Superior Effectiveness of Tofacitinib Compared to Vedolizumab in Anti-TNF-experienced Ulcerative Colitis Patients: A Nationwide Dutch Registry Study

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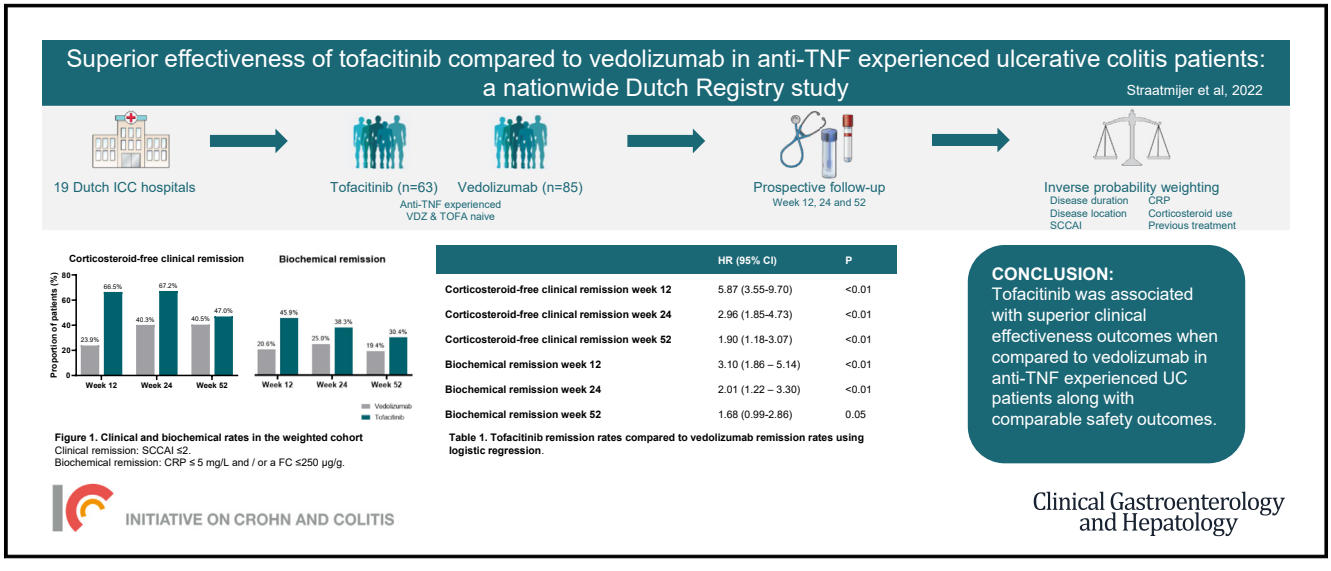

Figure 1. Clinical and biochemical rates in the weighted cohort
Clinical remission: SCCAI ≤2.
Biochemical remission: CRP ≤ 5 mg/L and / or a FC ≤250 µg/g.

Table 1. Tofacitinib remission rates compared to vedolizumab remission rates using logistic regression.

***Authors share co-senior authorship**

Abbreviations used in this paper: **BID, twice a day; CI, confidence interval; CRP, C-reactive protein; FC, fecal calprotectin; IBD, inflammatory bowel disease; ICC, Initiative on Crohn and Colitis; IPTW, inverse probability of treatment weighting; IQR, interquartile range; JAK, Janus kinase; OR, odds ratio; RCT, randomized controlled trial; SCCAI, Simple Clinical Colitis Activity Index; TNF, tumor necrosis factor-alpha; UC, ulcerative colitis.**

Most current article

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BACKGROUND & AIMS: **Clinicians face difficulty in when and in what order to position biologics and Janus kinase inhibitors in patients with anti-tumor necrosis factor-alpha (TNF) refractory ulcerative colitis (UC). We aimed to compare the effectiveness and safety of vedolizumab and tofacitinib in anti-TNF-exposed patients with UC in our prospective nationwide Initiative on Crohn and Colitis Registry.**

METHODS: **Patients with UC who failed anti-TNF treatment and initiated vedolizumab or tofacitinib treatment were identified in the Initiative on Crohn and Colitis Registry in the Netherlands. We selected patients with both clinical as well as biochemical or endoscopic disease activity at initiation of therapy. Patients previously treated with vedolizumab or tofacitinib were excluded. Corticosteroid-free clinical remission (Simple Clinical Colitis Activity Index ≤2), biochemical remission (C-reactive protein ≤5 mg/L or fecal calprotectin ≤250 μg/g), and safety outcomes were compared after 52 weeks of treatment. Inverse propensity score-weighted comparison was used to adjust for confounding and selection bias.**

RESULTS: **Overall, 83 vedolizumab- and 65 tofacitinib-treated patients were included. Propensity score-weighted analysis showed that tofacitinib-treated patients were more likely to achieve corticosteroid-free clinical remission and biochemical remission at weeks 12, 24, and 52 compared with vedolizumab-treated patients (odds ratio [OR], 6.33; 95% confidence interval [CI], 3.81–10.50; $P < .01$; OR, 3.02; 95% CI, 1.89–4.84; $P < .01$; and OR, 1.86; 95% CI, 1.15–2.99; $P = .01$; and OR, 3.27; 95% CI, 1.96–5.45; $P < .01$; OR, 1.87; 95% CI, 1.14–3.07; $P = .01$; and OR, 1.81; 95% CI, 1.06–3.09; $P = .03$, respectively). There was no difference in infection rate or severe adverse events.**

CONCLUSIONS: **Tofacitinib was associated with superior effectiveness outcomes compared with vedolizumab in anti-TNF-experienced patients with UC along with comparable safety outcomes.**

Keywords: Real-world Data; Tofacitinib; Ulcerative Colitis; Vedolizumab.

Several new therapeutic options for the treatment of ulcerative colitis (UC) have become available in the last decade, all with specific working mechanisms and safety profiles. For the last 20 years, the classical step-up maintenance therapy for mild to moderate UC is 5-amino-salacylic acid, thiopurine derivative and anti-tumor necrosis factor-alpha (TNF), consecutively. A considerable proportion of patients do not respond to anti-TNF agents, have side effects, or lose response over time.[1] Since 2014, more and more medication options (inhibitors of adhesion molecules [vedolizumab], interleukins-12 and 23 inhibitors [ustekinumab], and Janus kinase [JAK] inhibitors [tofacitinib, filgotinib (in Europe)]) became available. Because of experience and price, most commonly these medications are prescribed after failure of the anti-TNF.[2-4] Because head-to-head trials are scarce, optimal positioning of biologics and JAK inhibitors in the therapeutic strategy remains an area of ongoing research.

