ORIGINAL PAPERS

Efficacy and safety of tofacitinib in the treatment of ulcerative colitis: real-life experience in Andalusia

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ABSTRACT

Background: tofacitinib is a Janus kinase inhibitor approved for the treatment of moderate-severe ulcerative colitis (UC). This study aimed to evaluate its efficacy in a real-life setting.

Methods: a retrospective and multicenter observational study was performed with UC patients treated with tofacitinib. Short and long-term treatment effectiveness, treatment survival, need for dose escalation and safety were analyzed. Clinical response and remission were defined in accordance with the partial Mayo score.

Results: seventy-four patients were included, 98.3 % had received prior biological treatment, 55.4 % with three or more biologicals and up to 64.9% with two or three different mechanisms of action. Clinical remission and response rates were 37.8 % and 77 % at eight weeks, and 41.8 % and 70.1 % at 16 weeks. With regard to non-responders at eight weeks, 37.5 % achieved a delayed clinical response at 16 weeks. Mean treatment duration was 19 months (95 % CI: 16-22), with a treatment survival of 56 % at 28 months, and remission and response rates at 24 months of 53.8 % and 61.5 %. Twenty-three treatments were withdrawn, most of them (18) during the induction period. There were adverse events in a quarter of the patients; only four were severe and led to treatment discontinuation.

Conclusion: tofacitinib has a demonstrated efficacy in clinical practice to induce and maintain clinical response in treatment-refractory UC patients, with an acceptable safety profile.

Keywords: Tofacitinib. Ulcerative colitis. Real-life.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with alternating phases of activity and remission (1). Despite the benefit that the incorporation of biological drugs has entailed in the management of refractory to conventional treatment UC, up to 30 % of the patients do not respond to them and around 20-40 % lose response over time (2). Therefore, we need new therapeutic strategies with different mechanisms of action.

Tofacitinib is a small, orally administered, synthetic drug that acts by selectively and reversibly inhibiting Janus kinases (JAK), mainly JAK1 and JAK3. The signal transduction from receptors is blocked for several interferons and interleukins and modulating the inflammatory and immune response (3). The efficacy of tofacitinib in the treatment of moderate-severe UC has been validated in the OCTAVE clinical trials (Induction 1 and 2, and Sustain) (4). Subsequently, real-life studies have reported variable remission and response rates of 13-57 % and 60-74 % at eight weeks and 32-53 % and 55-76 % at 12-16 weeks, in highly treatment-refractory patients (5-12).

The position of tofacitinib in the UC therapeutic algorithm is not yet well defined. Thus, while American guidelines place it as a second-line treatment together with ustekinumab in patients previously exposed to anti-TNF (13), the recent national guidelines drawn up by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) place it as a potential alternative to anti-TNF, vedolizumab and ustekinumab for the induction and maintenance treatment of moderate UC (14). However, aspects such as the lower price of anti-TNFs, the greater accumulated experience with these drugs and the better knowledge of their safety profile mean that they are used as a second or third line treatment.

The aim of this study was to report our experience in the treatment of UC with tofacitinib in a real-life setting, where the available literature is still limited in terms of efficacy and safety.

METHODS

Study design

A retrospective, observational, analytical and multicenter study was performed with nine hospitals in our region. The efficacy of tofacitinib in UC was analyzed in both the short and medium-long term, as well as treatment survival and safety. The information was obtained via review and protocolized data collection from the clinical records of the participating patients, using an anonymous database created for this purpose.

Patient population

All patients over 18-years of age, diagnosed with UC and treated with tofacitinib until May 2021 in the participating centers were included in the study. Patients with Crohn's disease, indeterminate colitis or pouchitis were excluded. A sample size calculation was not necessary as this was a retrospective clinical practice study.

Objectives and definitions

The primary objective of the study was to analyze clinical remission and response rates after induction treatment at weeks 8 and 16. The secondary objectives were to analyze the maintenance of the obtained response in the medium-long term (months 6, 12, 18, and 24), treatment survival, need for dose escalation, reasons for treatment withdrawal and appearance of adverse events.

