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Effectiveness and safety of tofacitinib for ulcerative colitis: two-year results of the ICC Registry

Tessa Straatmijer[1,2] 📷 | Fiona D. M. van Schaik[3] | Alexander G. L. Bodelier[4] |
Marijn Visschedijk[5] | Annemarie C. de Vries[6] | Cyriel Y. Ponsioen[2] | Marieke Pierik[7] |
Ad A. van Bodegraven[8] 📷 | Rachel L. West[9] | Nanne K. H. de Boer[10] |
Nidhi Srivastava[11] | Tessa E. H. Romkens[12] | Jildou Hoekstra[4] | Bas Oldenburg[3] |
Gerard Dijkstra[5] | Janneke C. van der Woude[6] | Mark Löwenberg[2] | Zlatan Mujagic[7] |
Vince B. C. Biemans[3] | Andrea E. van der Meulen-de Jong[1] | Marjolijn Duijvestein[13]

[1]Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

[2]Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[3]University Medical Centre Utrecht, Utrecht, The Netherlands

[4]Amphia Hospital, Breda, The Netherlands

[5]University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[6]Erasmus Medical Centre, Rotterdam, The Netherlands

[7]Maastricht University Medical Centre, Maastricht, The Netherlands

[8]Department of Gastroenterology and Hepatology, Zuyderland Hospital, Sittard, The Netherlands

[9]Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands

[10]Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[11]Haaglanden Medical Centre, the Hague, The Netherlands

[12]Jeroen Bosch Hospital, S-Hertogenbosch, The Netherlands

[13]Radboud University Medical Centre, Nijmegen, The Netherlands

Correspondence
Marjolijn Duijvestein, Radboud University Medical Centre, Nijmegen, The Netherlands.
Email: marjolijn.duijvestein@radboudumc.nl

Summary

Background: Tofacitinib is an oral Janus kinase (JAK) inhibitor and is registered for the treatment of ulcerative colitis (UC). The effectiveness of tofacitinib has been evaluated up to 12 months of treatment.

Aim: The aim of this study was to assess the effectiveness and safety of 24 months of tofacitinib use in UC patients in the Netherlands.

Methods: Patients initiating tofacitinib treatment were included in the ICC Registry, a nationwide, observational registry. Patients were prospectively evaluated for up to 24 months. The primary outcome was corticosteroid-free clinical remission (CSFR, Simple Clinical Colitis Activity Index [SCCAI] ≤2) at week 104. Secondary outcomes

Andrea E. van der Meulen-de Jong and Marjolijn Duijvestein are shared last authors.

included biochemical remission (C-reactive protein (CRP) ≤5 mg/L and faecal calpro-tectin (FC) ≤250 μg/g), safety, and discontinuation rate.

Results: We included 110 patients of whom 104 (94.5%) were anti-TNF experienced. After 104 weeks of tofacitinib, 31.8% (34/107) were in CSFR, 23.4% (25/107) in biochemical remission and 18.7% (20/107) in combined clinical and biochemical remission. Of the patients in CSFR at week 52, 76.5% (26/34) remained so after 104 weeks of treatment. Sixty-one patients (55.5%) discontinued tofacitinib after a median duration of 13 weeks (IQR 7–34). The main reasons for discontinuation were non-response (59%), loss of response (14.8%), and adverse events (18%). There were 33.9 possible tofacitinib-related adverse events per 100 patient-years during follow-up. Adverse events most probably related to tofacitinib were skin reactions and headaches. There were 6.4 herpes zoster infections per 100 patient-years.

Conclusion: Tofacitinib was effective in 31.8% of patients after 24 months of treatment.