Both vedolizumab and tofacitinib have different mechanisms of action. Vedolizumab is a monoclonal antibody inhibiting the interaction between the $\alpha 4\beta 7$ integrin and mucosal addressin cell adhesion molecule-1 resulting in blocking of lymphocyte homing to the inflamed gut tissue.[5] Tofacitinib is an oral small molecule that preferentially inhibits JAK 1 and JAK 3 and interferes with the signal transducers and activators of transcription pathway.[6,7] These pathways play an prominent role in transducing multiple proinflammatory cytokines involved in the pathogenesis of a spectrum of inflammatory diseases.

Efficacy of both vedolizumab and tofacitinib in patients with UC has been studied in randomized placebo controlled trials (RCTs).[2,3] In the registration trial, 41.8% of the vedolizumab-treated patients receiving vedolizumab every 8 weeks achieved corticosteroid-free clinical remission (Mayo Clinic score ≤ 2 and no subscore >1) at week 52.[4] In tofacitinib-treated patients, 34.3% of the patients in the 5-mg group achieved clinical remission (Mayo clinic score of ≤ 2, with no subscore >1 and a rectal bleeding subscore of 0) at week 52.[5] Currently, head-to-head RCTs comparing the efficacy of these 2 treatment options in patients with anti-TNF refractory UC are lacking. However, to guide physician decision-making on the most suitable drug choice after anti-TNF failure, effectiveness data comparing tofacitinib with vedolizumab is pivotal. Previously, we have compared ustekinumab and vedolizumab in Crohn's disease with data from the Dutch Initiative on Crohn and Colitis (ICC) registry using propensity score matching to match cohorts and allow for comparison.[8]

In the absence of head-to-head RCTs, we assessed the comparative effectiveness and safety of vedolizumab and tofacitinib in UC through a propensity score-weighted prospective cohort study.

Methods

Study Design and Participants

The ICC Registry is a prospective, nationwide, observational registry of adult (≥18 years old) patients with inflammatory bowel disease (IBD) starting IBD therapies in regular care in the Netherlands. All patients in the registry are prospectively followed-up with scheduled outpatient clinic visits at weeks 12, 24, 52, and 104, designed to closely follow regular care. The decision to start any treatment is at the discretion of the treating physician. Currently, 19 centers participate in the ICC registry.

We selected patients meeting the following inclusion criteria at baseline: both clinical (Simple Clinical Colitis Activity Index [SCCAI] >2) and either biochemical disease activity (C-reactive protein [CRP] concentration >5mg/L or fecal calprotectin [FC] level >250 μg/g) or endoscopic disease activity (endoscopic Mayo score ≥1b,[9] according to the treating physician), prior anti-TNF failure, no prior exposure to vedolizumab and tofacitinib, and initiation of therapy at least 52 weeks prior to the analyses.

Patients initiating tofacitinib received 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 optimization in case of insufficient response according to label. Vedolizumab was administered intravenously according to the label with an induction infusion regimen of 300 mg vedolizumab at weeks 0, 2, and 6. The maintenance treatment consisted of 300 mg vedolizumab every 8 weeks, whereas the infusion interval could be shortened in case of inadequate response to the judgement of the treating physician.

Outcomes and Definitions

The primary outcome was corticosteroid-free clinical remission at week 52. Clinical remission was defined by a SCCAI ≤2. Secondary outcomes were biochemical remission (defined as a CRP ≤5 mg/L or FC ≤250 μg/g), combined corticosteroid-free clinical and biochemical remission, endoscopic remission (Mayo score ≤1), safety, and discontinuation rate. Adverse events were classified as possibly and probably related and as reasons for treatment discontinuation. Infections were classified as mild (no antibiotics or antiviral medication necessary), moderate (oral antibiotics or antiviral medication required), or severe (hospitalization and/or intravenously administrated antibiotics or anti-viral medication).

Reasons for treatment discontinuation were documented at the discretion of the treating physician. Patients who discontinued treatment due to a primary or secondary non-response, adverse events, or at patients' request without clinical remission were considered as a treatment failure and classified as non-responders. Patients who discontinued because of pregnancy were considered censored cases. In the case where data was missing, patients were considered non-responders.

What You Need to Know

Background

We aimed to compare the effectiveness and safety of vedolizumab and tofacitinib in anti-tumor necrosis factor-alpha (TNF)-exposed patients with ulcerative colitis (UC) in our prospective nationwide Initiative on Crohn and Colitis Registry.

Findings

Tofacitinib was associated with superior effectiveness outcomes compared with vedolizumab in anti-TNF experienced patients with UC along with comparable safety outcomes.

Implications for patient care

Because clinicians face difficulty in when and in what order to position biologics and Janus kinase inhibitors in patients with anti-TNF refractory UC, these results may help guiding clinical decision making after anti-TNF failure in patients with UC.

Statistical Methods

Sample size was calculated based on the real-world effectiveness of vedolizumab and tofacitinib in meta-analysis.[10,11] Sixty-five patients in each group were needed to demonstrate a non-inferiority of 10% with a power of 80%. Analysis started as soon as 65 patients per group met the inclusion criteria.

Because patients were not randomly assigned to receive vedolizumab or tofacitinib, confounding by indication may arise in comparative effectiveness studies when there are inherent differences in the patients prescribed the 2 treatments being compared. To adjust for baseline patient characteristics between the 2 groups, propensity score weighted analysis was performed. Inverse probability of treatment weighting (IPTW) method was chosen to retain all the patients in the estimation of the treatment effects and the consequent preservation of the statistical power.[12] Propensity scores were calculated using a multiple logistic regression model in which treatment assignment (vedolizumab or tofacitinib) was regressed based on the following covariates: disease duration (continuous), disease location at initiation of therapy (proctitis vs left-sided or pancolitis), SCCAI, CRP at baseline, concomitant corticosteroid use, the number of previous anti-TNF treatments, and previous ustekinumab use. Because CRP was missing in 5 patients, multiple imputation was used to impute the missing values. Weighting was performed using IPTW. Analyses

using IPTW are referred to as weighted analyses. Analyses in the unweighted cohort are referred to as unadjusted analyses.

