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Tofacitinib for ulcerative colitis in Brazil: a multicenter observational study on effectiveness and safety

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Abstract

Aim To assess the real-life, long-term effectiveness and safety of tofacitinib in a large cohort of patients with refractory or difficult-to-treat ulcerative colitis (UC).

Methods This multicenter, retrospective, observational cohort study included patients with moderately to severely active UC who received tofacitinib for at least 8 weeks. Clinical remission and response, endoscopic response and remission, biochemical response and remission, steroid-free clinical remission, primary and secondary loss of response, drug discontinuation, the need for dose optimization, the need for colectomy, and adverse events were evaluated over up to 30 months.

Results We included 127 patients with UC, with a mean age of 40.3 ± 14.2 years; 58.2% were male, 75.6% had pancolitis, and 79.5% had previously failed at least one biological therapy, predominantly anti-TNF agents (70.1%). Clinical remission was observed in 31.5% of patients at weeks 12–16, 46.5% at 26 ± 4 weeks, and 37.0% at 1 year. Steroid-free clinical remission was achieved in 28.6%, 44.8%, and 37.1% of patients at the same time points, respectively. Biochemical remission was achieved in 33.6% of patients at 26 ± 4 weeks and 29.3% at 1 year. Endoscopic response and endoscopic remission within 1 year were observed in 46.0% and 15.3% of patients, respectively. Ten patients (7.9%) required colectomy, and 13 patients (10.2%) required hospitalization, all of whom had been previously exposed to biologics. The colectomy rate was significantly greater in patients with serum albumin levels ≤ 3.5 g/dL (21.4% vs. 4.1%, $p = 0.013$).

Conclusion In this large, long-term real-world study involving patients with predominantly biologically refractory UC, tofacitinib effectively induced clinical remission and endoscopic improvement and prevented colectomy for more than 30 months, with a favorable safety profile. Notably, baseline hypoalbuminemia was associated with higher colectomy rates.

Keywords Jak inhibitors, Ulcerative colitis, Inflammatory bowel disease, Tofacitinib; Real-world

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by persistent inflammation of the colon [1]. The clinical course of the disease varies, with periods of activity and remission, as well as episodes of exacerbation, which negatively impact the quality of life of affected patients [2, 3]. The goal of treatment is to achieve clinical and endoscopic remission, restore quality of life, and prevent complications such as hospitalizations, neoplasms, and the need for stomas [4, 5].

The management of moderate to severe UC has undergone significant changes over the past two decades with the regulatory approval of the first biological drugs, such as infliximab [6]. In recent years, new molecules with different mechanisms of action have been identified, including antiintegrins, interleukin inhibitors, and Janus kinase (JAK) inhibitors [1]. Current treatment guidelines recommend early intervention with immunomodulators and/or biologics for high-risk patients who present with a severe disease phenotype or have failed conventional therapies [7].

While pivotal studies are crucial for determining the efficacy of a drug or therapeutic strategy, they often employ strict inclusion and exclusion criteria that exclude a significant portion of the patient population encountered in clinical practice, such as those with multiple or severe comorbidities or older age. In contrast, studies based on large clinical cohorts can offer valuable insights into the effectiveness and safety of a drug in real-world settings, thereby including much of the population that is ineligible for clinical trials [8].

In Brazil, patients with UC can access medications through two primary routes. The first is via the Unified Health System under the Specialized Component of Pharmaceutical Assistance, where available treatments include 5-aminosalicylic acid (5-ASA) derivatives (mesalamine and sulfasalazine), immunosuppressants (IS) such as azathioprine, two biologic medications (infliximab and vedolizumab), and one JAK inhibitor (tofacitinib). The second option is through health insurance providers, which guarantee access to four biologic medications (infliximab, golimumab, vedolizumab, and ustekinumab) but do not provide access to any oral molecules, including 5-ASA, IS, or advanced therapies such as tofacitinib and upadacitinib. Access to advanced therapies, such as biologics or small molecules, remains challenging in Brazil. A recent study highlighted the difficulties in obtaining or releasing medications, especially those associated with biological therapy [9].

Tofacitinib is a selective inhibitor of JAK1 and JAK3, thereby disrupting signaling pathways involved in the production of pro-inflammatory cytokines, including IL-6 and IL-2. By modulating the JAK-STAT signaling cascade, tofacitinib reduces mucosal inflammation and immune cell activation, which are key drivers of disease activity in UC [10]. A recent Brazilian real-world study, albeit with a limited sample size of UC patients, demonstrated that tofacitinib was effective in inducing and maintaining clinical response and remission, consistent with findings from other international real-world studies and meta-analyses [11]. Moreover, the final analysis of the OCTAVE Open study, a long-term extension study with up to 7.0 years of treatment, confirmed the efficacy and safety of tofacitinib for moderate to severe UC [12].

Although prior real-world studies have confirmed the efficacy and safety of tofacitinib, many have been limited by small sample sizes, shorter follow-up durations, or lack of representation from developing regions like Latin America. In addition, despite the robust data supporting its effectiveness and safety, hesitancy among some clinicians, structural issues within public healthcare, and the lack of access to tofacitinib through private health insurance hinder the use of oral drugs for treating patients with IBD in Brazil. In this study, we describe the long-term real-life effectiveness and safety of tofacitinib in a large cohort of patients with refractory or difficult-to-treat UC.

Methods

Study design and population

This was an observational, retrospective multicenter study, including patients ≥ 16 years at the start of tofacitinib, with moderately to severely active UC (Total Mayo score of 6–12, with an endoscopic subscore of 2 or 3 as defined by endoscopic assessment within 3 months before starting tofacitinib), who received at least 8 weeks of tofacitinib in 14 IBD centers in Brazil. Patients with UC had to have a previous history of at least one of the following criteria: steroid-refractory disease; steroid dependence; intolerance or failure to maintain therapy with thiopurines; or intolerance, primary failure, or secondary loss of response to anti-tumor necrosis factor (anti-TNF) therapy. In addition, microbial tests on stool samples had to be negative at the time of initiating tofacitinib. Patients may also be refractory to other biologics, such as anti-integrins or anti-interleukins.

Patients in remission or with mild activity at baseline (Total Mayo score of 0–5 or an endoscopic subscore of 0–1) were omitted. We also excluded patients with other types of colitis (undetermined, microscopic, ischemic, infectious, or Crohn's colitis), those with acute severe UC admitted to the hospital, pediatric patients under 16 years of age, and pregnant or breastfeeding women. Additionally, we excluded patients with a previous colectomy (partial or total colectomy, or ileoanal pouch), active or recent malignancy (i.e., within the last 5 years),

active infections, previous JAK inhibitor exposure, any absolute contraindication to JAK inhibitors, and those with missing data.

All patients were routinely screened for latent infections (i.e., hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]-1/2, and tuberculosis) prior to initiating tofacitinib therapy. In cases of positive results for any of these infections, appropriate treatment or chemoprophylaxis was initiated, in consultation with an infectious disease specialist, at least 1 month before starting tofacitinib.

