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# Tofacitinib for ulcerative colitis: results of the prospective Dutch Initiative on Crohn and Colitis (ICC) registry

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## Summary

**Background:** Tofacitinib is a Janus kinase inhibitor approved for the treatment of ulcerative colitis (UC).

**Aim:** To evaluate effectiveness, safety and use of tofacitinib in daily practice.

**Methods:** UC patients initiating tofacitinib were prospectively enrolled in 15 hospitals in the Netherlands. Corticosteroid-free clinical remission (short clinical colitis activity index [SCCAI] ≤2), biochemical remission (faecal calprotectin level ≤250 μg/g), combined corticosteroid-free clinical and biochemical remission, predictors of remission, safety outcomes, treatment dose and effect on lipids were determined at weeks 12 and 24. Endoscopic outcomes were evaluated in centres with routine endoscopic evaluation.

**Results:** In total, 123 UC patients (95% anti-TNF, 62% vedolizumab and 3% ustekinumab experienced) were followed for a median duration of 24 weeks (interquartile range 12-26). The proportion of patients in corticosteroid-free clinical, biochemical, and combined corticosteroid-free clinical and biochemical remission rate at week 24 was 29% (n: 22/77), 25% (n: 14/57), and 19% (n: 11/57) respectively. Endoscopic remission (Mayo = 0) was achieved in 21% of patients at week 12 (n: 7/33). Prior vedolizumab exposure was associated with reduced clinical remission (odds ratio 0.33, 95% confidence interval [CI] 0.11-0.94). At week 24, 33% (n: 14/42) of patients still on tofacitinib treatment used 10 mg twice daily. In total, 33 tofacitinib-related adverse events (89 per 100 patient years) occurred, 7 (6% of total cohort) resulted in

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discontinuation. Cholesterol, HDL and LDL levels increased during induction treatment by 18% (95% CI 9-26), 18% (95% CI 8-28) and 21% (95% CI 14-39) respectively.
**Conclusion:** Tofacitinib is an effective treatment for UC after anti-TNF and vedolizumab failure. However, a relatively high rate of adverse events was observed resulting in discontinuation in 6% of patients.

## 1 | INTRODUCTION

Tofacitinib is registered as an oral treatment option for ulcerative colitis (UC) in the Netherlands since the approval by the European Medicines Agency (EMA) in October 2018. It is a small-molecule Janus kinase (JAK) inhibitor which interferes with the intracellular JAK/signal transducer and activators of transcription (STAT) pathway. This pathway plays an important role in the signal transduction of multiple pro-inflammatory cytokines involved in the pathogenesis of a spectrum of inflammatory diseases.[1,2] The pivotal phase 3 clinical OCTAVE trial demonstrated dose-dependent efficacy in inducing and maintaining clinical remission in patients with moderately to severely active UC.[3] However, due to strict inclusion and exclusion criteria, the study population does not accurately reflect the actual patient population receiving tofacitinib in regular care.[4] For example, in real-life setting, novel treatments are generally prescribed for patients who previously failed not only anti-TNF but also newer therapies such as vedolizumab. Moreover, trial protocols demand wash-out periods of prior therapies, stable therapy dose and strict pre-specified follow-up, which do not reflect routine care. Different treatment strategies can be adopted beyond trial protocols including dose optimisation and the addition of concomitant medication.

To date, only two cohort studies are available that describe the use of tofacitinib in daily practice.[5,6] However, these cohorts are limited by the small population size and their retrospective nature. Using the Dutch *Initiative on Crohn and Colitis (ICC) Registry*, a prospective, nationwide, observational registry for novel IBD therapies, we aimed to determine real-world effectiveness, safety and the use of tofacitinib for UC.

## 2 | METHODS

### 2.1 | Study design and setting

The *ICC Registry* is a prospective, nationwide and observational registry of inflammatory bowel disease (IBD) patients initiating pre-specified IBD therapies in everyday care in the Netherlands. The design and rationale have previously been described in detail.[7,8] In short, IBD patients aged 16 years or older are included in eight university and seven non-university hospitals. The patients are followed for 2 years with planned visits at initiation of therapy (baseline) and during maintenance therapy (at weeks 12, 24, 52 and 104 or until medication is discontinued). Data are captured using electronic case report forms (eCRF) with automated reminders to ensure adherence to the protocol.