Depending on the normality of the underlying distribution, continuous variables were presented as means with standard deviation or as median with interquartile range (IQR). Categorical variables were presented as percentages and compared by using the χ^2 test. Differences between groups were evaluated using the Mann-Whitney U or the χ^2 test, as appropriate. Logistic regression was used for the IPTW analysis. Predictors of clinical response were evaluated using binary logistic regression.

$P < .05$ was considered to be statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 26.0.0.1.

Ethical Consideration

The protocol of the ICC Registry was reviewed and approved by the Committee on Research Involving Human Subjects at the Radboudumc, Nijmegen, The Netherlands (Institutional Review Board: 4076).

Results

Baseline Characteristics

A total of 159 patients with UC initiating vedolizumab and 175 patients initiating tofacitinib for UC were included in 17 hospitals between August 2014 and October 2020 (Figure 1). After excluding patients without prior anti-TNF treatment, with previous vedolizumab or tofacitinib treatment, and without clinical and biochemical or endoscopic disease activity at baseline, 83 vedolizumab- and 65 tofacitinib-treated patients were analyzed (Figure 1). Baseline characteristics of the unadjusted cohort are summarized in Table 1. In total, 17 patients (11 vedolizumab and 6 tofacitinib) did not have biochemical disease activity at initiation of therapy. Of these 17 patients, 14 patients had an endoscopic Mayo score of $\geq$2, 1 patient had an endoscopic Mayo score of 1b, and 1 patient had an endoscopic Mayo score of 1a. Statistically significant differences between vedolizumab- and tofacitinib-treated patients with UC were time since diagnosis of UC (12 years; IQR, 9–19 years vs 7 years; IQR 4–14 years) and concomitant oral prednisone at initiation of therapy (50.6% vs 30.8%). Other variables between the 2 groups were not different, including SCCAI score and biochemical parameters.

Baseline characteristics of the weighted cohort are summarized in Supplementary Table 1. Due to IPTW, in which a weight is added to each patient, sample sizes were inflated, leading to 150 vedolizumab- and 152 tofacitinib-treated patients. Tofacitinib-treated patients were older (median age of 51 years; IQR, 39–59 years vs 39 years; IQR, 31–53 years) and had a slightly higher CRP (median of 7 mg/L; IQR, 2–14 mg/L vs 4 mg/L; IQR, 2–12 mg/L) compared with vedolizumab-treated patients.

Clinical Outcomes

Unadjusted corticosteroid-free clinical remission rates in vedolizumab- and tofacitinib-treated patients at weeks 12, 24, and 52 were 27.7% (23/83) and 56.9% (37/65), 38.6% (32/83) and 60.0% (39/65), and 37.3% (31/83) and 55.4% (36/65), respectively. Propensity score-weighted analysis showed that tofacitinib-treated patients were more likely to achieve corticosteroid-free clinical remission at weeks 12, 24, and 52 compared with vedolizumab-treated patients (odds ratio [OR], 6.33; 95% confidence interval [CI], 3.81–10.50; $P < .01$; OR, 3.02; 95% CI, 1.89–4.84; $P < .01$, and OR, 1.86; 95% CI, 1.15–2.99; $P = .01$, respectively). Corticosteroid-free clinical remission rates in the propensity-weighted cohort are shown in Figure 2.

Biochemical Outcomes

Unadjusted biochemical remission rates in vedolizumab- and tofacitinib-treated patients at weeks 12, 24, and 52 were 25.3% (21/83) and 40.0% (26/65), 28.9% (24/83) and 36.9% (24/65), and 22.9% (19/83) and 27.7% (18/65), respectively.

Propensity score-weighted analysis showed that tofacitinib-treated patients were more likely to achieve biochemical remission at week 12, week 24, and week 52 compared with vedolizumab-treated patients (OR, 3.27; 95% CI, 1.96–5.45; $P < .01$; OR, 1.87; 95% CI, 1.14–3.07; $P = .01$; and OR, 1.81; 95% CI, 1.06-3.09; $P = .03$, respectively). Biochemical remission rates in the propensity-weighted cohort are given in Figure 2.

In patients with biochemical disease activity at baseline (n = 131), propensity score-weighted analysis showed that patients treated with tofacitinib were more likely to achieve biochemical remission at week 12 (OR, 2.80; 95% CI, 1.64–4.77; $P < .001$), but not at week 24 and week 52 (OR, 1.64; 95% CI, 0.97–2.77; $P = .06$; OR, 1.39; 95% CI, 0.80–2.43; $P = .24$) compared with vedolizumab-treated patients.

Combined Clinical and Biochemical Outcomes

Unadjusted combined remission rates in vedolizumab- and tofacitinib-treated patients at weeks 12, 24, and 52 were 14.5% (12/83) and 32.3% (21/65), 24.1% (20/83) and 32.3% (21/65), and 19.3% (16/83) and 16.9% (11/65), respectively.

Propensity score-weighted analysis showed that tofacitinib-treated patients were more likely to achieve combined remission at week 12 and week 24, but not at week 52 compared with vedolizumab-treated patients