Data collection and ethical approval

Patients were identified at each participating center through electronic medical record searches, with demographic and clinical data collected from October 2023 to May 2024. Key demographic information, including sex, age at treatment initiation, smoking habits, and disease duration from diagnosis to the initiation of tofacitinib, was collected and remotely monitored for quality control. Data on biomarkers (C-reactive protein [CRP], fecal calprotectin [FC]), serum albumin and hemoglobin levels, and the presence of extraintestinal manifestations (EIMs) or associated immune-mediated inflammatory diseases at baseline were also collected. Disease extension (proctitis, left-sided colitis, or extensive disease/pancolitis) according to the Montreal classification [13], and the total Mayo score and endoscopic Mayo subscore [14] at baseline were also evaluated. Endoscopic evaluation was performed within 3 months before inclusion in all centers.

Additionally, we evaluated both previous and current treatments for UC, including immunomodulators (methotrexate, azathioprine, or 6-mercaptopurine), steroids, anti-TNF therapies (infliximab, adalimumab, and golimumab), and other biologics, such as the anti-integrin vedolizumab and the anti-interleukin ustekinumab.

In the various participating centers, patients received tofacitinib at the standard induction dose of 10 mg twice daily for 8 weeks, followed by the standard maintenance dose of 5 mg twice daily, or the continuation of the induction dosage of 10 mg twice daily for a maximum of 16 weeks at the physician's discretion, typically for nonresponders or partial responders to tofacitinib. Dose optimization to 10 mg twice daily as a maintenance regimen could also be applied at the physician's discretion, along with the potential reduction or withdrawal of corticosteroids or immunomodulators during tofacitinib therapy.

Follow-up clinical data were collected at weeks 12–16, 26 (±4 weeks), and 52 (±4 weeks) weeks. These included measurements of the partial Mayo score, steroid intake, biochemical data, the induction and maintenance regimens used with tofacitinib, concomitant maintenance therapy with immunosuppressants, the occurrence of adverse events (AEs) and serious AE (SAEs), UC-related hospitalization, colectomy, and tofacitinib discontinuation. We also evaluated the need for colectomy during treatment with tofacitinib, primary nonresponse (PNR), secondary loss of response, reasons for drug discontinuation, and the need for dose optimization during maintenance therapy.

Colonoscopy records were checked at various times to evaluate endoscopic response or remission whenever available. Most centers performed control endoscopic examinations between 4 and 8 months after starting tofacitinib. The requirement for consent to participate was waived by an Institutional Review Board (IRB) due to the retrospective nature of the analysis. The study was approved by the ethics committee of the Hospital das Clínicas of the Ribeirão Preto Medical School at the University of São Paulo (CAAE: 71,008,923.0.1001.5440; Ethics Committee Number: 6.171.795/2023). All procedures were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Aims and definitions

The primary aim of this study was to evaluate clinical remission and endoscopic response rates after one year of treatment with tofacitinib. Secondary aims included assessing clinical remission rates after induction (at weeks 12–16) and up to 26 ± 4 weeks, clinical response after induction and at 26 ± 4 weeks, steroid-free clinical remission after induction, at 26 ± 4 weeks, and at one year, biochemical response after induction, at 26 ± 4 weeks, and at one year, biochemical remission at 26 ± 4 weeks and one year, and endoscopic remission within one year.

Clinical remission was defined as a total Mayo score of ≤ 2, with a combined rectal bleeding and stool frequency subscore of ≤ 1. Clinical response was defined as a decrease of at least 3 points in the partial Mayo score from baseline. Endoscopic remission was defined as an endoscopic Mayo subscore of zero, and endoscopic response was defined as a reduction of ≥ 1 point in the endoscopic Mayo subscore within one year of starting tofacitinib. Steroid-free clinical remission was defined as the complete discontinuation of steroids in patients maintaining clinical remission, with no new steroid prescription within 4 weeks after tapering. Biochemical response was defined as a reduction of > 50% in CRP and/or FC levels in patients with a baseline CRP > 5 mg/L or FC > 250 μg/g. Biochemical remission was defined as a CRP < 5 mg/L and FC < 150 μg/g in patients with a baseline CRP > 5 mg/L and FC > 250 μg/g.

We also evaluated UC-related hospitalization, the need for colectomy during tofacitinib treatment, primary

nonresponse (PNR), secondary loss of response, and the need for dose optimization during maintenance therapy. PNR was defined as a lack of clinical improvement (partial Mayo score equal to or greater than the baseline score) after 16 weeks, leading to drug discontinuation. Secondary loss of response was defined as active disease with an increase of 2 or more points in the partial Mayo score after an initial response, leading to dose optimization to 10 mg twice daily, or as recurrence of symptoms attributable to UC with a total Mayo score > 6 and objective signs of inflammation detected by endoscopy, CRP > 5 mg/L, and/or FC > 250 μg/g after responding to the drug during induction therapy. Treatment persistence was defined as the time from initiation to the last follow-up visit, discontinuation of tofacitinib, or switching to another treatment. In cases of treatment discontinuation, the last follow-up was defined as the patient's previous visit or the last recorded date of tofacitinib use.

Safety

We included information regarding AEs of interest (serious infections, including herpes zoster, thromboembolic events, upper respiratory tract infections, overall infections, other AEs, and mortality) during treatment with tofacitinib. We also evaluated reasons for drug discontinuation (including a lack of primary response, surgery for UC, secondary loss of response to tofacitinib despite dose escalation, or SAEs that would necessitate discontinuation the drug). AEs were considered serious when they resulted in the discontinuation of tofacitinib, hospitalization, persistent/permanent or significant disability, death, or as deemed by the attending physician at the time of occurrence. Infections were considered serious when intravenous antibiotics were required or when they led to the discontinuation of tofacitinib, hospitalization, permanent or significant disability, or death. We collected AE data throughout the follow-up period while patients were on treatment with tofacitinib.

Statistical analysis

Quantitative variables are presented according to their distribution pattern: mean and standard deviation (SD), or median, minimum, and maximum values. The Student's t-test was used to compare two independent samples. Categorical variables were presented as proportions, and we used either Pearson's $\chi 2$ test or Fisher's exact test to compare two proportions from independent samples. Kaplan–Meier curves were generated for time-to-event data (time until tofacitinib discontinuation in months) and the need for colectomy during follow-up. Data were reported using nonresponder imputation (NRI), meaning that patients who prematurely discontinued the study or had missing data were considered nonresponders in the statistical analyses for clinical, biochemical, and(or) endoscopic response/remission. We utilized IBM SPSS Statistics for Windows, version 20.0 (UNICOM Global, Mission Hills, United States). The significance level adopted for the statistical tests was 5%.

The incidence of AEs and SAEs was expressed as incidence rates (IRs) per 100 patient-years (PY), with 95% confidence intervals (CIs) calculated using the exact Poisson method.