### 2.2 | Participants

After formal approval of the regulatory authorities (October 2018), all UC patients who started tofacitinib treatment in regular care at the participating centres were consecutively enrolled until November 2019. The decision to start therapy was at the discretion of the treating physician and there were no exclusion criteria other than mentioned in the summary of product characteristics for tofacitinib. Tofacitinib was administrated according to label with an induction regimen of 10 mg twice daily for the first 8 weeks, followed by maintenance treatment of 5 mg twice daily with optional dose optimisation in case of insufficient response. Patients with combined clinical (short clinical colitis activity index [SCCAI] >2) and objective (endoscopy [Mayo ≥1] or biochemical (C-reactive protein, [CRP] concentration >5 mg/L or faecal calprotectin [FCP] level >250 μg/g)) disease activity at baseline were included to determine the effectiveness outcomes. Data of all enrolled patients, independent of disease activity scores at baseline, were used to determine safety and usage outcomes.

### 2.3 | Outcomes and definitions

The primary outcome was the proportion of patients in corticosteroid-free clinical remission (SCCAI ≤2) at week 24. Secondary

outcomes included: clinical response (decrease in SCCAI ≥3 compared with baseline), clinical remission (SCCAI ≤2), biochemical remission (FCP level ≤250 μg/g), combined corticosteroid-free clinical and biochemical remission, endoscopic remission (endoscopic Mayo score = 0) and endoscopic response (decrease in endoscopic Mayo score of ≥1 compared with baseline), and predictors of corticosteroid-free clinical remission. Changes in lipid concentrations, safety (possibly or probably related adverse events, adverse events requiring treatment discontinuation, mild infections: no antibiotics or anti-viral medication, moderate infections: oral antibiotics or anti-viral medication or severe infections: hospitalisation or intravenously administrated antibiotics or anti-viral medication), treatment dose and drug survival were assessed.

Follow-up time was defined as time between the date of the first dosing and the last visit used in the analysis. Patients who discontinued tofacitinib due to primary or secondary nonresponse, adverse events or at their own request were considered treatment failures and classified as nonresponders in the remaining visits when follow-up would have been adequate. Patients who discontinued tofacitinib due to pregnancy were considered censored cases and were not included in the subsequent analysis. To limit bias, only the endoscopic outcomes of patients treated in centres with systematic endoscopic evaluation regardless of clinical and biochemical parameters were used in the analysis.

## 2.4 | Statistical methods

All analyses were performed on an intention-to-treat basis. Continuous variables were presented as means with standard deviations (SD) or as medians with interquartile ranges (IQR) depending on the normality of the underlying distribution. Continuous variables were subsequently compared using paired sample *T* test, independent *T* test or Mann-Whitney *U* test. Categorical variables were presented as percentages and compared using the Chi-square test. Cumulative drug survival was assessed using the Kaplan-Meier method. We explored predictors of corticosteroid-free clinical remission at week 24 using a binary logistic regression. Due to the limited number of patients achieving this outcome, we a priori agreed on predictors associated with disease severity or refractory to test univariable. Variables with a *P* value of <0.2 in the univariable analysis were selected for the multivariable analysis. A two-sided *P* value of 0.05 or less was considered statistically significant. All analyses were performed using IBM SPSS statistics for Windows, version 24.0 (IBM Corp.).

## 2.5 | Ethical consideration

This study was reviewed and approved by the Committee on Research Involving Human Subjects at the Radboudumc (institutional review board: 4076).