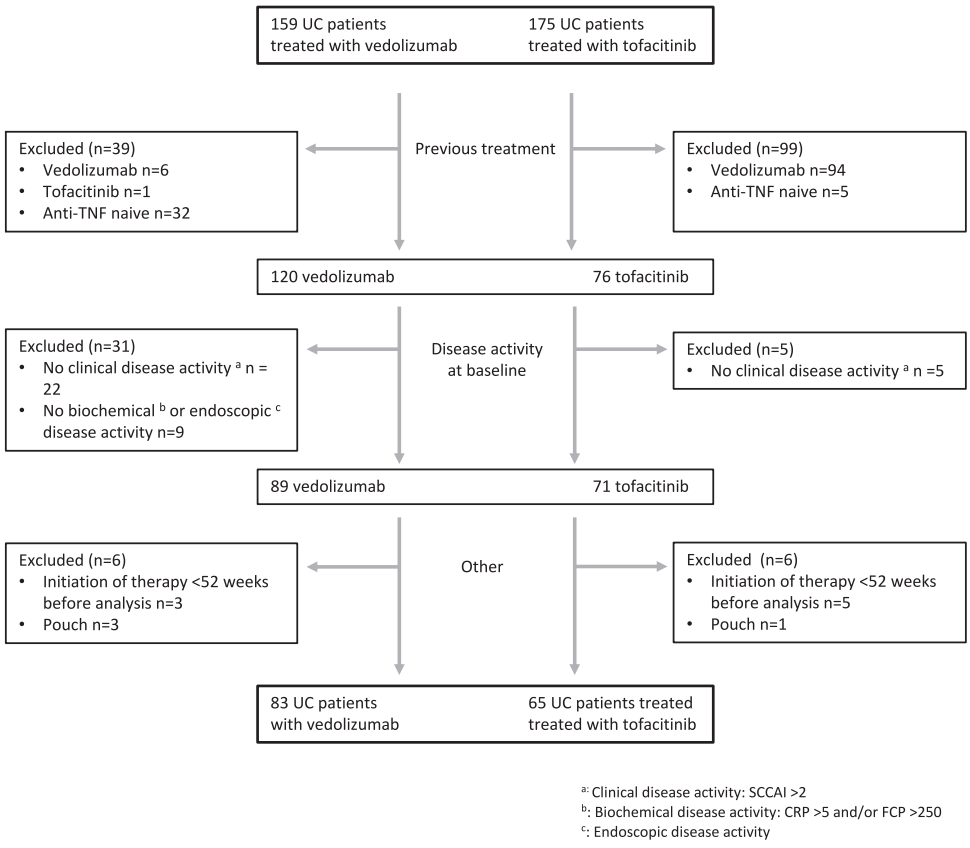

Figure 1. Patient flowchart of patients with UC treated with either vedolizumab or tofacitinib who are included in the current study.

(OR, 5.05; 95% CI, 2.78–9.18; $P < .01$; OR, 2.11; 95% CI, 1.26–3.55; $P < .01$; and OR, 1.17; 95% CI, 0.5–2.11; $P = .60$, respectively). Combined clinical and biochemical outcomes in the propensity-weighted cohort are shown in Figure 2.

Endoscopic Remission

In total, 29 vedolizumab-treated patients (54.7%) and 25 tofacitinib-treated patients (51.0%) with endoscopic disease activity at baseline (Mayo score $\geq$2) underwent at least one endoscopy during follow-up after a median duration of 15 weeks (IQR, 12–19 weeks) and 15 weeks (IQR, 11–36 weeks). Of these patients, 44.8% vedolizumab-treated patients and 37.5% tofacitinib-treated patients achieved endoscopic remission.

Dose Intensification

Seven vedolizumab-treated patients (12.7%) underwent dose intensification until week 52. Five patients were on a 4-week dosing scheme (9.1%), and 2 patients were on a 6-week dosing scheme (3.6%). In the tofacitinib-treated patients, 23 of 53 (43.4%), 13 of 47 (27.7%), and 10 of 40 (25%) patients were on a 10-mg twice a day (BID) dosing scheme. Patients treated with 10-mg BID tofacitinib dosing scheme did not achieve higher corticosteroid-free clinical remission rates after 52 weeks of treatment.

Safety

Patients were treated with vedolizumab and tofacitinib for 56.7 and 45.9 patient-years respectively. The total number of adverse events and infections are displayed in Table 2. Using IPTW, there was no difference in infection rate (OR, 1.057; 95% CI, 0.60–1.86; $P = .85$). Patients using concomitant medication did not have a statistically significantly higher amount of infections in both groups ($P = .92$ in vedolizumab-treated patients and $P = .42$ in tofacitinib-treated patients). Although vedolizumab-treated patients had an overall higher chance on experiencing adverse events (OR, 1.83; 95% CI, 1.10–3.03; $P = .02$), the number of severe adverse events was not different between both groups (OR, 0.39; 95% CI, 0.03–4.33; $P = .44$).

Three tofacitinib-treated patients experienced herpes simplex infections; this was not observed in the vedolizumab group. No cardiovascular or thromboembolic events were observed. One tofacitinib-treated patient died after 23 weeks of treatment due to euthanasia based on an unrelated disease.

Treatment Discontinuation

Therapy was stopped in 45.8% and 38.5% of the vedolizumab- and tofacitinib-treated patients after a median treatment duration of 14.5 weeks (IQR, 9–26.8 weeks) and 16 weeks (IQR, 6–39.3 weeks) (Figure 3).

Table 1. Baseline Characteristics

	Vedolizumab (n = 83)	Tofacitinib (n = 65)	*P* value
Age, *y*	44 (33–56)	48 (38–59)	.168
Male	42 (50.6)	36 (55.4)	.563
Disease duration, *y*	12 (9–19)	7 (4–14)	< .001
Follow-up, *w*	46 (15–52)	47 (20.3–52)	.920
BMI, kg/m^2	23.9 (21.7–29.3)	24.9 (21.7–29.3)	.527
Disease activity			
SCCAI score	7 (5–9)	6 (5–10)	.832
CRP, *mg/L*	6 (2–13) (n = 80)	5 (2–19.3) (n = 60)	.347
FC, *mg/kg*	1317 (448–2147.5) (n = 57)	1217 (337–2601) (n = 49)	.735
Mayo score[a]			.870
0	1 (1.7)	–	
1a	–	1 (1.9)	
1b	6 (10.2)	3 (5.8)	
2	21 (35.6)	21 (40.4)	
3	30 (50.8)	26 (50)	
Unknown	1 (1.7)	1 (1.9)	
Medical history			
Disease location[b]			.055
Proctitis	4 (4.8)	12 (18.8)	
Left sided	38 (45.8)	23 (35.9)	
Pancolitis	38 (45.8)	26 (40.6)	
Prior treatment			
Failed anti-TNF			.211
≥2	32 (39.7)	17 (26.2)	
3	5 (6)	2 (3.1)	
Ustekinumab	1 (1.2)	3 (4.6)	.204
Concomitant treatment			
Oral prednisone	42 (50.6)	20 (30.8)	.015
Oral prednisone dose, *mg*	30 (20–40)	20 (15–40)	.256
Thiopurine	27 (32.5)	7 (10.8)	.252
Methotrexate	4 (4.8)	2 (3.1)	.102

Note: Data are presented as number (%), median (IQR), or mean (SD).
BMI, Body mass index; CRP, C-reactive protein; FC, fecal calprotectin; IQR, interquartile range; SCCAI, Simple Clinical Colitis Activity Index; SD, standard deviation; TNF, tumor necrosis factor-alpha.
[a]In 59 patients with endoscopy at baseline.
[b]Maximum extend until inclusion.