1 | INTRODUCTION

Tofacitinib is the first JAK inhibitor approved for the treatment of moderate to severe ulcerative colitis (UC).[1] Tofacitinib is a small molecule Janus kinase (JAK) inhibitor, which inhibits JAK1 and JAK3. By preventing phosphorylation and subsequent dimerisation of signal transducer and activator of transcription (STATs) proteins, it impairs intracellular signalling in certain immune cells, resulting in reduced inflammatory cytokine production.[2]

In the phase 3 OCTAVE trial, a remission rate (defined as a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) in 34.3% of UC patients after 52 weeks of treatment with tofacitinib was shown.[1] This drug is administered orally and has a rapid onset of action in most patients.[3] The effect of tofacitinib cannot be reduced by the development of anti-drug antibodies, a potential advantage compared to biologicals, such as anti-tumour necrosis factor (aTNF) agents.[4] However, there are safety concerns about tofacitinib, such as interference with lipid metabolism, increased risk of venous thromboembolisms and infections.[5]

Although in the OCTAVE study it was demonstrated that the therapeutic efficacy of tofacitinib in UC, a study population did not accurately reflect patients who initiate tofacitinib in daily practice. This is partly due to strict in-and exclusion criteria of clinical trials and the pre-specified follow-up period.[6] Therefore, so-called real-world studies evaluating the effectiveness and safety of tofacitinib are of great importance. Several studies demonstrated the effectiveness of tofacitinib in UC patients, but the follow-up did not exceed 1 year.[7-13] In the current era of many (new) therapeutic options for UC, personalisation of an individual's treatment is a beckoning perspective. As much as up to one-third of UC patients lose therapeutic response within a year in the case of modern, complex therapies. This necessitates effectiveness and safety data over longer periods, best with standardisation of disease and clinical characterisation of included patients. In this study, we assessed the effectiveness and safety of 24 months of tofacitinib treatment in UC patients.

2 | METHODS

2.1 | Study design and participants

The ICC Registry is a prospective observational registry of patients with inflammatory bowel disease (IBD) starting novel IBD therapies in regular care in the Netherlands. Its rationale has previously been described in more detail.[14] Currently, 19 centres are actively recruiting and enrolling IBD patients in the ICC Registry. Patients in this study were enrolled between October 2018 and October 2019. Adult patients (aged ≥18 years) with an established diagnosis of IBD are prospectively followed-up with scheduled outpatient visits at weeks 12, 24, 52 and 104 or discontinuation of treatment. The decision to start tofacitinib treatment was at the discretion of the treating physician. Patients initiating tofacitinib received an induction regimen of 10 mg bi-daily (BID) for the first 8 weeks, followed by a maintenance treatment of 5 mg BID. Optional dose optimisation in case of insufficient response was at the discretion of the treating physician. There was no standard tapering regimen in case of concomitant treatment for steroids or other regimens for conventional immunosuppressants. Steroids and conventional immunosuppressants were prescribed at the initiation of the treating physician. At baseline, all patients included in the primary analysis had both clinical and objective (biochemical and/or endoscopic) disease activity.

2.2 | Outcomes and definitions

The primary outcome was a corticosteroid-free clinical remission rate at week 104. Clinical remission was defined as a Simple Clinical Colitis Activity Index (SCCAI) ≤2. Secondary outcomes included biochemical remission, combined corticosteroid-free clinical and biochemical remission, endoscopic remission, safety, and discontinuation rate. Biochemical remission was defined as a C-reactive protein (CRP) ≤ 5 mg/L and faecal calprotectin ≤250 μg/g (FC). Endoscopic remission was defined as an endoscopic Mayo score of 0. Patients who discontinued tofacitinib due to non-response, loss of response, adverse events or at the patients' request without clinical remission were considered a treatment failure and considered as non-responders. Patients who discontinued tofacitinib because of pregnancy or at patients' request with long-term sustained clinical and biochemical remission were considered censored cases. Patients were considered non-responders in case of missing data. In case patients were lost to follow-up as they changed treatment facilities, we contacted the new treatment facility to collect data on the remaining follow-up visits.

Adverse events leading to therapy withdrawal were classified as severe. The remaining adverse events were labelled as possibly- or probably-related by the treating physician. Infections not leading to antibiotic or antiviral medication were classified as mild infections. Infections requiring oral antibiotics of antiviral medication were classified as moderate infections and infections leading to hospitalisation and/or requiring intravenous (IV) administration of antibiotics or anti-viral medication were classified as severe infections. Reasons for treatment discontinuation were documented by the treating physician.