Results

Population and patient characteristics

Between 2020 and 2023, 137 patients with UC treated with tofacitinib were retrospectively enrolled in 14 IBD centers across Brazil. Per the study protocol, the analysis excluded 10 patients, resulting in a final sample of 127 patients with moderately to severely active UC. The reasons for exclusion were previous surgery (total colectomy or ileal pouch, $n = 6$), clinical remission ($n = 1$), or mild disease ($n = 3$) at tofacitinib initiation. Most of the patients were male ($n = 67$, 58.2%), with a mean age of 40.3 years (range 17–72 years, standard deviation [SD]: 14.25 years), and mean disease duration of 9.82 years (Range 1–36 years, SD: 7.3 years). Fourt-six patients (36.3%) presented with EIM, of which the most common were arthralgia/arthritis ($n = 21$, 45.7%). Overall, 96 patients presented with pancolitis/extensive disease (75.6%), 28 patients presented with left-sided colitis (22.0%), and 3 patients presented with proctitis (2.4%). The mean hemoglobin level at baseline were 12.37 g/dL (range: 6.0–16.0 g/dL), 56 patients (44.1%) had anemia, and 13 patients (10.2%) had moderate to severe anemia (hemoglobin ≤ 10 g/dL). The mean serum albumin level at baseline were 3.78 g/dL (range 2.0–5.0 g/dL), and it was ≤ 3.5 g/dL in 28 patients (27.4%). Most patients ($n = 116$, 91.3%) had increased biomarkers (CRP higher than 5.0 mg/L and(or) FC higher than 250 μg/g) at baseline. The mean CRP level was 13.73 mg/dL (range 0–111 mg/dL). The mean FC level at baseline was 1,905.98 μg/g (range 250–6000 μg/g).

The mean total Mayo score was 9.67 (range 6–12) and in 44 patients ($n = 44/124$, 36.5%) the score was severe disease (total Mayo score 11 or 12). Three patients did not have an endoscopic assessment within 3 months before starting tofacitinib. Thus, we calculated the total Mayo score for 124 patients. Endoscopic subscore 3 (severe disease) was present in 88 patients ($n = 88/124$, 71.0%). Concomitant use of corticosteroids (e.g., corticosteroid-dependent patients receiving at least 20 mg of prednisone) was present in 105 patients (82.7%), and 88 patients (69.3%) had previous exposure to immunomodulators (thiopurines [azathioprine or 6-mercaptopurine] or methotrexate).

Most of patients ($n=101$, 79.5%) were exposed to at least 1 biologic, including 89 patients (70.1%) previously exposed to anti-TNF drugs (infliximab, $n=77$, 60.6%; adalimumab, $n=21$, 16.5%; golimumab, $n=8$, 6.3%), 61 patients previously exposed to vedolizumab (48.0%), and 13 patients (10.2%) previously exposed to ustekinumab. Twenty-six patients (20.5%) were bionaïve to biologics, 46 patients (36.2%) were exposed to 1 biologic, 34 patients (36.2%) were previously exposed to 2 biologics, and 21 patients (16.5%) were exposed to 3 or more biologics. In terms of access to treatment, 102 patients (80.3%) obtained access to medication through public means, 18 patients (14.2%) obtained access through private health insurance, and 7 patients (5.5%) obtained access through legal action. The primary baseline clinical and demographic characteristics of the participants are described in Table 1.

Table 1 Demographics and Disease Characteristics at Baseline of Patients with Moderate to Severe Ulcerative Colitis Treated with Tofacitinib ($N=127$)

Characteristics	Results
Sex, male, n (%)	67 (58.2)
Mean age, years (IQR)	40.3 (17–72)
Mean age at diagnosis (IQR)	30.8 (9–67)
Mean disease duration, years (IQR)	9.8 (1–36)
Extraintestinal manifestations, n (%)	46 (36.3)
Disease extent, n (%)	
Proctitis	3 (2.4)
Left-sided colitis	28 (22.0)
Extensive colitis	96 (75.6)
Severe disease*, n (%)	44 (36.5)
Mean hemoglobin levels, g/dL (IQR)**	12.37 (6.0–16.0)
Anemia, n (%)	56 (44.1)
Moderate to severe anemia n (%)	13 (10.2)
Mean Albumin serum levels, g/dL (IQR)**	3.78 (2–5)
Albumin ≤ 3.5 g/dL, n (%)	28 (27.4)
Increased biomarkers***, n (%)	116 (91.3)
Mean C-reactive protein, mg/L (IQR)	13.73 (0–111)
Mean fecal calprotectin, µg/g (IQR)	1,905.98 (250–6000)
Total Mayo score, mean (IQR)****	9.67 (6–12)
Endoscopic subscore 3 (Severe disease), n (%)	88 (71.0)
Concomitant use of corticosteroids, n (%)	105 (82.7)
Previous exposure to immunomodulators*****	88 (69.3)
Previous biologic therapy	101 (79.5)
Number of previous biologics, n (%)	
0	26 (20.5)
1	46 (36.2)
2	34 (26.8)
3 or more	21 (16.5)
Previous exposure to specific biologics, n (%)	
Anti-TNF, n (%)	89 (70.1)
Infliximab	77 (60.6)
Adalimumab	21 (16.5)
Golimumab	8 (6.3)
Vedolizumab	61 (48.0)
Ustekinumab	13 (10.2)
Access to tofacitinib	102 (80.3)
Public health system	
Private health system	18 (14.2)
Legal Action	7 (5.5)

Abbreviations IQR interquartile range, *TNF* tumor necrosis factor

* Severe disease was defined as a total Mayo score of 11 or 12

** Serum albumin was available for 101 patients (missing data in 26 patients). Hemoglobin levels were missing in 2 patients at baseline. Moderate to severe anemia was considered hemoglobin levels lower than 10.0 g/dL

*** C-reactive protein (CRP) or fecal calprotectin (FC) higher than 5.0 mg/L or 150 µg/g, respectively. CRP levels were missing in 3 patients. Thirty-three patients had no FC data available at baseline

**** Three patients did not have an endoscopic assessment within 3 months before starting tofacitinib. Thus, we calculated the total Mayo score for 124 patients

***** Immunomodulators were defined as thiopurines (azathioprine or 6-mercaptopurine) and methotrexate

Clinical, biochemical, and endoscopic outcomes

According to the NRI analysis, the coprimary endpoint of clinical remission was observed in 31.5% of all patients ($n=40/127$) after induction (at weeks 12–16), in 46.5% ($n=59/127$) at 6 months, and in 37.0% ($n=47/127$) of all patients at 1 year. Endoscopic response and endoscopic remission were achieved in 46.0% ($n=57/124$) and 15.3% ($n=19/124$) of the patients, respectively. The results are presented in Fig. 1.

Thirty-one patients (67.4%, $n=31/46$) with active EIM presented improvement or resolution of the EIM during the follow-up. The secondary endpoints of clinical response, according to the NRI analysis, were observed in 67.7% ($n=86/127$) of the patients after induction (at weeks 12–16) and 63.0% ($n=80/127$) at 6 months. Steroid-free clinical remission was observed in 28.6% ($n=30/105$) of the patients after induction therapy (at weeks 12–16), in 44.8% ($n=47/105$) at 6 months, and in 37.1% ($n=39/105$) of the patients at 1 year. Biochemical responses after induction therapy (at weeks 12–16) and at 6 months were achieved in 51.7% ($n=60/116$) and 50.9% ($n=59/116$) of the patients, respectively. Additionally, biochemical remission at 6 months and at 1 year was attained in 33.6% ($n=39/116$) and 29.3% ($n=34/116$) of the patients, respectively. These results are summarized in Fig. 2.