The most common reasons for treatment discontinuation were primary non-response (vedolizumab 86.8% and tofacitinib 60%), secondary loss of response (vedolizumab 7.9% and tofacitinib 16%), and adverse events (vedolizumab 2.6% and tofacitinib 20%) (Table 3).In the unadjusted cohort, there was no difference in discontinuation of therapy before 52 weeks after initiation of treatment between vedolizumab- and tofacitinib -treated patients ($P = .37$). However, propensity score-weighted analysis showed that vedolizumab-treated patients were more likely to discontinue treatment before 52 weeks of treatment (OR, 1.819; 95% CI, 1.14–2.91; $P = .01$), mainly due to non-response.

Predictors of Response

In univariate analysis, there were no predictors of response in vedolizumab-treated patients. In tofacitinib-treated patients, shorter disease duration at initiation of therapy was associated with corticosteroid-free clinical remission at week 52 (Supplementary Table 2).

Discussion

In this nationwide, prospective study, we compared the effectiveness and safety of vedolizumab and tofacitinib in anti-TNF experienced patients with UC. To adjust for differences in baseline patient characteristics, propensity scores were weighted in the analysis. We observed that tofacitinib was superior to vedolizumab in achieving corticosteroid-free clinical remission and biochemical remission after 12, 24, and 52 weeks of treatment. Furthermore, there was no statistically significant difference in infection rate and severe adverse events.

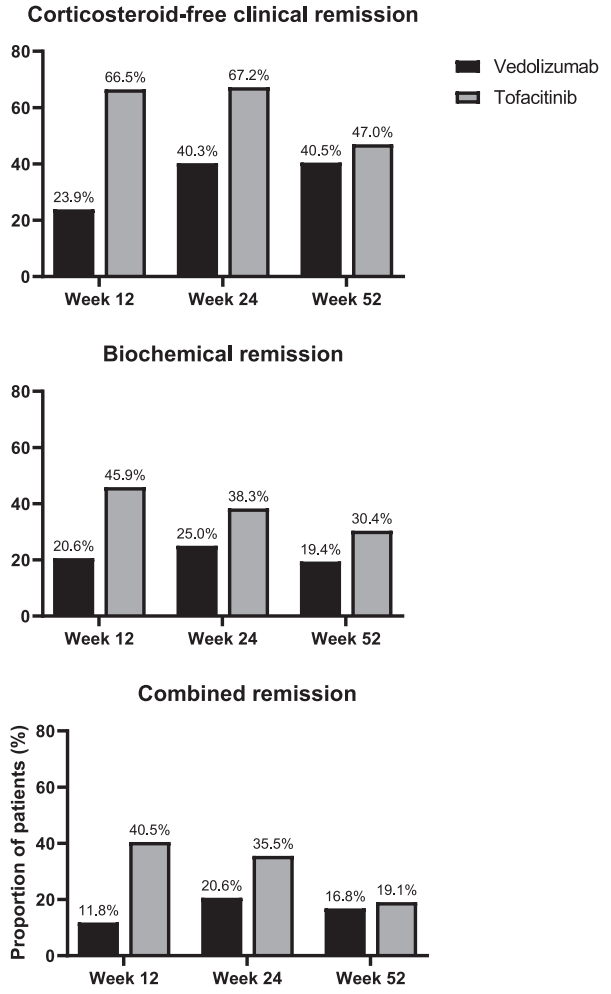

Figure 2. Clinical, biochemical, and combined outcomes in the weighted cohort. Proportion of patients achieving corticosteroid-free clinical, biochemical, and combined remission at weeks 12, 24 and 52. Clinical remission was defined as a SCCAI $\leq$2. Biochemical remission was defined as a CRP $\leq$5 mg/L and/or an FC $\leq$250 μg/g). Patients with missing data were considered non-responders.

The effectiveness rates in the presented cohort slightly differ from the efficacy rates in phase III trials. In this cohort, corticosteroid-free clinical remission was observed in 37.3% and 55.4% of vedolizumab- and tofacitinib-treated patients, respectively, at week 52. In phase III trials, 41.8% of the vedolizumab-treated patients (every 8 weeks) and 34.4% of tofacitinib-treated patients (5 mg BID) achieved remission (Mayo score $\leq$2 and no subscore $>$1 and a rectal bleeding subscore of 0) at week 52.[2,3] It must be taken into account that patients in phase III trials were all induction responders, whereas in the present cohort, all patients initiating vedolizumab or tofacitinib were included for follow-up until week 52. Additionally, about one-half of the patients included in the mentioned phase III trials were anti-TNF-naïve, and different definitions of remission were used compared with our cohort. As known, a major drawback of RCTs is that, in contrast to real-world data, efficacy and safety of IBD treatment options is assessed in a selected, well-controlled environment with a precisely defined study population, and with inclusion and exclusion criteria.[13]