2.3 | Statistical methods

Analyses were performed with the intention to treat base. Cumulative drug survival was assessed using the Kaplan–Meier method. Depending on the distribution, continuous variables were presented as means with standard deviation (SD) or as median with interquartile range (IQR). Categorical variables were presented as percentages and compared by using the χ^2 test. Predictors of corticosteroid-free clinical remission at week 104 were assessed using binary logistic regression. Variables with a p-value of ≤0.2 in the univariate analysis were selected for the multivariable analysis. $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics version 28.0.0.

2.4 | Ethical consideration

This study was reviewed and approved by the Committee on Research Involving Human Subjects at the Radboud University Medical Centre (institutional review board: 2018-4076).

3 | RESULTS

3.1 | Baseline characteristics

In total, 110 patients were included. Baseline characteristics are shown in Table 1. Most patients were anti-TNF experienced (94.5%) and vedolizumab experienced (60.9%), but not ustekinumab experienced (3.6%). The mean follow-up was 102 (7) weeks. Biochemical data at baseline were available in all patients and 96 out of 110 patients (87.3%) had biochemical disease activity at baseline (CRP results were available in 103 patients and increased in 53 patients [51.2%] and FC results were available in 88 patients and increased in 78 patients [88.6%]).

TABLE 1 Baseline characteristics.

		Tofacitinib (n = 110)
Age (years)	Mean (SD)	45 (14)
Female	N (%)	50 (45.5)
Disease duration (years)	Median (IQR)	7 (3–14)
Follow-up (weeks)	Mean (SD)	102 (7)
BMI	Mean (SD)	24.8 (4.2)
Disease activity		
SCCAI-score	Median (IQR)	7 (5–10)
CRP (mg/L), n = 103	Median (IQR)	5.9 (2–13)
FC (mg/kg), n = 88	Median (IQR)	1765 (633–2763)
Medical history		
Disease location[a]		
Proctitis	N (%)	8 (7.3)
Left-sided	N (%)	36 (32.7)
Pancolitis	N (%)	64 (58.2)
Unknown	N (%)	2 (1.8)
Prior treatment		
Prior thiopurine	N (%)	95 (86.4)
Prior ≥1 anti-TNF	N (%)	104 (94.5)
Prior ≥2 anti-TNF	N (%)	41 (37.2)
Prior vedolizumab	N (%)	67 (60.9)
Prior ustekinumab	N (%)	4 (3.6)
JAK inhibitor		
Concomitant treatment		
Oral prednisone	N (%)	41 (37.3)
Oral prednisone dose	mg (IQR)	20 (15–30)
Budesonide	N (%)	17 (15.5)
Mesalazine	N (%)	40 (36.4)
Thiopurine	N (%)	3 (2.7)
Methotrexate	N (%)	2 (1.8)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FC, faecal calprotectin; SCCAI, Simple Clinical Colitis Activity Index.
[a]Maximum extend until inclusion.

3.2 | Clinical outcomes

Corticosteroid-free clinical remission was achieved in 38.2% (42/110), 35.8% (39/109), 31.8% (34/107), and 31.8% (34/107) of patients at 12, 24, 52, and 104 weeks, respectively (Figure 1A). Of the patients in corticosteroid-free clinical remission at week 24, 66.7% (26/39) remained in corticosteroid-free clinical remission after 104 weeks of treatment. Of the patients in corticosteroid-free clinical remission at week 52, 76.5% (26/34) remained in corticosteroid-free clinical remission after 104 weeks of treatment. Corticosteroid-free clinical remission rates in patients treated with at least two different classes of biologicals (e.g. not two anti-TNF therapies) before initiating tofacitinib are displayed in Figure 1B.

3.3 | Biochemical outcomes

Biochemical remission was achieved in 37.3% (41/110), 32.1% (35/109), 33.6% (36/107) and 23.4% (25/107) of patients after 12, 24, 52 and 104 weeks respectively (Figure 1A). Of the patients in biochemical remission at week 24, 89.5% (17/35) remained in biochemical remission after 104 weeks of treatment. Of the patients in biochemical remission at week 52, 55.6% (20/36) remained in biochemical remission after 104 weeks of treatment. Biochemical remission rates in patients treated with at least two different classes of biologic therapies before initiating tofacitinib are displayed in Figure 1B.