**TABLE 1** Baseline characteristics of ulcerative colitis patients initiating tofacitinib therapy

| Baseline characteristics | | UC (N = 123) |
|---|---|---|
| Age[a] | Median (IQR) | 46.4 (32.9-55.7) |
| Gender—male | N (%) | 72 (58.5) |
| Body mass index[a] | Mean (SD) | 24.8 (4.2) |
| Current smoker | N (%) | 6 (4.9) |
| Disease duration in years | Median (IQR) | 7.6 (3.7-14.8) |
| Follow-up duration | Median (IQR) | 24.0 (12.0-25.7) |
| UC disease location[b] | | |
| Proctitis | N (%) | 11 (8.9) |
| Left sided | N (%) | 47 (38.5) |
| Pancolitis | N (%) | 63 (51.6) |
| Prior anti-TNF therapy use | | |
| ≥1 | N (%) | 116 (95.1) |
| ≥2 | N (%) | 48 (39.1) |
| 3 | N (%) | 5 (4.1) |
| Unknown | N (%) | 1 (0.8) |
| Prior vedolizumab use | N (%) | 76 (62.3) |
| Prior vedolizumab and anti-TNF use | | 73 (59.3) |
| Prior ustekinumab use | N (%) | 4 (3.3) |
| Clinical and biochemical disease activity[a] | | |
| SCCAI | Median (IQR) | 8 (5-10) |
| CRP, mg/L | Median (IQR) | 5 (2-13) |
| Faecal calprotectin, μg/g | Median (IQR) | 1730 (550-2604) |
| Endoscopic disease activity (performed in 86 patients) | | |
| Mayo 1 | N (%) | 10 (10.9) |
| Mayo 2 | N (%) | 29 (31.5) |
| Mayo 3 | N (%) | 51 (55.4) |
| Unknown | N (%) | 2 (2.3) |
| Concomitant medication | | |
| No concomitant medication | N (%) | 71 (57.7) |
| Systemic corticosteroids | N (%) | 44 (35.8) |
| Corticosteroids range | mg (IQR) | 20 (15-30) |
| Immunosuppressants | N (%) | 6 (4.9) |
| Both systemic corticosteroids and immunosuppressants | N (%) | 1 (0.8) |
| Corticosteroids range | mg (IQR) | 25 |
| Unknown | N (%) | 1 (0.8) |
| Lipids[a] | | |
| Triglycerides—mmol/L (n: 65) | Mean (SD) | 1.52 (0.75) |
| Cholesterol—mmol/L (n: 71) | Mean (SD) | 4.65 (1.03) |
| High-density lipoprotein (HDL)—mmol/L (n: 69) | Mean (SD) | 1.42 (0.48) |
| Low-density lipoprotein (LDL)—mmol/L (n: 65) | Mean (SD) | 2.80 (0.85) |

Abbreviations: anti-TNF, anti-tumour necrosis factor; CRP, C-reactive protein; immunosuppressants, thiopurines or methotrexate; IQR, interquartile range; N, number; SCCAI, short clinical colitis activity index.

[a]At inclusion.

[b]Maximum extent until inclusion.

## 3 | RESULTS

### 3.1 | Baseline characteristics

Baseline characteristics are displayed in Table 1. In total, 123 patients (118 UC and 5 IBD unclassified) were included. Patients were followed for a median duration of 24.0 weeks (IQR: 12.0-25.7) and were predominately men (58.5%) with a median disease duration of 7.6 years (IQR: 3.7-14.8). At inclusion, 51.6% of patients had a pancolitis, 38.5% left-sided disease, and 8.9% had a proctitis. Prior to initiating tofacitinib treatment, 95.1% had previously been exposed to 1 or more anti-TNF drugs, 62.3% to vedolizumab and 59.3% to both anti-TNF and vedolizumab treatment while 3.3% had previously been exposed to ustekinumab. At baseline 41.5% received systemic corticosteroids, immunosuppressants or both (35.8% corticosteroids, 4.9% immunosuppressants (thiopurines or methotrexate) and 0.8% both corticosteroids and an immunosuppressant).

Effectiveness outcomes were assessed in 111 patients who had both clinical and objective disease activity at baseline. These patients had a median SCCAI of 8 (IQR: 5-11), a median FCP level of 1800 µg/g (IQR: 633-2682) and a median CRP concentration of 6 mg/L (IQR: 2-14). Eighty-six patients underwent endoscopic evaluation at baseline and the majority of patients had an endoscopic Mayo score of 3 (57.0%) (Mayo 1:9.3%, Mayo 2:31.4%).

### 3.2 | Clinical effectiveness

The proportion of patients in corticosteroid-free clinical remission at weeks 12 and 24 was 35.4% (n: 35/99) and 28.6% (n: 22/77) respectively (Figure 1). The proportion of patients without prior exposure to vedolizumab showed significantly better results at week 12 (vedolizumab naïve: 47.4% (n: 18/38) vs vedolizumab exposed: 26.7% (n: 16/60), $P = 0.036$) and at week 24 (44.4% (n: 12/27) vs 20.4% (n: 10/49), $P = 0.027$). A smaller proportion of patients without prior exposure to vedolizumab had a pancolitis at inclusion when compared to patients with exposure to vedolizumab (41.9% vs 56.7%, $P = 0.017$), while other baseline variables including clinical, biochemical and endoscopic disease activity were comparable ($P = 0.763$, 0.354, 0.663) at baseline.