Table 2. Vedolizumab- and Tofacitinib-related Adverse Events

	Vedolizumab: 56.7 patient years	Tofacitinib: 45.9 patient years
Mild infections	20 (35.3 per 100 patient-years)	10 (21.8 per 100 patient-years)
Upper respiratory tract	15	1
Flu-like symptoms	2	2
Fever of unknown origin	1	2
Urinary tract	1	1
Herpes simplex	–	2
COVID	–	1
Herpes zoster	–	1
Gastrointestinal	1	
Moderate infections	12 (21.2 per 100 patient-years)	15 (32.7 per 100 patient-years)
Upper respiratory tract	6	–
Urinary tract	1	2
Other	3	–
Lower respiratory tract	2	–
Flu-like symptoms	–	3
Herpes zoster	–	3
Gastrointestinal	–	2
Herpes simplex	–	2
Arthritis	–	1
Fever of unknown origin	–	1
Upper respiratory tract	–	1
Severe infections	1 (1.8 per 100 patient-years)	0 (0 per 100 patient-years)
Gastrointestinal	1	–
Possibly related	18 (31.7 per 100 patient-years)	9 (19.6 per 100 patient-years)
Skin	11	3
Musculoskeletal	2	3
Respiratory	2	1
Infusion-related	2	–
Kidney and urinary tract	1	–
Cardiac	–	1
Nerve system	–	1
Probably related	13 (22.9 per 100 patient-years)	3 (6.5 per 100 patient-years)
Musculoskeletal	2	2
Skin	2	1
Infusion-related	4	–
Nerve system	2	–
Headache	1	–
Respiratory	1	–
Vascular	1	–
Serious adverse events	1 (1.8 per 100 patient-year)	1 (2.2 per 100 patient-years)
Infusion-related	1	–
Malaise	–	1

Note: Number of adverse events during treatment of patients with UC with vedolizumab or 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.

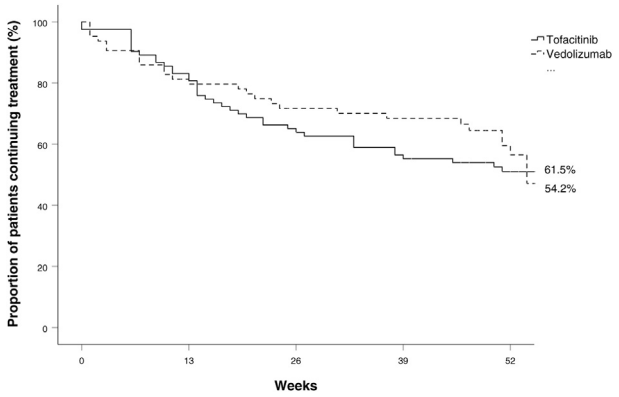

Figure 3. Drug survival. Kaplan-Meier probability curve of vedolizumab and tofacitinib treatment survival during a 52-week follow-up.

In several real-world studies, corticosteroid-free clinical remission rates of vedolizumab and tofacitinib in patients with UC have been assessed. The clinical effectiveness rate of vedolizumab ranges from 40.5% to 60%, after 52 weeks of treatment. Comparable corticosteroid-free clinical remission rates to our cohort were seen in a French cohort and a large United States retrospective cohort in which 40.5% and 37% of patients achieved corticosteroid-free clinical remission, respectively.[14,15] In other real-world cohorts, higher corticosteroid-free clinical remission rates between 46% and 60% were achieved. However, in these studies, not all patients were anti-TNF-experienced, and the primary outcome was clinical remission defined as a partial Mayo score <2.[16,17] In one German cohort, with patient characteristics and inclusion criteria similar to this cohort, a lower corticosteroid-free clinical remission rate was found (22%).[18]

Few real-world studies described effectiveness of tofacitinib up to 52 weeks of treatment. A higher corticosteroid-free clinical remission rate was found in this study when compared with other reports. In a French cohort, a corticosteroid-free clinical remission rate of 34% was observed in a relatively small group of patients with UC (n = 38) after 48 weeks of tofacitinib therapy.[19] Also, in a small retrospective, real-world study from the United States, a 27% corticosteroid-free clinical remission rate was shown after 52 weeks in 26 patients.[20] Yet these differences might be explained by the fact that, in these studies, patients with more refractory disease were included, as most patients were vedolizumab-experienced and more patients were on systemic corticosteroids at initiation of therapy (53% and 47%). In addition, in the United States cohort, almost 40% of patients initiating tofacitinib received an induction dose of only 5 mg BID.

Table 3. Discontinuation Within 52 Weeks of Treatment

Discontinuation visit	Vedolizumab n = 38 (45.8%)	Tofacitinib n = 25 (38.5%)
Treatment duration, *w*	14.5 (9–26.8)	16 (6–39.3)
Reason discontinuation		
No response	33 (86.8)	15 (60)
Loss of response	3 (7.9)	4 (16)
Adverse events	1 (2.6)	5 (20)
Request patient	1 (2.6)	–
Other (death due to euthanasia)	–	1 (4)

Note: Data are presented as median (IQR) or number (%).
IQR, Interquartile range.

Currently, there is no data available directly comparing vedolizumab and tofacitinib treatment outcomes in patients with UC. Indirect comparison was done in 3 meta-analyses describing the efficacy and safety of both vedolizumab and tofacitinib.[21-23] In one meta-analysis, 7 randomized trials of anti-TNF-experienced adults with moderate to severe UC treated with adalimumab, vedolizumab, tofacitinib, or ustekinumab were included. It was shown that overall, tofacitinib and ustekinumab were ranked higher for inducing clinical remission, with or without concomitant steroid use.[21] In the maintenance phase, with only induction responders included, all agents were equally effective in retaining remission. In meta-analysis, no statistical significance in indirect comparisons between tofacitinib and biologics in patients not previously exposed to anti-TNF has been reported.[22] Finally, in a Spanish meta-analysis with data of 14 studies including the phase II and III RTCs of infliximab, adalimumab, golimumab, vedolizumab, etrolizumab, tofacitinib, and ozanimod, it was shown that tofacitinib had the highest rate of maintaining clinical remission.[23]

The present study underlines that both vedolizumab and tofacitinib are relatively safe treatment options in patients with UC in a 12-month period. The number of observed severe adverse events and infection rates were not statistically significantly different between both treatment groups using IPTW, although this study was not statistically powered to identify subtle differences or infrequent (serious) adverse events. In line with this, no cardiovascular or thromboembolic events were observed in this tofacitinib group, even though it is known that tofacitinib treatment is associated with a limited, but increased, risk of serious heart-related events, cancer, thromboembolic events, and death in patients with rheumatoid arthritis.[24,25] Furthermore, indication bias (vs vedolizumab), including risk for cardiovascular or thromboembolic events or cancer, seems more likely.