In patients with elevated CRP concentrations at baseline ($n = 53$), 39.6% ($n = 21$), 35.8% ($n = 10$), 32.1% ($n = 17$) and 18.9% ($n = 10$) were in biochemical remission at week 12, 24, 52 and 104 based on CRP concentrations.

In patients with elevated FC concentrations at baseline ($n = 78$), 34.6% ($n = 27$), 25.6% ($n = 20$), 21.8% ($n = 21$) and 12.8% ($n = 10$) were in biochemical remission at week 12, 24, 52 and 104 based on FC concentrations.

3.4 | Combined corticosteroid-free clinical and biochemical outcomes

Combined corticosteroid-free clinical and biochemical remission was achieved in 25.5% (28/110), 25.7% (28/109), 22.4% (24/107) and 18.7% (20/107) patients after 12, 24, 52 and 104 weeks, respectively (Figure 1A). Of the patients in combined corticosteroid-free clinical and biochemical remission at week 24, 42.9% (12/28) remained in corticosteroid-free clinical and biochemical remission after 104 weeks of treatment. Of the patients in combined corticosteroid-free clinical and biochemical remission at week 52, 76.5% (26/34) remained in corticosteroid-free clinical and biochemical remission after 104 weeks of treatment. Combined corticosteroid-free clinical and biochemical remission rated in patients treated with at least two different classes of biologic therapies before initiating tofacitinib are displayed in Figure 1B.
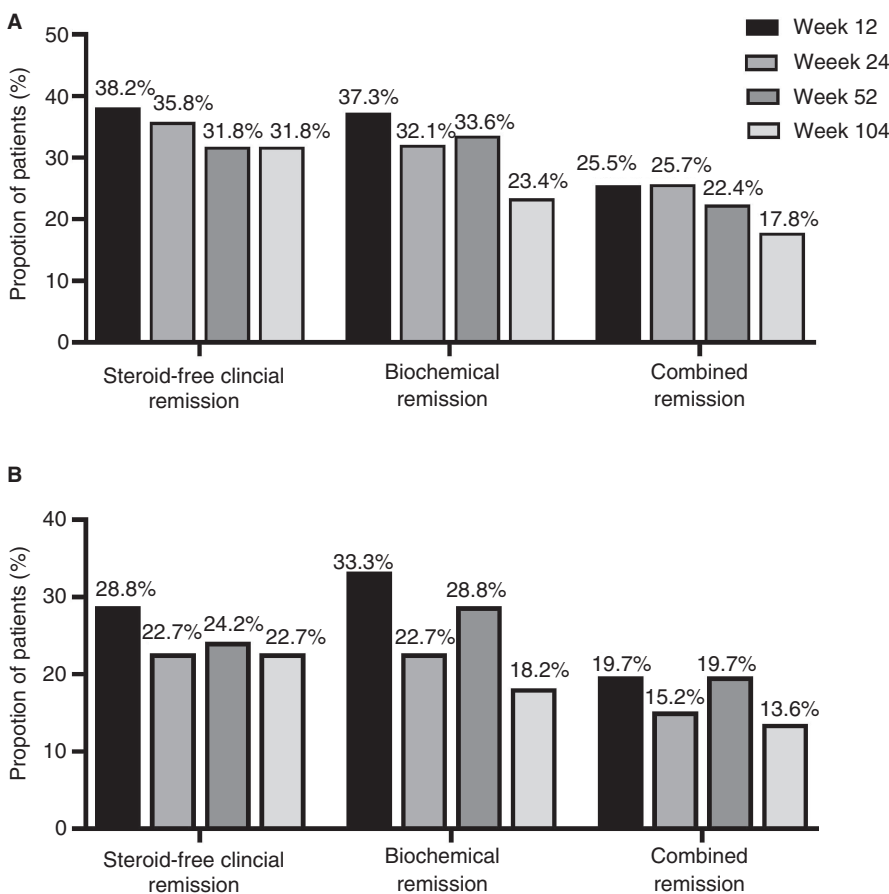
FIGURE 1 Corticosteroid-free clinical remission rates, biochemical remission rates and combined remission rates in all patients (A) and patients treated with at least two different classes of biologicals therapies (e.g. not two anti-TNF therapies) before initiating tofacitinib (B).