Comparison of the primary outcomes between bionaïve and bio-exposed UC patients

We compared the clinical, biochemical, and endoscopic outcomes between patients who were naïve to biologics ($n=26$) and those who experienced biological failure ($n=101$). Despite the numerical trend toward more

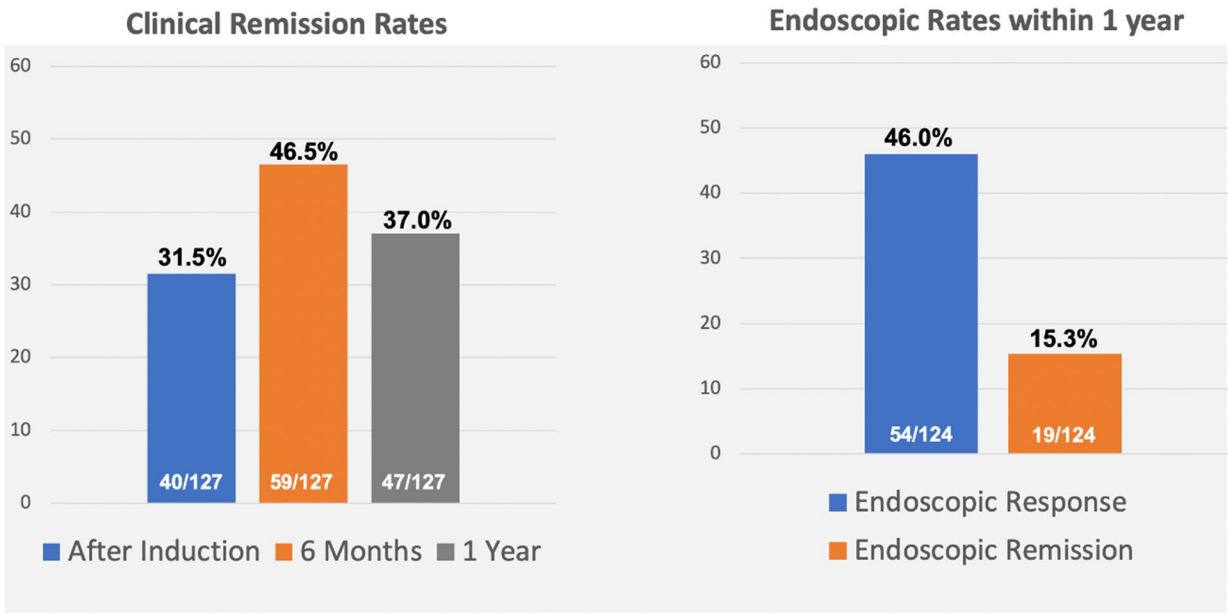

Fig. 1 Clinical Remission After Induction, at 6 Months and at 1 Year, and Endoscopic Response and Remission Rates within 1 Year of Treatment with Tofacitinib

severe disease in the biologic-exposed group (37.6% vs. 23.1%, $p=0.102$), the baseline clinical and demographic characteristics were generally similar between the groups, except for steroid use at baseline, which was higher in patients exposed to biologics (89.1% vs. 57.7%, $p=0.007$).

Clinical remission rates at weeks 12–16 (30.8%, $n=8/26$, vs. 31.7%, $n=32/101$, $p=0.487$) and at 6 months (50.0%, $n=13/26$, vs. 45.5%, $n=46/101$, $p=0.401$) were similar in bionaïve and biologic-exposed patients. However, clinical remission at 1 year was significantly greater in bionaïve patients (53.8%, $n=14/26$, vs. 32.7%, $n=33/101$, $p=0.005$).

Eighteen patients (14.2%) were considered PNR, with no differences between bionaïve and biologic-exposed patients (15.4%, $n=4/26$ vs. 13.9%, $n=14/101$, $p=0.791$). Fifty-four patients (42.5%) experienced a secondary loss of response to tofacitinib during follow-up and required dose escalation to 10 mg twice a day. Optimization was significantly more common in

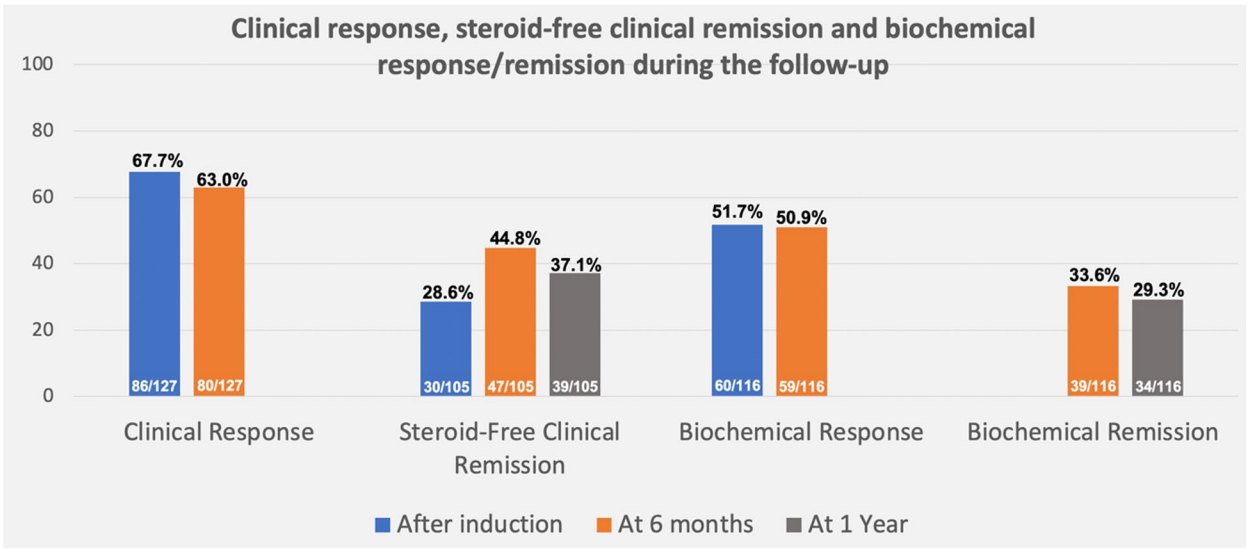

Fig. 2 Bar Graph Depicting Rates of Clinical Response and Biochemical Response After Induction (Weeks 12–16) and at 6 Months, Steroid-Free Clinical Remission after Induction, at 6 Months and at 1 Year, and Biochemical Remission at 6 Months and at 1 Year

patients exposed to biologics than bionaïve patients (46.5%, $n=47/101$ vs. 26.9%, $n=7/26$, $p=0.048$). Thirty-five patients (27.6%) discontinued treatment, with no difference between bionaïve patients (26.9%, $n=7/26$) and those exposed to biologics (27.7%, $n=28/101$) ($p=0.754$). Additionally, 10 patients (7.9%) required colectomy, and 13 (10.2%) needed hospitalization while receiving tofacitinib treatment; all these patients had been previously exposed to biologics. A summary of these results is provided in Table 2.