Clinical activity was assessed with the partial Mayo score (without endoscopic assessment) to avoid bias when evaluating the response. Clinical remission was defined when this index was ≤ 2 points and clinical response when there was a decrease of at least three points from baseline (including patients in remission). Otherwise, patients were considered as non-responders. Loss of response was defined when after an initial response, patients had evolving non-response criteria.

Statistical analysis

Qualitative variables are presented as absolute frequencies and percentages; quantitative variables as mean ± standard deviation (SD), or median with interquartile ranges (IQR). Comparisons of categorical variables were performed using the Chi-squared test (χ^2) and quantitative variables using the Student's t-test for normally distributed variables, or the corresponding non-parametric test (Mann-Whitney U test or Wilcoxon rank test). Multivariate analysis was performed with a binary logistic regression test. Drug survival was analyzed using the Kaplan-Meier method. All statistical hypothesis tests were bilateral and a value of $p < 0.05$ was considered as statistically significant. SPSS software 23th version was used for the analysis.

Ethical considerations

The study was performed in compliance with regulatory requirements and respecting patient confidentiality. The study was approved by the Research Ethics Committee of Hospital Torrecárdenas.

RESULTS

Baseline patient characteristics

Seventy-four patients we included in the study and the baseline characteristics are summarized in table 1. All the patients except one had received prior biological treatment: 41 patients (55.4 %) had been treated with three or more biological drugs and 53 patients (64.9 %) with two or three different mechanisms of action. Figure 1 shows the patients study flowchart.

Short-term effectiveness

All patients received tofacitinib 10 mg/12 h for eight weeks as an induction regimen, except for one patient who was given a dose of 5 mg/12 h due to comorbidities. This regimen was extended for an additional eight weeks in 26 patients (35.1 %).

Table 1. *Patients baseline characteristics*

	Mean ± SD, median (IQR) or n (%)
Age (years)	45.4 ± 15.6
Gender	
Male	51 (68.9 %)
Female	23 (31.1 %)
Disease duration (years)	7 (4-13)
Severity	
Moderate	45 (60.8 %)
Severe	29 (39.2 %)
Extent	
Proctitis	4 (5.4 %)
Left-sided colitis	35 (47.3 %)
Extensive colitis	35 (47.3 %)
Steroid-dependence	52 (70.3 %)
Steroid-refractoriness	11 (15 %)
CRP (mg/ml)	0.67 (0.28-1.59)
Calprotectine (µg/g)	1,748 (505-2,450)
Prior biological treatments:	
Anti-TNF	72 (97.3 %)
1	24 (32.4 %)
2	38 (51.4 %)
3	10 (13.5 %)
Vedolizumab	47 (63.5 %)
Ustekinumab	8 (10.8 %)
Mechanisms of action used:	
1	25 (35.1 %)
2 or more	48 (64.9 %)
Concomitants steroids	46 (62.2 %)

At week 8, 28 patients (37.8 %) were in clinical remission and 57 (77 %) obtained a clinical response (Fig. 2A). The median CRP and fecal calprotectin at this time were 0.31 mg/dl (IQR: 0.1-1.28) and 747 µg/g (IQR: 225-1,835), respectively, both showing a statistically significant decrease ($p < 0.05$) from baseline.

The results at week 16 were analyzed in 67 patients; 28 (41.8 %) were in clinical remission and 47 (70.1 %) achieved response (Fig. 2B). Median CRP and calprotectin were 0.35 mg/dl (IQR: 0.15-1.03) and 571 µg/g (IQR: 174-1,045), and were statistically significantly lower than baseline levels ($p < 0.05$). Three of eight non-responders at week 8 who maintained treatment achieved a delayed clinical response at week 16 (37.5 %); two were in clinical remission. Of the patients receiving baseline steroids, 58.6 % were able to stop using them in these first 16 weeks.

There were no differences according to the univariate study in the observed response at either weeks 8 and 16 that were attributable to age, gender, years of evolution, extension, severity, steroid-refractoriness, number of therapeutic targets previously used or baseline calprotectin figures. Steroid-dependence was statistically significantly associated with a better response at week 8 ($p < 0.05$) but not at week 16. Lower baseline CRP levels observed in responders, especially at week 8, did not reach statistical significance (Table 2). None of the variables showed significant differences in the multivariate analysis.