Several strengths of this study allowed us to reliably assess effectiveness outcomes between vedolizumab and tofacitinib after anti-TNF failure in a large cohort of patients with UC. All patient visits were scheduled at the same time points using pre-defined clinical and biochemical outcome measures. Furthermore, propensity scores were used to correct for confounding. In the weighted cohort, there were no statistically significant differences identified in baseline characteristics possibly

influencing clinical outcomes. Although we used the number of previous anti-TNF agents, the reason for anti-TNF discontinuation was not noted and was not taken into account for calculating the propensity scores. Also, CRP and FC at baseline were not included as variables in calculating the propensity scores, as we did not have both parameters in all patients.

A limitation of this study is that no standard dose-optimization scheme was applied nor was taken into account in the analysis. Patients were included in both academic and non-academic hospitals and less of the more useful dose optimization schemes might be center- or treating physician-dependent. Also, endoscopic assessment was not mandatory and only performed at the discretion of the treating physician. Endoscopy was often performed when clinical and biochemical outcomes were inconclusive; thus these data might be biased. Lastly, the cohort treatments were not randomly assigned. Therefore, we adjusted for important factors widely recognized for being associated with disease severity or a refractory phenotype in UC in the statistical analyses.

In conclusion, a higher proportion of anti-TNF-experienced patients on tofacitinib achieved corticosteroid-free remission and biochemical remission after 12, 24, and 52 weeks compared with vedolizumab-treated patients. Safety profiles were comparable in these cohorts, at least over a 12-month period and with a probable selection bias for serious adverse events. These results may help guiding clinical decision-making after anti-TNF failure in patients with UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.04.038.

References

1. Ma C, Huang V, Fedorak DK, et al. Outpatient ulcerative colitis primary anti-TNF responders receiving adalimumab or infliximab maintenance therapy have similar rates of secondary loss of response. J Clin Gastroenterol 2015;49:675–782.
2. Feagan BG, Rutgeerts P, Sands BE, et al. GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699–710.
3. Sandborn WJ, Su C, Sands BE, et al. OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–1736.
4. Sands BE, Sandborn WJ, Panaccione R, et al. UNIFI Study Group. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381:1201–1214.
5. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. J Crohns Colitis 2016;10:1437–1444.
6. Hodge JA, Kawabata TT, Krishnaswami S, et al. The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin Exp Rheumatol 2016; 34:318–328.
7. Levy DE, Darnell JE Jr. Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol 2002;3:651–662.
8. Biemans VBC, van der Woude CJ, Dijkstra G, et al. Dutch Initiative on Crohn and Colitis (ICC). Ustekinumab is associated with superior effectiveness outcomes compared to vedolizumab in Crohn's disease patients with prior failure to anti-TNF treatment. Aliment Pharmacol Ther 2020;52:123–134.
9. Sandborn WJ, Peyrin-Biroulet L, Zhang J, et al. Efficacy and Safety of Etrasimod in a Phase 2 Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology 2020;158:550–561.
10. Taxonera C, Olivares D, Alba C. Real-world effectiveness and safety of tofacitinib in patients with ulcerative colitis: systematic review with meta-analysis. Inflamm Bowel Dis 2022; 28:32–40.
11. Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. J Gastroenterol 2018;53:1048–1064.
12. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–3679.
13. Ha C, Ullman TA, Siegel CA, et al. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clin Gastroenterol Hepatol 2012;10:1002–1007, quiz: e78.
14. Amiot A, Serrero M, Peyrin-Biroulet L, et al. OBSERV-IBD study group and the GETAID. One-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multicentre cohort study. Aliment Pharmacol Ther 2017;46:310–321.
15. Narula N, Peerani F, Meserve J, et al. Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY consortium. Am J Gastroenterol 2018;113:1345.
16. Pulusu SSR, Srinivasan A, Krishnaprasad K, et al. Vedolizumab for ulcerative colitis: real world outcomes from a multicenter observational cohort of Australia and Oxford. World J Gastroenterol 2020;26:4428–4441.
17. Eriksson C, Rundquist S, Lykiardopoulos V, et al. SWIBREG SVEAH Study Group. Real-world effectiveness of vedolizumab in inflammatory bowel disease: week 52 results from the Swedish prospective multicentre SVEAH study. Therap Adv Gastroenterol 2021;14:17562848211023386.
18. Stallmach A, Langbien C, Atreya R, et al. Vedolizumab provides clinical benefit over 1 year in patients with active inflammatory bowel disease - a prospective multicenter observational study. Aliment Pharmacol Ther 2016;44:1199–1212.
19. Lair-Mehiri L, Stefanescu C, Vaysse T, et al. Real-world evidence of tofacitinib effectiveness and safety in patients with refractory ulcerative colitis. Dig Liver Dis 2020;52:268–273.
20. Weisshof R, Aharoni Golan M, Sossenheimer PH, et al. Real-world experience with tofacitinib in IBD at a tertiary center. Dig Dis Sci 2019;64:1945–1951.
21. Singh S, Murad MH, Fumery M, et al. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. Clin Gastroenterol Hepatol 2020;18:2179–2191.e6.
22. Bonovas S, Lytras T, Nikolopoulos G, et al. Systematic review with network meta-analysis: comparative assessment of

tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther 2018;47:454–465.
23. Trigo-Vicente C, Gimeno-Ballester V, García-López S, et al. Systematic review and network meta-analysis of treatment for moderate-to-severe ulcerative colitis. Int J Clin Pharm 2018;40:1411–1419.
24. United States Food and Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death. Accessed September 1, 2021.
25. Olivera PA, Zuily S, Kotze PG, et al. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2021;18:857–873.

