being the most frequent ones (Table 3). The major cardiovascular event and thromboembolic events are summarized in Supplementary Digital Content (see Supplementary text, http://links.lww.com/AJG/C840).

A total of 46 patients (11%) had infections in our cohort: 11 gastrointestinal infections, 10 SARS-CoV-2 infections, 7 respiratory infections, 4 urinary infections, 2 skin infections, 2 perianal abscesses, 1 bartolinitis, 1 sepsis of unknown origin, and 8 patients had other infections. Of those infections, there were 18 that met the criteria of serious adverse events (39% of all the infections): 7 gastrointestinal infections, 7 SARS-CoV-2

infections, 2 perianal abscesses, 1 orchiepididymitis, and 1 sepsis of unknown origin.

DISCUSSION

Tofacitinib has been shown to be effective in the treatment of UC in randomized clinical trials (11,12,14,15). In this clinical practice study, which includes the largest number with the longest follow-up ever published, we have been able to demonstrate that tofacitinib is also effective in real life even in very refractory patients.

In our cohort, the incidence rate of tofacitinib discontinuation was approximately 40% per patient-year of follow-up (which is slightly higher to that described for anti-TNF agents). This may reflect a more refractory cohort but may also be a consequence of the availability of a number of targeted drugs that allow for more ambitious treatment goals in these patients. In fact, after discontinuation of tofacitinib, only 20% of patients underwent surgery; the remaining 80% received other medical treatments. Of note, most treatment discontinuations occurred within the first 6 months of treatment, and the main cause of treatment withdrawal was primary nonresponse. However, after the first 6 months of treatment, the ability to maintain tofacitinib treatment remained stable over time. Therefore, according to the results of our study, patients who respond and maintain treatment beyond 6 months have a high probability that the benefit of tofacitinib will be maintained in the long-term.

The persistence of tofacitinib treatment in the long-term was recently evaluated in the Oral Clinical Trials for tofAcitinib in ulceratiVE colitis (OCTAVE) Open trial (15). Authors observed that, overall, 79% of patients dropped out from the trial during a total of 2,440 patient-years of exposure (approximately 30% per patient-year). These figures were lower in patients who responded to tofacitinib treatment, where the overall persistence rate was 73.9% and 54.5% at 2 and 5 years, respectively (15). Regarding clinical practice, Lucaciu et al (13) performed a meta-analysis on the real-world evidence of tofacitinib treatment up to 2021; treatment discontinuation was reported in 35% of patients across 8 studies (the median follow-up was 31 weeks).

In general, the main reason for tofacitinib discontinuation was lack of/insufficient primary response both in randomized clinical trials and in clinical practice setting (13–26). Regarding predictive factors of tofacitinib discontinuation, in the OCTAVE open trial, younger age (younger than 40 years), female sex, tofacitinib 10 mg bid at baseline, and previous anti-TNF failure were associated with an increased risk of discontinuation in patients who responded to tofacitinib (15). Our results confirm that, in clinical practice, older age was associated with a higher probability of maintaining the treatment, while the severity of clinical activity at baseline was associated with a higher likelihood of tofacitinib withdrawal.

We also evaluated tofacitinib short-term effectiveness. We observed that almost 40% of patients at week 4 and almost 50% at weeks 8 and 16 reached remission. At week 8, 18.5% of patients in OCTAVE 1 and 16.6% of patients in OCTAVE 2 were in clinical remission (remission was assessed with full Mayo score with centrally assessed endoscopic subscores) (12). Other clinical practice studies have shown similar results to ours. In the meta-analysis by Lucaciu et al (13), the percentage of patients in clinical remission after induction (weeks 8, 12, or 14) was 37% (range: 31%–51%), although the heterogeneity of the included studies was significant.

Regarding predictive factors of short-term effectiveness, we observed that the severity of the disease at baseline impaired the likelihood of achieving remission, while older age was associated with better results. These findings agreed with those described by Honap et al (21) who observed that younger age at treatment initiation and elevated CRP at baseline were independently associated with primary nonresponse. These findings are in line with those previously described in clinical trials, where both CRP and PMS at baseline were associated with short-term response, confirming that patients with higher inflammatory burden are at a higher risk of treatment failure (27). On the contrary, in OCTAVE 1 and 2 trials, the treatment effect was similar between those who had received previous treatment with an anti-TNF agent and those who had not (12). The impact of previous biologic failure cannot be assessed in clinical practice studies where more than 90% of the patients had been exposed to biologics previously to the initiation of tofacitinib.