Association of primary outcomes with clinical characteristics of patients, UC phenotype, and endoscopic disease activity

We also compared sex, age, disease duration, UC phenotype (pancolitis/extensive colitis vs. proctitis/left colitis; moderate vs. severe disease), presence of EIM, anemia, hypoalbuminemia (e.g., albumin ≤ 3.5 mg/dL), baseline endoscopic activity (Mayo endoscopic score 2 vs. 3), and number of previously used biologics (1 vs. 2 or more biologics) with the primary outcomes. We observed that the clinical remission rate after induction was significantly higher in patients with moderate disease compared to patients with severe disease (38.6% vs. 18.2%, $p=0.016$). In addition, both the clinical response rate and the clinical remission rate after induction therapy (weeks 12–16) were significantly higher in patients with endoscopic Mayo scores 2 vs. 3 (66.7% vs. 27.3%, $p=0.032$ and 23.8% vs. 0.0%, $p=0.03$, respectively). Similarly, the clinical response and clinical remission rates at 6 months were significantly higher in patients with endoscopic moderate activity (endoscopic Mayo score 2) than in those with endoscopic Mayo score 3 (71.4% vs. 18.2%, $p=0.003$ and 38.1% vs. 0.0%, $p=0.004$, respectively). Finally, hypoalbuminemia at baseline was not associated with a higher treatment discontinuation rate ($p=0.488$) or loss of response to tofacitinib ($p=0.570$) during follow-up. Conversely, the colectomy rate was significantly higher in patients with low albumin levels (3/73, 4.1% vs 6/28, 21.4%, $p=0.013$). All other analyzed parameters (gender, age, disease duration, colitis extension, presence of EIM or anemia, and the number of previously used biologics had no statistical associations with the primary outcomes. The results with significant statistics are summarized in Table 3.

Table 2 Comparison of Clinical Characteristics and Outcomes Between the Bionaïve and Biologic-Exposed

Outcomes	Bionaïve ($n=26$)	Biologic-Exposed ($n=101$)	*P*
Gender, female, n (%)	9 (34.6)	51 (50.5)	0.126
Median age at baseline, years, SD	45.4 (15.1)	37.0 (14.1)	0.521
Disease duration, years, SD	8.1 (6.9)	10.2 (7.4)	0.799
Severe disease, n (%)	6 (23.1)	38 (37.6)	0.103
Clinical response at week 12–16, n (%)	16 (61.5)	70 (69.3)	0.548
Clinical remission at week 12–16, n (%)	8 (30.8)	32 (31.7)	0.487
Clinical response at 6 months, n (%)	17 (65.4)	63 (62.4)	0.677
Clinical remission at 6 months, n (%)	13 (50.0)	46 (45.5)	0.401
Clinical remission at 1 year, n (%)	14 (53.8)	33 (32.7)	0.005
Endoscopic response within 1 year, n (%)	14 (53.8)	43 (43.9)	0.134
Mucosal healing within 1 year, n (%)	5 (19.2)	14 (14.3)	0.690
Steroids at baseline, n (%)	15 (57.7)	90 (89.1)	0.007
SFCR* at week 12–16, n (%)	4 (26.6)	28 (31.1)	0.423
SFCR* at 1 year, n (%)	8 (53.3)	30 (33.3)	0.076
Higher biomarkers at baseline, n (%)	24 (92.3)	92 (91.1)	0.823
Biochemical response at weeks 12–16, n (%)	14 (58.3)	46 (50.0)	0.441
Biochemical remission 6 months, n (%)	10 (41.7)	29 (31.5)	0.138
Biochemical remission 1 year, n (%)	8 (33.3)	26 (28.3)	0.595
Nonprimary response, n (%)	4 (15.4)	14 (13.9)	0.791
Loss of response, n (%)	6 (23.1)	23 (22.8)	0.822
Need of optimization, n (%)	7 (26.9)	47 (46.5)	0.048
Treatment interruption, n (%)	7 (26.9)	28 (27.7)	0.754
Need of hospitalization, n (%)	0 (0.0)	13 (12.9)	0.016
Need of colectomy, n (%)	0 (0.0)	10 (9.9)	0.036

* SFCR (steroid-free clinical remission)

Table 3 Associations of the main outcomes with the clinical, laboratory, and endoscopic variables were statistically significant

Outcome	Variables	*P-value**
Clinical remission at weeks 12–16	Moderate vs Severe**	0.016
Clinical response at weeks 12–16	Endoscopic Mayo***	0.03
	Endoscopic Mayo***	0.032
Clinical remission at 6 months	Endoscopic Mayo***	0.004
Clinical response at 6 months	Endoscopic Mayo***	0.003
Colectomy rates during follow-up	Albumin serum levels at baseline****	0.013

* Chi-square test

** Moderate disease (total Mayo score of 6–10); Severe disease (Total Mayo score of 11–12)

*** Endoscopic Mayo score of 2 versus 3

**** Albumin ≤ 3.5 g/dL versus albumin > 3.5 g/dL

Drug persistence and colectomy-free survival

We calculated the duration of treatment with tofacitinib during the follow-up and the meantime to colectomy. Figure 3 illustrates the duration of tofacitinib treatment in our cohort, considering the time until discontinuation of the drug. The average total duration of tofacitinib use was 21.99 ± 1.22 months (95% CI: 19.60–24.38). At the end of 12, 24 and 36 months, the drug persistence rate was 73.3% ($n=93$), 63.8% ($n=81$) and 54.3% ($n=69$), respectively. Figure 4 illustrates the Kaplan–Meier curve for colectomy-free survival, with a mean time to colectomy of 26.87 ± 0.94 months (95% CI: 25.01–28.72). At the end of 12, 24, and 36 months, the colectomy-free survival rate was 87.4% ($n=111$), 78.0% ($n=99$), and 68.5% ($n=87$), respectively.

Safety

In total, 26 out of 127 patients (20.5%; IR = 8.19 per 100 PY, 95% CI: 5.04 to 11.34) experienced AEs, and 17 out of 127 (13.4%; IR = 5.35 per 100 PY, 95% CI: 2.81 to 7.90) experienced SAEs during the follow-up period (mean of 30 months or 2.5 years, 317.5 PY). The most common SAEs were colectomy (IR = 3.15 per 100 PY, 95% CI: 1.51 to 5.73) and serious infections (IR = 1.58 per 100 PY, 95% CI: 0.51 to 3.68), including herpes zoster (IR = 0.63 per 100 PY, 95% CI: 0.07 to 2.29). The severity and type of adverse events are described in Table 4.