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Conflicts of interest
These authors disclose the following: Alexander Bodelier has participated in advisory boards of Takeda, Janssen Pharmaceutica, Ferring, and Mundipharma. Adriaan A. van Bodegraven has served as consultant or speaker for AbbVie, ARENA, Ferring, Janssen, MSD, Pfizer, Takeda, TEVA, Tramedico, VIFOR, and Dutch Ministry of Health (ZonMW); has received (unrestricted) research grants from Aventis and Ferring, Pfizer, TEVA, and the Dutch Ministry of Health; and has performed as (local) principal investigator in studies sponsored by Schering-Plough, Roche, Teva, Janssen, MSD, Pfizer, ARENA and Centocor. Marijn Visschedijk has served on the advisory board for Janssen-Cilag and received a speakers fee from Takeda, outside the submitted work. Fiona van Schaik has served on advisory boards for Takeda and Galapagos. Janneke van der Woude received grant support from Falk Benelux, Ferring and Pfizer; received speaker fees from AbbVie, Takeda, Ferring, Dr Falk Pharma, Pfizer; and served as a consultant for Janssen. Nanne K. H. de Boer has served as a speaker for AbbVie and MSD and has served as consultant and/or principal investigator for TEVA Pharma BV and Takeda; has received a (unrestricted) research grant from Dr Falk, TEVA Pharma BV, MLDS and Takeda, all outside the submitted work. Frank Hoentjen has served on advisory boards or as speaker for Abbvie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr Falk; has received funding (grants/honoraria) from Dr Falk, Janssen-Cilag, and Abbvie; and has received consulting fees from Celgene. Marjolijn Duijvestein reports advisory fees from Echo Pharma and Robarts Clinical Trials, Inc; speaker fees from Janssen, Merck & Co., Inc., Pfizer, Takeda, and Tillotts Pharma; and nonfinancial support from Dr Falk Pharm. Gerard Dijkstra has received grant support from DSM nutritional products LTD and speaker's fees from Janssen Pharmaceuticals, Abbvie, and Takeda, outside of the submitted work. Andrea E van der Meulen-de Jong has received a presentation fee from Janssen and served on the advisory board of Takeda and Galapagos, outside of the submitted work. Rachel West has served on the advisory board and as an invited speaker for Janssen, Pfizer and Takeda, outside of the submitted work. Jeroen M. Jansen has served on advisory boards, or as speaker or consultant for Abbvie, Amgen, Ferring, Fresenius, Janssen, MSD, Pfizer, Takeda, and A.G.L. Annemarie C. de Vries has participated in advisory boards and/or received financial compensation from the following companies: Jansen, Takeda, Abbvie, and Tramedico. Marieke J. Pierik has served on advisory boards, or as speaker or consultant for Abbvie, Janssen-Cilag, MSD, Takeda, Ferring, Dr Falk, and Sandoz; and has received unrestricted grants from, Janssen-Cilag, Abbvie, and Takeda, outside the submitted work. Cyriel Ponsioen received grants or contracts from Takeda, Pliant, and Gilead Sciences; consulting fees from Pliant and Shire (Takeda); and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Takeda, Tillotts Pharma, and Pfizer, outside of the submitted work. The remaining authors disclose no conflicts.

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Supplementary Table 1. Baseline Characteristics in the Weighted Cohort

	Vedolizumab (n = 150)	Tofacitinib (n = 152)	*P* value
Age, *y*	39 (31–53)	51 (39–59)	.000
Male	77 (51.4)	79 (52.0)	.911
Disease duration, *y*	10 (8–16)	11 (6–20)	.735
Follow-up, *w*	46 (16–52)	47 (23–52)	.498
BMI	24.4 (21.8–28.7)	25.5 (21.9–29.3)	.733
Disease activity			
SCCAI score	7 (5–9)	6 (4–9)	.179
CRP, *mg/L*	4 (2–12)	7 (2–14)	.029
FC, *mg/kg*	1316 (429–2103)	1177 (191–2535)	.401
Mayo score[a]			.058
0	2 (1.6)	–	
1	13 (12.3)	7 (5.6)	
2	35 (32.3)	59 (48.2)	
3	57 (52.7)	55 (45)	
Unknown	1 (1.1)	1 (1.1)	
Medical history			
Disease location[b]			.744
Proctitis	22 (14.5)	19 (12.5)	
Left sided	61 (40.5)	66 (43.3)	
Pancolitis	62 (41.5)	58 (38.3)	
Prior treatment			
Failed anti-TNF			.954
≥2	50 (33.5)	49 (32.8)	
3	7 (4.6)	6 (4.1)	
Ustekinumab use	3 (2.1)	4 (2.6)	.715
Concomitant treatment			
Oral prednisone	65 (43.7)	58 (38.1)	.335
Oral prednisone dose, *mg*	30 (20–40)	25 (15–40)	.041
Thiopurine	45 (29.9)	4 (2.9)	.111
MTx	7 (4.5)	5 (3.3)	.005

Note: Data are presented as number (%), median (IQR), or mean (SD).
Note: Due to IPTW, in which a weight is added to each patient, sample sizes were inflated.
BMI, Body mass index; CRP, C-reactive protein; FC, fecal calprotectin; IQR, interquartile range; MTx, methotrexate; SCCAI, Simple Clinical Colitis Activity Index; SD, standard deviation; TNF, tumor necrosis factor-alpha.
[a]In 59 patients with endoscopy at baseline.
[b]Maximum extend until inclusion.

Supplementary Table 2. Predictors of Corticosteroid-free Clinical Remission at Week 52

	Vedolizumab			Tofacitinib		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age at inclusion, *y*	0.98	0.95–1.01	.207	1.03	0.99–1.07	.146
BMI per point	1.05	0.95–1.17	.327	0.94	0.83–1.06	.303
Sex						
Male	Ref			Ref		
Female	1.31	0.54–3.20	.552	0.70	0.26–1.89	.476
Disease duration per year	0.99	0.94–1.05	.783	1.10	1.02–1.19	.013
Disease location[a]			.544			.810
Proctitis	Ref			Ref		
Left sided	1.04	0.09–12.57	.975	1.54	0.12–19.47	.739
Pancolitis	1.17	0.10–14.06	.903	1.06	0.08–13.33	.965
Clinical disease activity[b]						
SCCAI per point	1.03	0.88–1.21	.722	0.95	0.81–1.11	.496
Biochemical disease activity[b]						
CRP, *mg/L*	1.00	0.97–1.03	.794	1.00	1.00–1.02	.274
FC, *μg/g*	1.00	1.00–1.00	.622	1.00	1.00–1.00	.359
Concomitant medication[b]						
Corticosteroids	1.07	0.44–2.60	.887	1.81	0.62–5.27	.275

Note: Because disease duration was the only variable with $P < .2$, no multivariate analysis was performed.
BMI, Body mass index; CI, confidence interval; CRP, C-reactive protein; FC, fecal calprotectin; OR, odds ratio; Ref, reference; SCCAI, Simple Clinical Colitis Activity Index.
[a]At inclusion.
[b]Maximum extend until inclusion.