The durability of response to treatment in the long-term is of upmost importance. In clinical trials, remission at 52 weeks occurred in 34.3% of the patients in the 5 mg bid group and in 40.6% in the 10 mg bid group (12). To our knowledge, our study is the first one providing long-term data in real life; we observed that more than 40% of patients were in remission in the long-term (44% at 12 months). Of note, approximately 50% of our patients were receiving 10 mg bid in the long run.

We found that approximately 50% of patients who achieved remission at week 8 relapsed during follow-up. In two-thirds of patients, the dose was escalated from 5 to 10 mg bid, and 60% of them regained remission. The response to dose escalation was greater in our study than in the OCTAVE study, where after dose escalation, 35% and 49% were in remission, at months 2 and 12, respectively (28). Our results suggest that dose escalation after relapsing is a feasible and effective strategy to recapture remission in clinical practice.

The comparison between clinical trials and clinical practice must be undertaken with caution. The design and modality of a real-world observational study are clearly different from those of a randomized clinical trial. Indeed, the outcomes of the OCTAVE trials were based on full Mayo score with centrally assessed endoscopic subscores, which are associated with lower rates of remission or response (29); on the contrary, studies from clinical practice use mostly the PMS or the simple clinical colitis activity index. Nevertheless, our results reassure the effectiveness of tofacitinib in UC in clinical practice, even in highly refractory patients, both in the short-term and long-term.

One of the advantages of tofacitinib is its potential for the treatment of other disease-associated EIM and IMID (30). Regarding EIM or IMID active at tofacitinib start, we observed that most of those who are considered to depend on disease activity became inactive under tofacitinib treatment. Our results agree with those previously published from the OCTAVE 1 and 2 trials (31).

Regarding safety, the prevalence and the incidence of adverse events in our clinical practice study was similar to those previously described for tofacitinib, and there was no new safety signal from clinical practice (14,32). In this sense, the only major cardiovascular event occurred in a patient with risk factors; regarding thromboembolic events, 3 of 4 patients had previous risk factors, and to have active UC is also a risk factor by itself.

Our study has some limitations inherent to its retrospective nature and clinical practice design. There was no predefined protocol for the management of these patients and the recording of information, but it was retrospectively collected from the information registered in the medical records. Endoscopic evaluations at follow-up were lacking in most patients and were only available in those where the evolution after initiation of treatment was not good (as is often the case in clinical practice). Analytical data, such as fecal calprotectin, were not routinely performed but at the discretion of the clinicians responsible for the care of the patients and were therefore not available for all patients. Finally, there could be a selection bias, as a consequence of the retrospective inclusion, of only those patients remembered by the investigator; however, investigators were asked to include all patients who met the criteria at their center, contacting, if necessary, the hospital pharmacy, so we believe that recall bias should not have had a negative impact on the reliability of our results.

However, our study has also several strengths because, to our knowledge, this is the largest study and with the longest follow-up published up to now on the effectiveness of tofacitinib on UC in real life. Accordingly, we could assess the durability of tofacitinib treatment, relapse rate, and response to dose escalation. Furthermore, we were able to describe how tofacitinib is used in clinical practice, its influence on EIM and IMID, and its safety profile in a large cohort in clinical practice.

In conclusion, tofacitinib is relatively effective for UC treatment, even in a highly refractory cohort. A relevant proportion of patients discontinue the drug over time, mainly during the first 6 months and due to primary failure. A relevant proportion of the patients who achieve remission after induction relapse over time, although dose escalation can recapture remission in 60% of them. More than 40% of patients maintain the 10 mg bid dose in clinical practice. Finally, safety was consistent with the known profile of tofacitinib.

CONFLICTS OF INTEREST

Guarantor of the article: María Chaparro, MD, PhD and Javier P. Gisbert, MD, PhD.

Specific author contributions: M.C., D.A., and J.P.G.: study design, data collection, data analysis, data interpretation, and writing the manuscript. Rest of authors: patient inclusion. All authors approved the final version of the manuscript. M.C. and J.P.G. are the guarantors of the article.

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Data availability: The data underlying this article will be shared upon reasonable request to the corresponding author.

Study Highlights

WHAT IS KNOWN

- ✓ Tofacitinib is effective in ulcerative colitis in clinical trials.
- ✓ Treatment survival, effectiveness, and safety in clinical practice remains poorly known.

WHAT IS NEW HERE

- ✓ Tofacitinib is relatively effective for ulcerative colitis treatment, even in a highly refractory cohort.
- ✓ A relevant proportion of patients discontinue the drug over time, mainly during the first 6 months and due to primary failure.
- ✓ A relevant proportion of the patients who achieve remission after induction relapse over time, although dose escalation can recapture remission in 60% of them.
- ✓ More than 40% of patients maintain the 10 mg bid dose in clinical practice.
- ✓ Safety was consistent with the known profile of tofacitinib.

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