3.5 | Endoscopic outcomes

Out of 88 patients with documented endoscopic disease activity at baseline, 52 patients (59.1%) underwent endoscopy during follow-up after a median treatment duration of 15 weeks (IQR 8–43). Thirty-seven of these patients (71.2%) achieved endoscopic remission during follow-up and 17 (32.7%) achieved corticosteroid-free clinical remission (CSFR) after 104 weeks.

3.6 | Clinical factors associated with corticosteroid-free clinical remission

Univariate and multivariate predictors of corticosteroid-free clinical remission at week 104 are depicted in Table 2. None of the assessed factors was predictive of achieving corticosteroid-free clinical remission.

Univariate and multivariate predictors of biochemical remission and combined corticosteroid-free clinical and biochemical remission at week 104 are shown in Tables S1 and S2. None of the assessed factors was predictive for biochemical of combined corticosteroid-free clinical and biochemical remission. Prior exposure to anti-TNF therapy or ustekinumab treatment could not be assessed due to the small patient number who were naïve for anti-TNF or with ustekinumab treatment.

3.7 | Drug survival

Cumulative tofacitinib treatment survival is illustrated in Figure 2. Sixty-one patients stopped tofacitinib treatment after a median treatment duration of 13 weeks (IQR 7–34) (Table 3). After 1 year of treatment, five patients discontinued tofacitinib therapy. These five patients constituted 9.3% of all patients treated with tofacitinib for at least 52 weeks. The most common reasons for treatment discontinuation were primary non-response (59%), adverse events (18%) and loss of response (14.8%). One patient received euthanasia for non-IBD-related disease and died after 23 weeks of follow-up. Three patients stopped treatment due to an infection (urinary tract, herpes zoster and CMV infections). Two patients discontinued therapy on their own initiative after 20 and 26 weeks of treatment after achieving corticosteroid-free clinical remission. Of the patients discontinuing tofacitinib, 15 patients continued treatment with concomitant corticosteroids, 15 patients with mesalazine and three patients with budesonide.

3.8 | Safety

During follow-up, 13.8 moderate and 1.8 severe infections were reported per 100 patient-years (Table 4). The most common infections reported were urinary tract infections and herpes zoster infections.
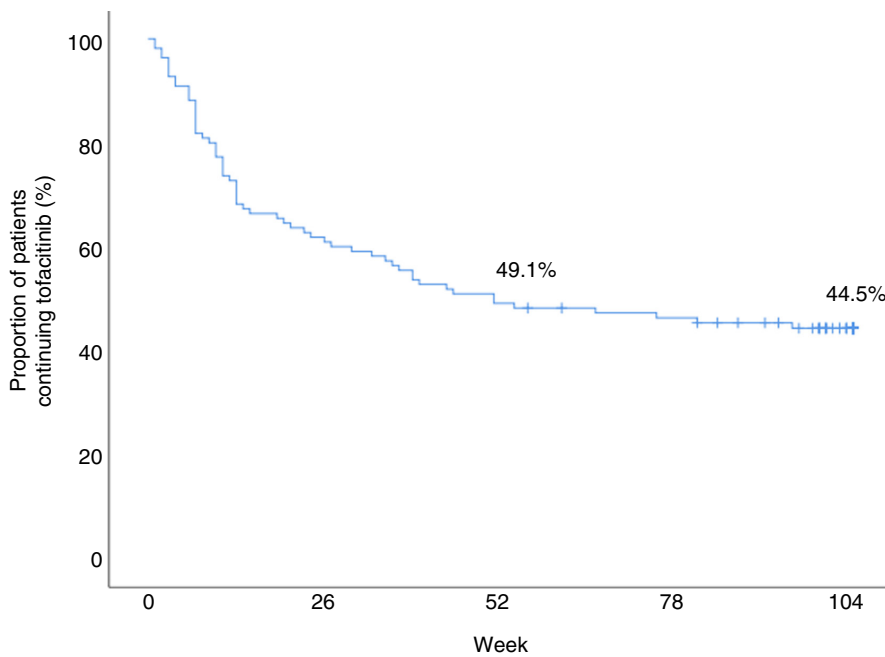
TABLE 2 Univariate and multivariate predictors of corticosteroid-free clinical remission at week 104.