Discussion

This study represents the largest cohort of UC patients treated with tofacitinib in a real-world setting in Brazil and Latin America. Our findings provide new insights into the real-world effectiveness of tofacitinib, which is highly valuable for positioning this treatment in UC management in clinical practice. We found that patients with moderate disease and those with moderate endoscopic activity achieved better clinical outcomes. In particular, the clinical remission rates at 1 year, the need for dose escalation due to loss of response, hospitalization, and colectomy were significantly higher in bio-exposed

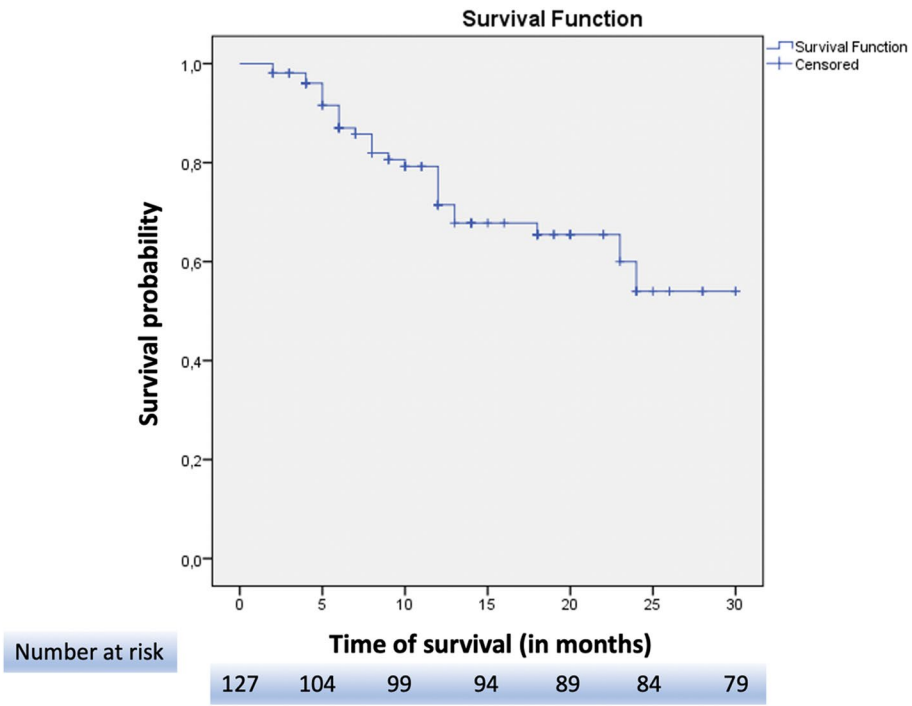

Fig. 3 Kaplan–Meier Curve for Tofacitinib Persistence in the Whole Cohort of Patients with Ulcerative Colitis Over the 30 Months of Follow-Up

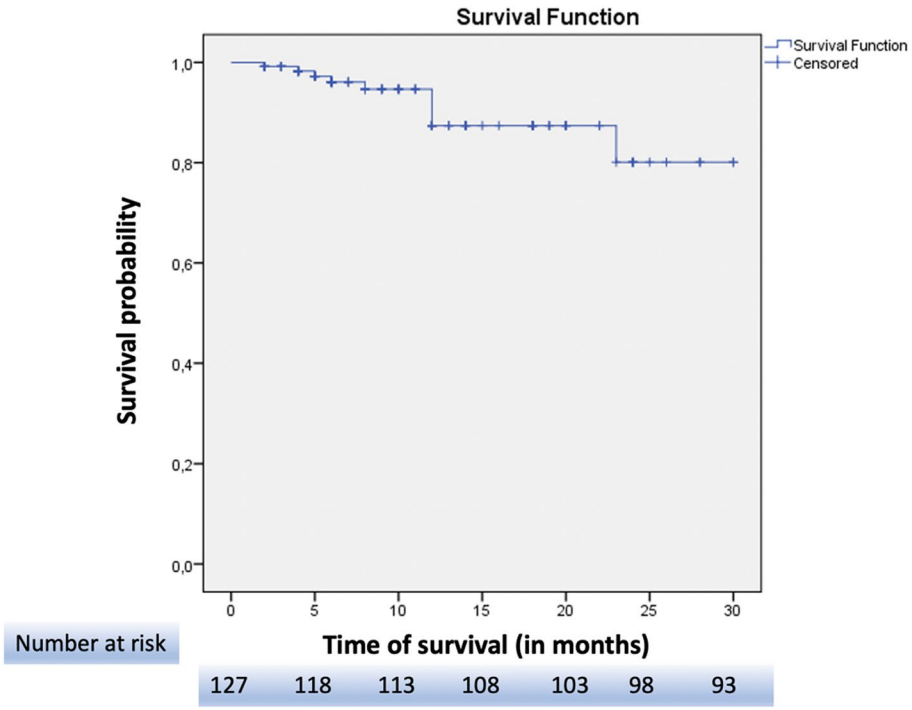

Fig. 4 Kaplan–Meier Curve Showing Colectomy-Free Survival in a 30 Months-Long Follow-up Between 127 Patients with Ulcerative Colitis Under Treatment with Tofacitinib

patients. Notably, the presence of hypoalbuminemia at baseline was strongly associated with the need for colectomy during follow-up. Consequently, our results highlight the importance of ensuring access to this therapy in the public health system and the private setting.

In this multicenter observational study, we evaluated the efficacy and safety of tofacitinib in Brazilian patients with moderate to severe UC. Clinical remission was achieved by 31.5% of patients at 12–16 weeks, 46.5% at 6 months, and 37.0% at 1 year; 46.0% and 15.3% achieved

Table 4 Safety events with tofacitinib treatment during the follow-up

Adverse events / serious adverse events	Number of events ($N=26$)	Incidence rate (IR) per 100 patient-years (PY)
Adverse events		
Dyslipidemia		
Asthenia and fatigue		
Mild to moderate infections		
Herpes simples	1	0.31
Urinary infection	2	0.63
Acute upper respiratory tract infections	1	0.31
COVID-19	1	0.31
Folliculitis	1	0.31
Serious Adverse Events		
Colectomy	10	3.1
Prostatic cancer	1	0.31
Significant increase in liver transaminases	1	0.31
Herpes zoster	2	0.63
Cellulitis	1	0.31
Cytomegalovirus colitis	1	0.31
Clostridioides difficile colitis	1	0.31

endoscopic response and remission, respectively, within 1 year. Steroid-free clinical remission was observed in 28.6% of the patients at 12–16 weeks, 44.8% at 6 months, and 37.1% at 1 year. The biochemical response rate was observed in 51.7% at 12–16 weeks and 50.9% at 6 months. Our findings corroborate previous real-life experiences that demonstrated that tofacitinib was rapidly effective in inducing clinical remission, sparing steroids, promoting endoscopic improvement, and sustaining long-term response in patients with difficult-to-treat UC who were primarily refractory to anti-TNF therapy. Another real-world Brazilian study reported a clinical remission rate of 57.9% at week 52. This discrepancy may be attributed to the higher proportion of biologic-naïve patients in that study (32.14% compared with 16.5% in our study) [11].