The proportion of patients with clinical response at weeks 12 and 24 was 55.6% (n:55/99) and 45.5% (n: 35/77) respectively. The proportion of patients in clinical remission at weeks 12 and 24 was 41.4% (n: 41/99) and 32.5% (n: 25/77) respectively.

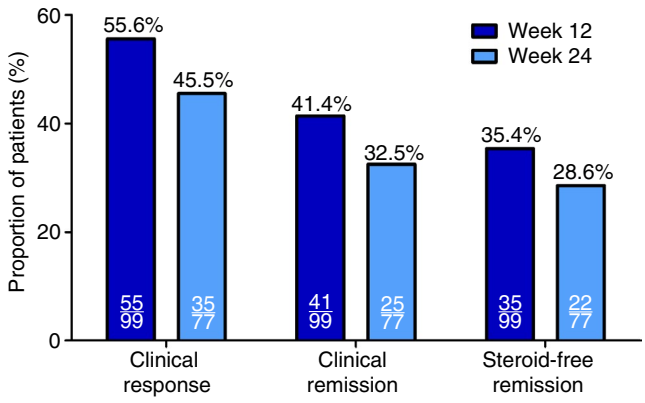


**FIGURE 1** Proportion of ulcerative colitis patients with clinical response (SCCAI decrease of ≥3 compared with baseline), clinical remission (SCCAI ≤2) and corticosteroid-free clinical remission at week 12 and 24. SCCAI, short clinical colitis activity index

### 3.3 | Biochemical disease activity

The proportion of patients in biochemical remission (FCP ≤250 µg/g) at weeks 12 and 24 was 37.0% (n: 30/81) and 24.6% (n: 14/57) respectively (Figure 2). Imputing missing FCP data as nonresponder, the biochemical remission rates at weeks 12 and 24 were 30.3% (n: 30/99) and 18.2% (n: 14/77) respectively. The median FCP level of patients treated with tofacitinib at weeks 0, 12 and 24 was 1800 µg/g (IQR: 633-2682), 143 µg/g (IQR: 32-871) and 230 µg/g (IQR: 39-984) respectively. The median CRP concentration of patients treated with tofacitinib at weeks 0, 12, and 24 was as follows: 6 mg/L (IQR: 2-14), 1 mg/L (IQR: 0-6) and 2 mg/L (IQR: 0-4) respectively.

### 3.4 | Combined clinical and biochemical remission

The proportion of patients in combined corticosteroid-free clinical and biochemical remission at weeks 12 and 24 was 28.4% (n: 23/81) and 19.3% (n: 11/57) respectively (Figure 2).

### 3.5 | Endoscopic outcomes

Three participating centres systematically scheduled endoscopies, independent of clinical and biochemical outcomes. In these centres, 33 patients underwent endoscopic evaluation after a median

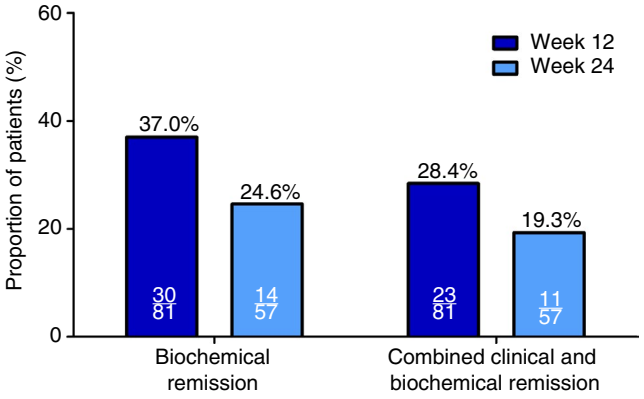


**FIGURE 2** Proportion of ulcerative colitis patients in biochemical remission (FCP ≤250 µg/g) and combined corticosteroid-free clinical and biochemical (SCCAI ≤2 and FCP ≤250 µg/g) remission at weeks 12 and 24. FCP, faecal calprotectin; SCCAI, short clinical colitis activity index

treatment duration of 9.9 weeks (IQR: 7.6-11.4). Endoscopic remission (endoscopic Mayo score 0) was achieved in 21.2% (n: 7/33) and endoscopic response was obtained in 36.4% (n: 12/33).