Maintenance of response

Of a total of 40 patients who had responded to the induction treatment, 52.5 % were in clinical remission, continued maintenance treatment with tofacitinib for a minimum of six months and had a median follow-up of ten months (IQR: 6-20). The tofacitinib dose initially used was 5 mg/12 h in 31 patients (77.5 %) and 10 mg/12 h in the remaining nine patients (22.5 %).

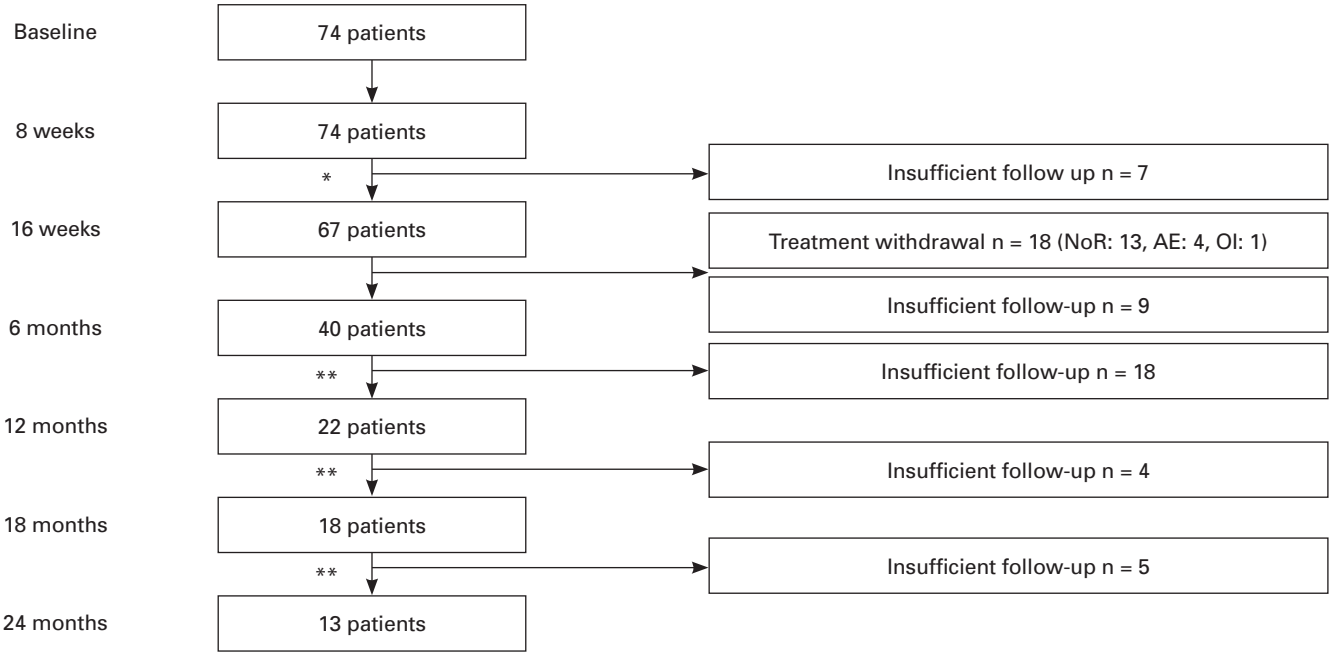

Fig. 1. *Patients flowchart. NoR: no response; AE: adverse events; OI: own initiative. Withdrawals due to no response are considered non-responders at week 16* and later timepoints**.*