Our findings align with previous studies' findings, including the OCTAVE trials, which also reported significant efficacy of tofacitinib in induction and maintenance phases. The response rates in our study are comparable to those reported in other real-world settings, which ranged from 51 to 66%, reinforcing the therapeutic potential of tofacitinib for moderate to severe UC [15–18]. A recently meta-analysis of real-world studies indicated that treatment of UC with tofacitinib was associated with favorable clinical response and remission rates in the induction and maintenance phases [19].

The safety profile observed was comparable to that reported in other real-world observational studies [11, 15, 16, 20–24]. AEs were reported in 20.5% of patients, with 13.4% experiencing severe AEs. Except for colectomy and serious infections, IRs for AE and SAEs were < 1 case/100 PY. Ten patients (7.9%) required colectomy, all of whom had previously been exposed to biologic therapies. No thromboembolic or cardiovascular events were observed during the follow-up, reinforcing the favorable safety profile of tofacitinib in the studied population, as recently published in the long-term assessment for safety [25].

Two meta-analyses of real-world cohort studies reported colectomy rates ranging from 9 to 13% [16, 26]. No cardiovascular or thromboembolic events were reported in our cohort, demonstrating the favorable safety profile of this drug in a predominantly young UC patient population without severe comorbidities.

Eighteen patients (14.2%) were PNR, with no significant difference between biologic-naïve (15.4%) and biologic-exposed patients (13.9%, $p=0.791$). Additionally, 35 patients (27.6%) discontinued treatment, with similar rates between biologic-naïve (26.9%) and biologic-exposed patients (27.7%, $p=0.754$). In a meta-analysis, Lucaciu et al. reported a 35% discontinuation rate for tofacitinib. The primary reasons for discontinuation were loss of response (51%), adverse events (20%), and colectomy (19%) [16].

Our results demonstrate that tofacitinib is effective in clinical practice for a population predominantly composed of patients with prior biologic therapy exposure (79.5%), severe disease as indicated by a Mayo endoscopic subscore of 3 (71%), and longer disease duration (mean of 9.82 years). The high effectiveness of tofacitinib in a population with extensive previous exposure to biologic therapies highlights its potential as a viable option for patients who have not responded adequately to other treatments [20].

Our analysis revealed that patients with moderate disease (Mayo score 2) had significantly higher clinical response and remission rates than those with severe disease (Mayo score 3). Additionally, the requirement for dose optimization was more frequent among patients previously exposed to biologics, suggesting a need for personalized treatment strategies based on prior therapy exposure.

The Brazilian label permits the use of tofacitinib for patients naïve to biologic therapy, but in our cohort, only 21 out of 127 patients (16.5%) fell into this category. In the OCTAVE trials, approximately half of the patients had not been previously treated with biologic agents [12, 27]. A recent real-world multicenter collaborative study on the efficacy of tofacitinib reported that among the 391 patients included, only 11.8% were naïve to biologic therapy. In contrast, 83.6% had previously received anti-TNF treatment, and 64.2% had been treated with vedolizumab [28]. In a meta-analysis conducted by Taxonera et al., which included 17 real-world studies on the use of tofacitinib in UC, 88.4% of the 1,162 patients had prior exposure to biologic therapies [26].

A smaller number of patients were included in the bio-naïve group compared to bio-exposed group. Several factors may limit the first-line prescription of tofacitinib, including its recent market introduction, concerns about long-term safety, potential side effects such as increased infection and thromboembolic risks, and the availability of more established biologic therapies with extensive clinical experience and safety data [29]. Additionally, insurance coverage policies vary across countries and may favor other biological therapies as initial treatment options.

There is ongoing debate in real-world studies about whether the effectiveness of tofacitinib varies based on prior exposure to biological agents. In our study, clinical remission rates at weeks 12–16 (30.8% vs. 31.7%, $p=0.487$) and 6 months (50.0% vs. 45.5%, $p=0.401$) were similar between biologic-naïve and biologic-exposed patients. A recent Asian study showed that the efficacy of tofacitinib is not influenced by prior treatment with anti-TNF-α agents [22]. However, at 1 year, remission was significantly higher in biologic-naïve patients (53.8% vs.

32.7%, $p = 0.005$). This difference likely reflects variations in disease biology and treatment history. Biologic-naïve patients may exhibit a more favorable immunological response due to less refractory disease, whereas biologic-exposed patients often present with a more severe disease phenotype and persistent cytokine dysregulation, which may limit the sustained efficacy of tofacitinib. While short-term remission rates were comparable, biologic-naïve patients may achieve more sustained long-term remission with tofacitinib.

The improvement in EIM in 67.4% of patients further underscores the broad therapeutic benefits of tofacitinib. EIMs are common in patients with UC, with a 25% to 40% prevalence, and can significantly affect the quality of life [30]. The most common EIMs in our study were arthralgia and arthritis, conditions that can be particularly debilitating. The reduction in EIMs with tofacitinib treatment aligns with findings from other studies [31]. For example, the OCTAVE trials also noted improvements in EIMs, suggesting that tofacitinib's action on multiple inflammatory pathways contributes to these benefits. Other JAK inhibitors have shown similar efficacy in reducing EIMs, suggesting that targeting the JAK-STAT pathway can provide comprehensive benefits beyond gut-specific inflammation [32].

Another interesting finding in our study was that baseline hypoalbuminemia may serve as a surrogate marker for the need for colectomy during tofacitinib therapy. Patients with IBD who exhibit reduced serum albumin levels tend to have a diminished response to treatment with biological agents due to altered pharmacokinetics induced by hypoalbuminemia [33]. Furthermore, patients with severe acute colitis and hypoalbuminemia are at an increased risk of requiring colectomy during hospitalization [34–36]. Although hypoalbuminemia does not affect the pharmacokinetics of JAK inhibitors [37], it remains a biochemical marker of UC severity, which may explain our observation of a higher colectomy rate in this context [34, 35]. The elevated colectomy rate observed in patients with low albumin levels underscores the importance of careful monitoring and prompt, appropriate management of these patients.

Despite a high proportion of patients refractory to anti-TNF therapy, tofacitinib has been shown to be effective in preventing colectomy, as demonstrated by other studies [38]. In our study, a higher endoscopic Mayo score was identified as a predictive factor for colectomy, which is consistent with findings from other authors [36].

Persistence analysis of a specific therapy evaluates medication durability in real-world scenarios, serving as a surrogate marker for efficacy, tolerance/safety, and adherence to therapy [39]. In the current study, the mean duration of tofacitinib use was 21.99 ± 1.22 months, and at 24 months of follow-up, 63.8% of patients continued to use tofacitinib. Moreover, the mean time to colectomy was 26.87 ± 0.94 months. These findings suggest that patients can stay on this treatment significantly, indicating its long-term effectiveness and tolerability/safety. The extended time to colectomy implies that tofacitinib effectively manages the disease and helps avoid or delay the need for surgical intervention in many UC patients.

Our study has several limitations, including its retrospective nature, which could result in an underestimation of adverse events, particularly mild ones, as these may have been under-reported by patients or under-recorded by clinicians. The retrospective design may also introduce selection biases and the absence of a comparative control group, limiting the direct interpretation of the results. Another bias includes the variability in treatment protocols across centers, such as differences in steroid tapering strategies and criteria for dose escalation. These factors could influence clinical outcomes and should be considered when interpreting our results. Secondly, due to the high percentage of prior biologic use in this cohort, tofacitinib was likely maintained in some patients with a partial clinical response because of the lack of alternative therapeutic options.