### 3.6 | Clinical factors associated with corticosteroid-free clinical remission

Univariable and multivariable predictors of corticosteroid-free clinical remission at week 24 are depicted in Table 2. Prior exposure to vedolizumab and SCCAI per point were associated with a reduced corticosteroid-free clinical remission rate at week 24 in multivariable analysis (OR: 0.301 95% CI: 0.100-0.907, $P$ = 0.033, and OR: 0.825 95% CI: 0.686-0.992, $P$ = 0.041, respectively). Prior exposure to anti-TNF or ustekinumab treatment could not be assessed due to the small number of patients without previous anti-TNF or with ustekinumab treatment.

### 3.7 | Safety profile

The 123 patients included in the safety analysis were followed for a total of 37.0 patient years (Table 3). During follow-up, 7 (5.7%) patients discontinued tofacitinib due to adverse events, of whom 4 (57.1%) were treated with 10 mg twice daily while the other 3 received 5 mg twice daily at the time of treatment discontinuation. Twenty-three possibly (62.2 per 100 patient years) and three probably (8.1 per 100 patient years) tofacitinib-related adverse events were encountered, of which cutaneous lesions and headache were the most common. A 10 mg twice daily dose at week 12 was not associated with adverse events during follow-up (OR: 0.971, 95% CI: 0.740-1.275, $P$ = 0.834). Thromboembolic events were not reported during this study. There were eight mild (21.6 per 100 patient years) infections and eight moderate (21.6 per 100 patient years) infections but no severe infections during follow-up (Table 3). Four herpes zoster infections/reactivations

**TABLE 2** Clinical parameters associated with corticosteroid-free clinical remission in tofacitinib-treated ulcerative colitis patients at week 24 were tested by binary logistic regression model

| | Univariable analyses | | | Multivariable analyses | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Age at inclusion—per year | 1.040 | 0.999-1.082 | 0.057 | 1.041 | 0.997-1.088 | 0.069 |
| BMI per point[a] | 1.057 | 0.934-1.197 | 0.381 | | | |
| Gender | | | | | | |
| Male | ref | | | | | |
| Female | 1.391 | 0.516-3.755 | 0.514 | | | |
| Disease duration—per year | 1.015 | 0.955-1.078 | 0.636 | | | |
| Disease location UC[b] | | | 0.801 | | | |
| Proctitis | 0.000 | 0.000-0.000 | 0.999 | | | |
| Left sided | 1.409 | 0.515-3.855 | 0.505 | | | |
| Pancolitis | ref | | | | | |
| Prior biological treatments | | | | | | |
| ≥2 anti-TNF agents | 0.484 | 0.165-1.425 | 0.188 | 0.489 | 0.151-1.587 | 0.234 |
| Vedolizumab | 0.321 | 0.115-0.897 | 0.030 | 0.327 | 0.100-0.907 | 0.033 |
| Clinical disease activity | | | | | | |
| SCCAI per point | 0.865 | 0.734-1.020 | 0.084 | 0.825 | 0.686-0.992 | 0.041 |
| Biochemical disease activity | | | | | | |
| CRP per mg/L | 0.994 | 0.976-1.012 | 0.522 | | | |
| FCP per 100 µg/g | 1.008 | 0.989-1.028 | 0.425 | | | |
| Concomitant medication | | | | | | |
| Corticosteroids | 1.038 | 0.379-2.842 | 0.941 | | | |

*Note:* A priori chosen variables with a $P$ value of < 0.2 were selected for multivariable analysis, in which consequently a two-sided $P$ value of ≤ 0.05 was considered statistically significant.

Abbreviations: anti-TNF, anti-tumour necrosis factor; BMI, body mass index; CRP, C-reactive protein; FCP, faecal calprotectin; OR, odds ratio; SCCAI, short clinical colitis activity index; ref, reference; 95% CI, 95% confidence interval.

[a]At inclusion.

[b]Maximum extent until inclusion.