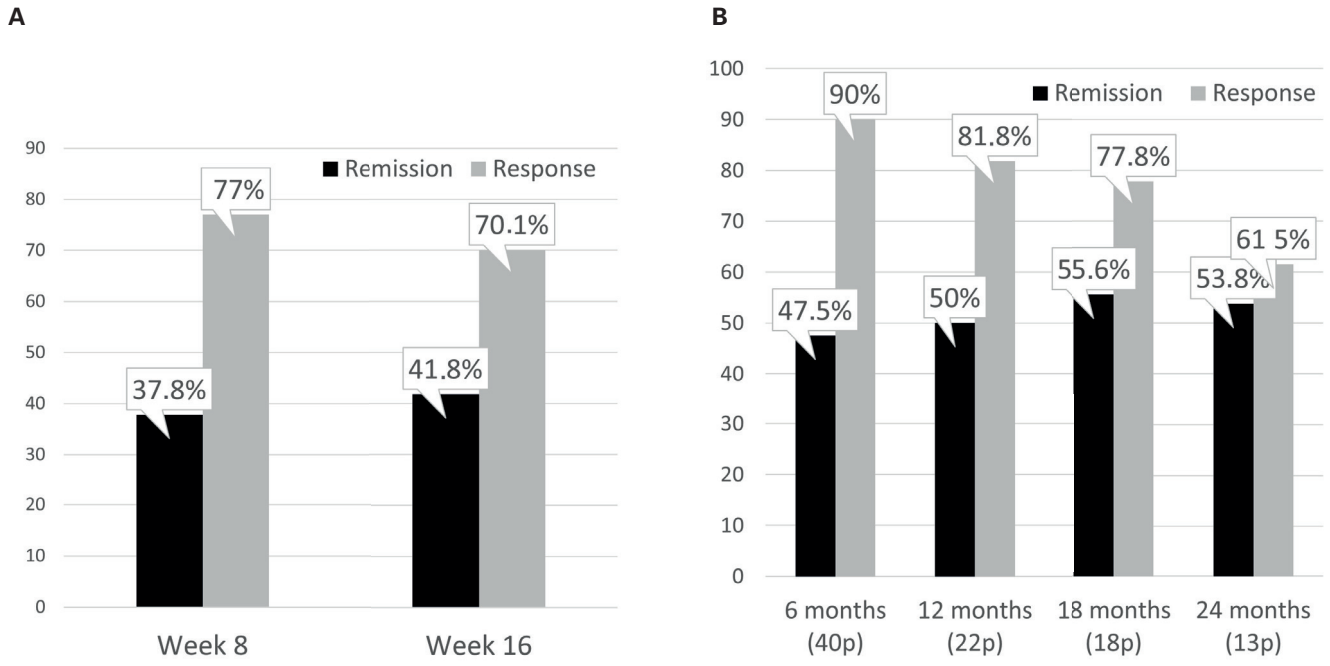

Fig. 2. *Clinical remission/response rates at short term (A) and medium-long term (B).*

Table 2. *Short-term clinical response based on baseline characteristics*

	Week 8			Week 16		
	Response	No response	p	Response	No response	p
	Mean ± SD, median (IQR) or n (%)			Mean ± SD, median (IQR) or n (%)		
Age (years)	47 ± 15.3	40 ± 15.9	0.144	47 ± 15.6	44 ± 16.9	0.482
Gender						
Male	37 (65 %)	14 (82 %)	0.173	34 (72 %)	12 (60 %)	0.319
Female	20 (35 %)	3 (18 %)		13 (28 %)	8 (40 %)	
Disease duration (years)	9 (5-13)	5 (4-10.5)	0.127	7 (5-13)	6 (4-11.7)	0.731
Extent						
Proctitis	4 (7 %)	0	0.511	3 (7 %)	1 (5 %)	0.621
Left-sided C.	27 (47 %)	8 (47 %)		25 (53 %)	10 (50 %)	
Extensive C.	26 (44 %)	9 (53 %)		19 (40 %)	9 (45 %)	
Severity						
Moderate	35 (62 %)	10 (59 %)	0.848	30 (64 %)	12 (60 %)	0.767
Severe	22 (38 %)	7 (41 %)		17 (36 %)	8 (40 %)	
Steroid-dependence	44 (77 %)	8 (47 %)	0.017	35 (74 %)	12 (60 %)	0.236
Steroid-refractoriness	7 (12 %)	4 (23 %)	0.253	8 (17 %)	2 (10 %)	0.460
Mechanisms of action used:						
1	22 (38 %)	4 (23 %)	0.253	14 (30 %)	7 (35 %)	0.674
2 or more	35 (62 %)	13 (77 %)		33 (70 %)	13 (65 %)	
Baseline CRP (mg/dl)	0.61 (0.25-1.43)	1.56 (0.4-4.38)	0.104	0.62 (0.28-1.21)	1.16 (0.3-3.45)	0.236
Baseline Calprotectin (µg/g)	1,541 (505-2,354)	2,129 (678-3,212)	0.288	1,574 (541-2,234)	1,881 (1,148-3,100)	0.246