	Univariate analyses			Multivariate analyses		
	OR	95% CI	p-value	OR	95% CI	p-value
Age at inclusion	1.01	0.96–1.07	0.67			
BMI per point	1.13	0.86–1.47	0.39			
Sex						
Male	Ref					
Female	1.27	0.22–7.20	0.79			
Disease duration (year)	1.13	0.94–1.37	0.20	1.11	0.91–1.35	0.31
Disease location[a]						
Proctitis	0.19	0.01–3.72	0.60			
Left-sided	2.10	0.01–21.10	0.27			
Pancolitis	Ref		0.53			
Prior biological treatments						
Vedolizumab	2.25	0.36–13.97	0.38			
≥2 biologic therapy	3.95	0.42–37.50	0.23			
Clinical disease activity[b]						
SCCAI per point	0.77	0.56–1.06	0.11	1.13	0.94–1.37	0.20
Biochemical disease activity[a]						
CRP (mg/L)	1.02	0.94–1.11	0.64			
Faecal calprotectin (μg/g)	1.00	1.00–1.00	0.79			
Concomitant medication[a]						
Corticosteroids	2.78	0.47–16.35	0.26			

[a]At inclusion.

FIGURE 2 Tofacitinib drug survival in ulcerative colitis patients after 104 weeks of follow-up.

After 52 weeks, one severe respiratory tract infection, five moderate infections (gynecologic, urinary tract, herpes zoster, respiratory tract and skin), two mild COVID-19, one mild herpes zoster and one mild herpes simplex occurred. None of the patients with a herpes zoster infection was vaccinated.

In total, 7.3 probably and 33.9 possible tofacitinib-related adverse events per 100 patients years were seen during follow-up (Table 4). The most probably related adverse events were skin reactions and headaches. Only one patient experienced possibly related headaches after 52 weeks of treatment. One patient developed hypertension during tofacitinib treatment and one patient experienced an increased heart rate after initiating tofacitinib, this was not objectified. No other cardiovascular of thromboembolic events were seen during follow-up.

Adverse events led to therapy withdrawal in 10 patients and two of these patients, this was after 52 weeks of treatment, including a CMV infection (viremia) and a urinary tract infection at week 54 and one herpes zoster and urinary tract infection at week 81.

The mean relative difference between baseline and after induction therapy for triglycerides ($n = 46$), cholesterol ($n = 49$), HDL-cholesterol ($n = 47$) and LDL-cholesterol ($n = 44$) concentrations were −0.06 (95% CI: −0.32 to 0.20, $p = 0.656$), −0.31 (95%CI: −0.59 to 0.03, $p = 0.031$), −0.13 (95% CI: −0.25 to 0.01, $p = 0.031$) and − 0.16 (95% CI: −0.41 to 0.09, $p = 0.215$), respectively.

3.9 | Dosage and concomitant treatment

Two patients were treated with a tofacitinib induction scheme of 5 mg BID. Both patients had cardiovascular risk factors (hypertension, hypercholesterolemia, smoking and substance abuse). All other patients initiated tofacitinib with an induction regimen of 10 mg BID. After 12, 24, 52 and 104 weeks of treatment, 32/78 (41%), 18/67 (26.9%) 12/53 (22.6%) and 9/49 (18.4%) patients were on a 10 mg

TABLE 3 Discontinuation within 104 weeks of treatment.