**TABLE 3** Number and details of adverse events during treatment of ulcerative colitis patients with tofacitinib

| | | |
|---|---|---|
| Possibly related | | 23 (62.2 per 100 patient years) |
| Cutaneous lesions | 7 | |
| Headache | 5 | |
| Oedema | 2 | |
| Hypertension | 1 | |
| Dyspnoea | 1 | |
| Insomnia | 1 | |
| Arthralgia | 1 | |
| Glaucoma | 1 | |
| Mood swings | 1 | |
| Galactorrhoea | 1 | |
| Cold sensation | 1 | |
| Itch | 1 | |
| Probably related | | 3 (8.1 per 100 patient years) |
| Headache | 2 | |
| Cutaneous lesions | 1 | |
| Adverse event as reason for discontinuation | | 7 (18.9 per 100 patient years) |
| Recurrent infections | 2 | |
| Hepatitis | 1 | |
| Globus | 1 | |
| Arthralgia | 1 | |
| Nausea | 1 | |
| Herpes zoster | 1 | |
| Mild infections | | 8 (21.6 per 100 patient years) |
| Fever (no focus) | 3 | |
| Flu-like symptoms | 3 | |
| Upper respiratory | 1 | |
| Herpes zoster | 1 | |
| Moderate infections | | 8 (21.6 per 100 patient years) |
| Urinary tract | 3 | |
| Herpes zoster | 2 | |
| Gastrointestinal | 1 | |
| Eye infection | 1 | |
| Fever (no focus) | 1 | |
| Severe infections | | |
| – | | |
| Hospitalisations | | 15 (40.5 per 100 patient years) |

*Note:* Infections were classified as: mild infections: no antibiotics or anti-viral medication; moderate infections: oral antibiotics or anti-viral medication; severe infections: hospitalisation or intravenously administrated antibiotics or anti-viral medication.

were reported. Fifteen hospitalisations (40.5 per 100 patient years) all due to disease worsening occurred during follow-up. Six patients underwent a colectomy (16.2 per 100 patient years).

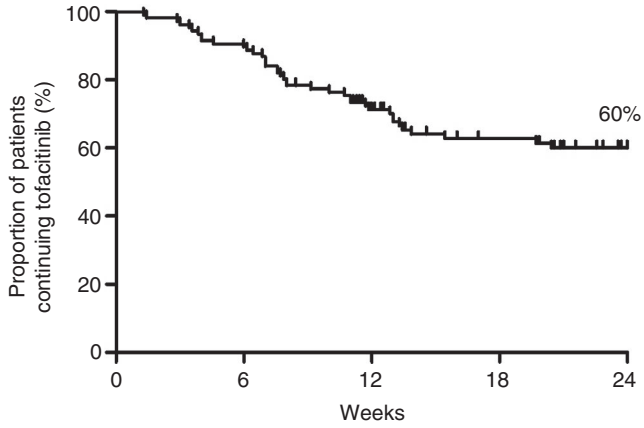


**FIGURE 3** Cumulative tofacitinib drug survival in ulcerative colitis patients after 24 wks of follow-up

### 3.8 | Changes in lipid concentrations

The mean relative difference between baseline and after induction therapy for triglycerides (n:42), cholesterol (n:45), HDL cholesterol (n:44) and LDL cholesterol (n:44) levels was as follows: −4.4% (95% CI: −16.9%-8.1%, $P = 0.246$), 15.7% (95% CI: 8.0%-23.3%, $P < 0.001$), 17.7% (95% CI: 6.9%-28.5%, $P = 0.015$) and 21.2% (95% CI: 10.5%-32.0%, $P = 0.001$) respectively.

### 3.9 | Tofacitinib dose

Two patients were started on tofacitinib 5 mg twice daily (patient 1: smoker with hypertension, arrhythmia, valvular heart disease, alcohol and drug abuse and axial spondyloarthritis, patient 2: hypercholesterolemia and hypertension), all others used the registered induction regimen of 10 mg twice daily. At week 12 and week 24, 43.1% (n: 31/72) and 33.3% (n: 14/42) of patients used 10 mg twice daily respectively. Of the patients who discontinued tofacitinib, 76.1% (n: 35/46) used 10 mg twice daily, 21.7% (n: 10/46) used 5 mg twice daily and 2.2% (n: 1/46) used 15 mg twice daily.

### 3.10 | Drug survival

Cumulative tofacitinib drug survival is depicted in Figure 2. After 24 weeks of follow-up, 60% of patients remained on tofacitinib (Figure 3). Of the patients who discontinued treatment, the median treatment duration was 8.5 weeks (IQR: 6.1-13.5). Main reasons for treatment discontinuation were lack of response (76.1%) and adverse events (15.2%) (Table 4).