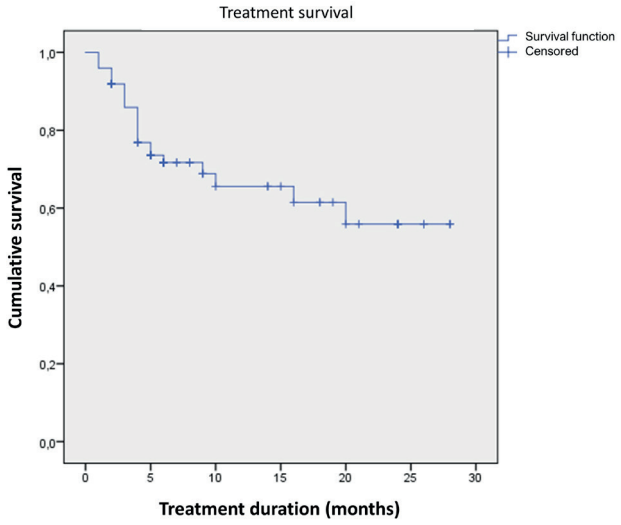

Fig. 3. *Treatment persistence curve.*

Remission and clinical response rates at six, 12, 18 and 24 months are shown in figure 2B.

Fourteen patients (35 %) had loss of response throughout follow-up. Treatment was intensified with a dose escalation to 10 mg/12 h in 12 patients (30 %), regaining response in nine cases (75 %). Treatment was finally withdrawn in five patients (12.5 %) due to loss of response.

Treatment survival

The mean treatment time was 19 months (95 % CI: 16-22), with a treatment survival of 64 % after one year and 56 % after 28 months (Fig. 3). Twenty-three treatments were withdrawn throughout follow-up, most of them during the induction period (18) and only five in the follow-up period. Primary failure was the most frequent reason for treatment discontinuation (10; 43.5 %), followed by loss of response (8; 34.8 %), adverse events (4; 17.4 %) and one case due to the patient's own choice despite being in remission (4.3 %). The median time until withdrawal was 16 weeks (IQR: 8-16).

Safety

Adverse events attributable to tofacitinib occurred in 19 patients (25.7 %). The most common were hyperlipemia (seven cases; 9.4 %) and infections (seven cases; 9.4 %), three of which were herpes zoster reactivation. Four patients had a drug-attributed headache (5.4 %) and there was one case of deep vein thrombosis (DVT) (1.3 %). Only four (5.4 %) were serious enough to definitively stop the treatment and all occurred within the first 16 weeks. These included the aforementioned DVT, one herpes zoster infection, one bilateral pneumonia caused by SARS-CoV-2 and one disabling headache.

DISCUSSION

The efficacy and safety of treatment with tofacitinib in a real-life setting was assessed in patients with UC refractory to other therapies. There are few references in the literature in this regard and this study had a longer follow-up period than published studies. Clinical remission and response rates observed at weeks 8 and 16 were notably higher than those described in the pivotal studies (18.5 % and 16.6 % at eight weeks) (4), and are in accordance with those reported in real-life studies that also have a highly refractory population (5-12). Almost all of our patients had received biological treatment, accounting for nearly two thirds with at least two different mechanisms of action, whereas in the OCTAVE trial studies, 45 % of the patients were naive to biological treatment. The stricter definition of remission in the aforementioned clinical trial, by requiring a sub-score of 0 in the rectal bleeding item, may account for these differences, since the observed efficacy was similar between those who had previously received anti-TNF inhibitors and those who had not (15).