	UC, N = 61 (55.5%)
Treatment duration—weeks, Median (IQR)	13 (7–34)
Reason discontinuation, N (%)	
No response	36 (59)
Adverse events	11 (18)
Secondary loss of response	9 (14.8)
Request patient	2 (3.3)
Death after euthanasia (non-IBD related)	1 (1.6)
Long-term biochemical remission	1 (1.6)
No effect on arthralgia	1 (1.6)

BID dosing schema respectively. Of the patients withdrawing from therapy, 45 patients (73.8%) were on a 10 mg BID dosing scheme and one patient (1.6%) was on a 15 mg BID dosing scheme.

Two patients received concomitant treatment with methotrexate (MTX) at the initiation of tofacitinib therapy. One patient discontinued MTX treatment after 24 weeks, whilst in biochemical remission. The other patient continued MTX throughout 24 months of follow-up. Out of these three patients who received concomitant treatment with thiopurines at the start of therapy, two stopped thiopurine agents within 12 weeks and the third patient within 52 weeks.

4 | DISCUSSION

This is the first prospective cohort describing the effectiveness of tofacitinib in UC patients up to 24 months of treatment. In this prospective, real-world cohort we observed that 32% of UC patients were in corticosteroid-free clinical remission at 24 months after

TABLE 4 Tofacitinib-related adverse events.

	Tofacitinib: 109 years
Mild infections	24 (22.0 per 100 patient-years)
Flu-like symptoms	4
Upper respiratory tract	4
Herpes simplex	3
Herpes zoster	3
Covid-19	2
Fever of unknown origin	2
Dental	1
Ear	1
Gynaecologic	1
Lower respiratory tract	1
Skin	1
Urinary tract	1
Moderate infections	15 (13.8 per 100 patient-years)
Urinary tract	6
Herpes zoster	4
CMV	3
Herpes simplex	3
Flu-like symptoms	2
Fever of unknown origin	1
Gastrointestinal	1
Gynaecologic	1
Lower respiratory tract	1
Skin	1
Throat	1
Upper respiratory tract	1
Severe infections	2 (1.8 per 100 patient-years)
Flu-like symptoms	1
Lower respiratory tract	1
Possibly related	37 (33.9 per 100 patient-years)
Skin	10
Headache	6
Gastrointestinal	3
Respiratory	3
Cardiac	2
Musculoskeletal	2
Glaucoma	1
Genital	1
Hepatobiliary	1
Kidney and urinary tract	1
Malaise	1
Mouth	1
Nerve system	1
Oedema	1
Psychiatric	1

(Continues)

TABLE 4 (Continued)

	Tofacitinib: 109 years
Sleep disturbance	1
Vascular	1
Probably related	8 (7.3 per 100 patient-years)
Musculoskeletal	3
Skin	3
Cardiac	1
Headache	1
Serious adverse events	10 (9.2 per 100 patient-years)
Severe headache	2
Dizziness	1
Gastrointestinal	1
Hepatocellular hepatitis	1
Malaise	1
Musculoskeletal	1
Nausea	1
Skin	1
Throat	1

Note: Number of adverse events during treatment of ulcerative colitis patients with tofacitinib. Infections were classified as: mild infections: no antibiotics or antiviral medication; moderate infections: oral antibiotics or antiviral medication; severe infections: hospitalisation or intravenously administrated antibiotic or antiviral medication.

initiating tofacitinib treatment. Seventy-seven per cent of patients who were in corticosteroid-free clinical remission at 1 year, remained in corticosteroid-free clinical remission after 24 months.

By applying non-responder imputation, approximately 60% of UC patients included in the OCTAVE trial were in remission after 24 months treatment.[15] This percentage of patients with remission-in-remitters (to induction therapy with tofacitinib) is about twice that high as was observed in common practice, as represented in the current study.