Third, the exclusion of patients with acute severe UC requiring hospitalization or prior colectomy limits the generalizability of our findings to these subsets. However, our study design aligns with clinical practice, where tofacitinib is often initiated in patients with moderately to severely active UC who have not yet progressed to colectomy [12, 27]. Finally, differences in treatment protocols among the participating centers (such as the steroid reduction strategy) may have influenced the outcomes. Despite these limitations, our observational experience has several strengths. It highlights the long-term effectiveness and safety of tofacitinib in UC patients from a large cohort in the largest country in Latin America. Additionally, in this study, patient data were obtained through a structured questionnaire, with standardized data collection by the researchers. Lastly, the clinical, biochemical, and endoscopic parameters used in this multicenter study are commonly applied in real-world observational research to evaluate meaningful objective outcomes induced by therapy in UC patients.

Approximately 75.5% of the Brazilian population is served solely and exclusively by the public system [40]. Patients with UC are guaranteed access to tofacitinib through the public health system. However, health insurance companies are not required to provide high-cost oral medications, such as those for treating autoimmune diseases such as UC and CD. An exception to this rule is access to oral chemotherapy to treat neoplasms. In low- and middle-income countries where biologicals

are expensive, oral small molecules are an effective low-cost option [29]. The publication of this data can help to increase access to oral drugs in our country. Future prospective studies are needed to confirm our findings and provide a deeper understanding of the role of tofacitinib in treating UC. Furthermore, healthcare policies should be adjusted to improve access to advanced therapies in Brazil, addressing the barriers that currently limit the use of oral medications for IBD.

Conclusions

In a large, long-term real-world study involving predominantly biologic-refractory UC patients, tofacitinib effectively induced steroid-free clinical and endoscopic remission. Baseline hypoalbuminemia was associated with higher colectomy rates. However, tofacitinib prevented colectomy over 30 months while maintaining a good safety profile. Therefore, this drug should be considered a valuable therapeutic option in clinical practice for patients with refractory and difficult-to-treat UC. We hope that these findings will contribute to improving national access to small oral molecules.

Abbreviations

UC	Ulcerative colitis
IBD	Inflammatory bowel disease
JAK	Janus kinase
5-ASA	5-Aminosalicylic acid
IS	Immunosuppressants
Anti-TNF	Anti-tumor necrosis factor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
CRP	C-reactive protein
FC	Fecal calprotectin
EIM	Extraintestinal manifestations
AE	Adverse event
PNR	Primary nonresponse
SAE	Serious adverse events
SD	Standard deviation
NRI	Nonresponder imputation
IQR	Interquartile range
CI	Confidence interval

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None.

Authors' contributions

All authors (Rogerio Serafim Parra [Parra RS], Renata de Sá Brito Fróes [Fróes RSB], Daniela Oliveira Magro [Magro DO], Sandro da Costa Ferreira [Ferreira SC], Munique Kurtz de Mello [Mello MK], Matheus Freitas Cardoso de Azevedo [Azevedo MFC], Aderson Omar Mourão Cintra Damião [Damião AOMC], Alexandre Sousa Carlos [Carlos AS], Luísa Leite Barros [Barros LL], Maria Luiza Queiroz Miranda [Miranda MLQ], Andrea Vieira [Vieira A], Marcos Paulo Moraes Sales [Sales MPM], Gilmara Pandolfo Zabot [Zabot GP], Ornella Sari Cassol [Cassol OS], Antônio José Tiburcio Alves Jr [Alves Jr AJT], Márcio Lubini [Lubini M], Marta Brenner Machado [Machado MB], Cristina Flores [Flores C], Fabio Vieira Teixeira [Teixeira FV], Claudio Saddy Rodrigues Coy [Coy CSR], Cyrla Zaltman [Zaltman C], Liliana Andrade Chebli [Chebli LA], Ligia Yukie Sassaki [Sassaki LY], Omar Féres [Féres O], and Júlio Maria Fonseca Chebli [Chebli JMF]) contributed to data collection, data analysis, and data interpretation. Fróes RSB and Parra RS contributed to the study design. Parra RS created all the figures and tables. Parra RS contributed to drafting, writing, and revising the manuscript. Chebli JMF, Ferreira SC, Mello MK, and Sassaki LY contributed to writing and revising the manuscript. All authors contributed to the analysis and interpretation of the data, revised the manuscript for important intellectual content, granted final approval of the version to be published, and agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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Data availability

The study's full data are available upon request and approval of the central IRB.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the coordinating site, the Hospital das Clínicas of the Ribeirão Preto Medical School at the University of São Paulo, with the following approval details: CAAE 71008923.0.1001.5440; Ethics Committee Number 6.171.795/2023. Based on this ethical approval, we are authorized to retrospectively collect data from all patients receiving treatment with small molecules, such as tofacitinib. All procedures were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication

Not Applicable.

Competing interests

Parra RS has received fees for serving as a speaker and/or an advisory board member for Takeda, Janssen, Abbvie, Celltrion and Pfizer. Fróes RSB has received fees for serving as a speaker and/or an advisory board member for Takeda, Janssen, Abbvie, and is a speaker for Celltrion, Nestle, Ferring, Pfizer, and CSL Vifor. Ferreira SC has received fees for serving as a speaker and/or an advisory board member for Janssen, Takeda, and Pfizer. Mello MK has received fees for serving as a speaker and/or an advisory board member for Takeda, Janssen, Abbvie, Sandoz and Ferring. Azevedo MFC has received fees for serving as a speaker and/or an advisory board member for Takeda, Abbvie, Pfizer and Janssen. Damião AOMC has received fees for serving as a speaker and/or an advisory board member for Takeda, Abbvie, Ferring, and Janssen Carlos AS has received fees for serving as a speaker and/or an advisory board member for Takeda, Janssen, Abbvie Miranda MLQ has received fees for serving as speaker for Takeda, Janssen and Abbvie Zabot GP has received fees for serving as a speaker and/or an advisory board member for Janssen, Abbvie, and Takeda. Cassol OS has received fees for serving as a speaker and/or an advisory board member for Nestle, Abbvie, Janssen, Takeda, and Buhlmann. Alves Junior AJT has received fees for serving as a speaker and/or an advisory board member for Janssen, Takeda, UCB, and Abbvie. Machado MB has received fees for serving as a speaker and/or na Advisory board for Takeda, Jassen, Abbvie, Ferring and Pfizer. Teixeira FV is a speaker and an advisory board member of Takeda. Chebli JMF has received fees for serving as a speaker and/or an advisory board member for Takeda, Janssen, AbbVie, Abbott, and Sandoz. Magro, DO, Sales MPM, Barros LL, Sassaki LY, Flores C, Vieira A, Lubini M, Coy CSR, Zaltmann C, and Féres O report no conflicts of interest.

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