Only steroid-dependence was significantly associated with a higher response rate at week 8 according to the univariate analysis. Real-life studies report a better response in patients with lower baseline CRP figures (5,7) and a lower likelihood of response with greater endoscopic severity (7,16), which may suggest that response is lower in those patients with a higher inflammatory burden. Other factors associated with a lower probability of response reported in other studies are previous treatment with vedolizumab (5) or biological therapies (8), female sex (8), young age (5) or greater extension (16).

One third of non-responder patients at week 8 who maintained treatment finally achieved a delayed clinical response, as described in the OCTAVE Open trial. In this trial, non-responder patients at week 8 were treated for an additional eight weeks with 10 mg/12 h, achieving response in 52 % of cases (17), that was maintained by 70 % of the delayed responders at one year and 56 % at three years (18).

Our medium-long term results show that tofacitinib is effective at maintaining response over time, with higher remission and clinical response rates than pivotal studies, with patients reaching two years of follow-up and a treatment survival of 56 % at 28 months. In the OCTAVE Sustain trial, clinical remission rates at 52 weeks were 34.3 % with doses of 5 mg/12 h, and 40.6 % with 10 mg/12 h (4). In the long term extension study (OCTAVE Open), 73.9 % of patients in remission at the end of the OCTAVE Sustain trial were still in clinical remission at one year and 50.4 % at three years (19). Few real-life studies evaluate tofacitinib long term efficacy beyond one year, showing clinical remission rates of 34-41 %, clinical response rates of 42 % and treatment survival 54-58 % at one year, all of them lower than those observed in our study (7,12,20). One third of our patients had a loss of response throughout follow-up. Treatment intensification by increasing the dose to 10 mg/12 h regained response in 75 % of the patients. These figures are consistent with those of the OCTAVE Open trial, which showed that 49 % achieved remission and 65 % regained response after dose escalation (21). In real-life studies, treatment intensification is effective in 47-58 % of patients (5,20).

The observed safety profile was acceptable, with mostly mild adverse events recorded, as reported in clinical trials (22) and real-life studies (20), which attribute a safety profile of tofacitinib similar to that of biological treatments, except for an increased risk of herpes zoster infections. The recent pub-

lication of preliminary safety results from the ORAL Surveillance A3921133 study showed a higher incidence of major adverse cardiovascular events and neoplasms in patients treated with tofacitinib compared to those treated with anti-TNF inhibitors. This has prompted regulatory agencies to advise limiting its use in patients over 65 years of age with cardiovascular risk factors or for the development of neoplasms, unless there are no other alternatives (23). Our study included eleven patients over 65 years of age and the only case of DVT that was recorded occurred in this subgroup.

The main limitations of our study are its retrospective nature, the limited sample size and the fact that the assessment of the response was based solely on clinical criteria, as endoscopic controls were not available in all patients as this was a clinical practice study. In conclusion, tofacitinib is effective in the treatment of UC in a real clinical practice setting with patients refractory to other treatments. Responders maintain long-term response in a high percentage of cases, although a considerable proportion require high doses.

CONFLICT OF INTEREST

A. Hernández has received payments as fees-for-service, participation in scientific meetings and funding for attendance from Abbvie, Ferring, Janssen, MSD, Pfizer, Sandoz and Takeda. M. M. Martín has received payments for advisory, participation in scientific meetings and attendance from MSD, Takeda, Janssen, Abbvie, Tillots Pharma, Chiesi and Ferring. M. Lázaro has received payments as fees-for-service, participation in scientific meetings and funding for attendance from Janssen, Pfizer and Takeda. R. Olmedo has received payments as fees-for-service and advisory from MSD, Abbvie, Takeda, Ferring, Faes Farma and Janssen. F. Argüelles has received payments for advisory, consultancy and research fundings from Janssen, MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Sandoz, Takeda, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillots Pharma, Gebro Pharma, Amgen and Vifor Pharma. F. Gallardo has received payments for his participation in scientific meetings from Janssen and Takeda. J. M. Vázquez has received payments as fees-for-service and advisory from MSD, Abbvie, Takeda, Janssen, Pfizer, Kern, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Gebro Pharma and Tillots Pharma. P. Navajas, A. Núñez, M. C. Fernández, S. Marín and J. González declare no conflicts of interest.

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