Up to now, in only one relatively small, retrospective cohort remission rates of tofacitinib in UC patients after 24 months of treatment were described.[16] In 13 patients, 53.8% were in remission after 24 months (defined as a partial Mayo score ≤2), but it was unclear whether an intention to treat analysis was used. Other studies evaluated the effectiveness of tofacitinib up to 1 year of treatment.[8,11,12] Two retrospective cohorts described corticosteroid-free clinical remission rates of 34.2% and 42% in 38 and 36 patients, respectively, after 1 year of tofacitinib treatment, which is comparable to the here presented results.[11,12] In another, Spanish cohort maintenance remission rates were not documented, but similar discontinuation rates of 40% (*n* = 45/113) of patients were reported in a time period of up to 44 weeks of follow-up.[8]

Adverse events in the current study were higher compared to other real-world studies assessing the safety of tofacitinib.[12,17] These studies had a retrospective design which may have resulted in underreporting of adverse events. Although the Food and Drug Administration (FDA)

has expressed concerns about the risk of cancer, cardiovascular and thromboembolic events, none were reported in 109 patient-years of follow-up in our cohort. This was in line with other real-world studies, However, long-term registries with large sample sizes are required to obtain more details regarding these uncommon but severe adverse events. Due to the risk of cardiovascular and thromboembolic events, the FDA recommends dosing tofacitinib 10 mg BID only during induction therapy for 8 weeks and subsequently dose tofacitinib 5 mg BID. Notwithstanding, in our cohort, 32/78 (41%), 18/67 (26.9%) 12/53 (22.6%) and 9/49 (18.4%) patients were on a 10 mg BID dosing scheme, at 12, 24, 52 and 104 weeks of treatment, respectively. This was due to prolonged induction therapy in case of (partially) non-response or re-induction in patients with loss of response. It is unclear for how many weeks patients were treated with a 10 mg BID tofacitinib as this was not part of the collected data at each visit.

Treating physicians face challenges with the positioning of JAK inhibitors in UC patients. Tofacitinib is currently mostly prescribed after anti-TNF failure in UC patients due to experience, price and safety concerns. Considering the lack of head-to-head trials, the exact positioning of tofacitinib after anti-TNF failure remains an ongoing field of uncertainty and thus research. A meta-analysis evaluating second-line pharmacotherapies after anti-TNF failure for patients with moderate-to-severe UC showed that tofacitinib was significantly superior to vedolizumab and adalimumab for induction of clinical remission.[18] Also, comparative real-world studies showed that tofacitinib was shown to be superior to vedolizumab in achieving biochemical remission up to 1 year of treatment.[19] To determine the optimal positioning of JAK inhibitors in individual patients several aspects should be taken into account including disease severity, immunogenicity, prior anti-TNF exposure, and patient characteristics such as age and comorbidity.

One of the strengths of this study was the prospective follow-up of 24 months and its relatively large sample size. Since patients were included in both tertiary and secondary centres and no restricting inclusion criteria other than objectified disease activity and lack of drug-associated contraindications were used, the presented cohort was representative of patients initiating tofacitinib in daily clinical care. The limitation of this study was the lack of systematic endoscopic evaluation of disease activity, randomisation and direct treatment (strategy) comparison, successively. Since the endoscopic assessment was not mandatory, treating physicians performed endoscopy at their own discretion. This may have led to bias since some centres did not as per standard perform endoscopy for ascertainment of endoscopic healing.

In conclusion, tofacitinib was a relatively effective and safe treatment modality in approximately one-third (31.8%) of UC patients after 24 months of treatment.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

COLLABORATORS

Malena Schlotter, Martine van Workum, Dirk de Jong, Willemijn van Dop, Frank Hoentjen, S. van der Marel, Hayat El Ghabzouri, Kamila Talhaoui, Nynke Boontje, Herma Fidder, Meike Hirdes, Rob H Creemers, Annemarie van der Spek, Jael Smid, Noortje Festen, Carmen Horjus, Bindia Jharap, Wout Mares, Michael van der Voorn, Marthe François-Verweij, Toos Schakel-van den Berge, Jeroen Maljaars, Rosaline Theeuwen, Denise van den Berg, Suzanne Gerretsen, Xenia Yocarini, Geert D'Haens, Mark Lowenberg, Joep Grootjans, Krisztina Gecse, Gerd Bouma, Petra Waaijenberg, Bart Muskens.

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The manuscript, including figures and tables, has not been previously published and is not under consideration elsewhere.

ORCID

Tessa Straatmijer https://orcid.org/0000-0001-6989-5226
Ad A. van Bodegraven https://orcid.org/0000-0003-2636-303X

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.