## 4 | DISCUSSION

We assessed the real-world effectiveness, safety and drug use of tofacitinib in the nationwide prospective Dutch *ICC Registry*. In this anti-TNF

**TABLE 4** Reasons for discontinuation of tofacitinib treatment in ulcerative colitis patients

| | | N = 46 (37.4%) |
|---|---|---|
| Treatment duration—weeks | Median (IQR) | 8.5 (6.1-13.5) |
| Reason discontinuation | | |
| No response | N (%) | 35 (76.1) |
| Loss of response | N (%) | 3 (6.5) |
| Adverse events | N (%) | 7 (15.2) |
| At request of patient | N (%) | 1 (2.2) |

and vedolizumab refractory cohort, the corticosteroid-free clinical remission rates at weeks 12 and 24 were 35% and 29% respectively. The number of adverse events (89 per 100 patient years) in general and as reason for discontinuation (6%) was relative high. The highest dose (10 mg twice daily) was prescribed in one-third of patients at week 24.

The results of our study show a discrepancy with the clinical trials (OCTAVE) in terms of the decline in effectiveness outcomes over time. Several factors may contribute to this observation, including the relative shorter duration of follow-up, the intention-to-treat design as well as corticosteroid taper for a subgroup of patients during follow-up. Indeed, other real-life cohort confirmed this finding (week 8 clinical remission 33%, week 26:25%).[5] To date, only two real-world retrospective cohorts have reported the effectiveness and safety of patients receiving tofacitinib before market authorisation. A single-centre cohort study reported 58 patients (93% anti-TNF and 81% vedolizumab exposed) treated with tofacitinib. After 26 weeks of treatment, 21% was in corticosteroid-free clinical remission (physician global assessment).[5] In a compassionate early-access programme in France, 38 patients received tofacitinib after failure of both anti-TNF and vedolizumab treatment. In this treatment-refractory cohort, corticosteroid-free clinical remission (partial Mayo <3) at week 24 was 32%.[6] The comparison with cohorts receiving treatment before market authorisation is difficult and outcomes should be interpreted cautiously due to the retrospective nature and different endpoints as compared with our systematic and prospective cohort with pre-defined endpoints.

With 89 treatment-related adverse events per 100 patient years, the rate of adverse events in tofacitinib-treated patients was relatively high when compared with other treatments given to anti-TNF exposed patients.[7,8] A recent review of clinical trials showed a comparable safety profile of tofacitinib when compared with vedolizumab and anti-TNF with the exception of herpes zoster infections/reactivations.[9] Another systematic review of clinical trials showed no increased risk of adverse events when JAK inhibitors were compared with placebo.[10] However, in these reviews, not the number of adverse events but the number of patients with adverse events was compared. We were able to compare the real-world total number of tofacitinib-related adverse events with other treatments prescribed to anti-TNF refractory patients such as vedolizumab (inflammatory bowel disease [IBD]) and ustekinumab (Crohn's disease [CD]) following an identical methodology from our *ICC Registry*. This comparison yielded 30 treatment-related adverse events per 100 patient years for vedolizumab,[8] 24 treatment-related adverse events per 100 patient years for ustekinumab[7] and 89 treatment-related adverse events per 100 patient years for tofacitinib, suggesting a less desirable profile in terms of adverse events for the latter. The rate of infections was relative low with no severe infections and 43 mild-to-moderate infections per 100 patient years including 4 herpes zoster reactivations. The rate of infections was comparable with vedolizumab (IBD: 38 per 100 patient years)[8] and ustekinumab (CD: 36 per 100 patient years).[7] However, the limited follow-up period could have biased these results as JAK inhibitors are associated with an increased risk of infections when compared with placebo (RR 1.40 [95% CI 1.18-1.67], $P < 0.0001$).[10]

In the first half of 2019, the FDA and EMA issued new safety warnings about an increased risk of venous thromboembolic events and related death, following the results of the ORAL Surveillance study in rheumatoid arthritis. In this study, patients aged >50 years with at least one additional cardiovascular risk factor, used tofacitinib 10 mg twice daily as maintenance therapy.[11] In our cohort one-third of patients at week 24 received 10 mg twice daily while no thromboembolic events were reported. However, our follow-up period (median follow-up of 24 weeks [IQR: 12-26]) might be too short to detect a potential increased risk for thromboembolic or cardiovascular events. In the OCTAVE studies, no significant difference was found with regard to efficacy in 5 or 10 mg twice daily during the maintenance study in induction responders.[3] However, in the OCTAVE trial only 50% of patients was anti-TNF exposed and none of these patients received prior treatment with vedolizumab. Our real-world study represents a more therapy-refractory patient population, including partial induction responders who are possibly in need of a higher maintenance dose. Furthermore, physicians might prefer a higher maintenance dose due to the limited alternative therapeutic options remaining. The OCTAVE open programme showed a recapture of response rate of 64.9% (37/57) after dose escalation, indicating that dose escalation could be an option for secondary non-responders before switching out of class.[12] Receiving 10 mg twice daily at week 12 was not associated with adverse events, however, cohorts with longer follow-up are needed to determine this effect.

A 16%-21% increase in serum lipid levels after tofacitinib induction therapy has been observed in this cohort, comparable to the results of tofacitinib clinical trials in UC, rheumatoid arthritis, psoriasis and psoriatic arthritis patients.[13-15] Although an overall increase in cholesterol and in particular in LDL levels is unwanted, an increase in HDL can be beneficial. Therefore, the clinical relevance of these changes is presently not clear. In the OCTAVE programme, four major adverse cardiovascular events were observed (incidence rate 0.24 per 100 years of exposure [95% CI 0.07-0.62]), of whom three patients had ≥4 cardiovascular risk factors including hyperlipidaemia at baseline.[16] This incidence rate is similar to that observed in RA.[17] Up to now, no correlation between tofacitinib and cardiovascular morbidity and mortality in UC patients has been found, but long-term data are needed.[16]

The positioning of novel treatments for UC, and IBD in general, is complex and depends on a multitude of variables. Outcomes such as efficacy, safety, mode of administration and costs should

all be considered before selecting a treatment option for an individual patient. Tofacitinib differs from recently approved biologicals for UC, such as vedolizumab and ustekinumab, with respect to its mode of administration (oral vs intravenous or subcutaneous) and the short induction period with potential rapid clinical response to treatment.[18] In accordance with other treatments, prior failure to biological treatment is an important negative predictor to response. In our cohort, vedolizumab therapy was associated with a significantly lower corticosteroid-free clinical remission rate at week 24 in multivariable analysis (OR: 0.327 95% CI: 0.114-0.938, $P$ = 0.038). Whether this reflects the selection of refractory patients, or an impact on the responsiveness of the inflammatory condition to subsequent therapies, remains to be determined. To further establish the treatment algorithm for UC, head-to-head trials are needed in patients both prior to, but also after anti-TNF failure.

The strength of this study lies in the systematic prospective follow-up with pre-defined clinically relevant endpoints and the substantial cohort size since all patients initiating tofacitinib in regular care in the 15 participating hospitals were included. Due to the balanced participation of academic (n:8) and non-academic hospitals (n:7) and the patient characteristics of our cohort (anti-TNF and vedolizumab experienced), our data reflect daily practice that justifies generalisability. Our study has some limitations. As endoscopic evaluation was not mandatory and often performed when mucosal inflammation was expected, a substantial bias would have been introduced when these data were presented. To limit this bias we only analysed endoscopic results of centres with systematic endoscopic follow-up regardless of disease activity, resulting in a limited number of patients available for endoscopic analysis. There was no mandatory adjudication process to determine the drug-related adverse events. The relation to treatment was based on physician assessment and it is therefore possible that causality of adverse events was subjective. The effect of tofacitinib on lipid profile was measured in a subset of patients. The evaluation of the lipid profile was not part of standard IBD care in the Netherlands before the introduction of tofacitinib and this assessment was not fully implemented in daily practice at the start of our study. With increasing experience of tofacitinib prescription in UC, we expect the number of patients with systematic lipid evaluations to increase over time. Finally, although this is the largest cohort of tofacitinib to date, the follow-up period is relatively short and long-term follow-up is required to further evaluate the safety profile.

To conclude, this real-world study shows that tofacitinib is an effective treatment in 29% of this therapy-refractory cohort of UC patients after 24 weeks of treatment. A substantial proportion of patients experienced adverse events leading to treatment discontinuation in 6% of patients. No thromboembolic events were observed in this relatively short follow-up period. Prior failure to vedolizumab treatment was associated with a reduced clinical remission rate. Further studies are needed to investigate whether this finding merely represents a refractory UC population or whether this is due to a change in the inflammatory profile, to adequately position tofacitinib in the expanding field of treatment options for UC.

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