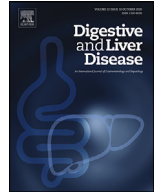




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Alimentary Tract

Real-life effectiveness and safety of tofacitinib and vedolizumab as 2nd-line for ulcerative colitis after anti-TNFs: A multicenter cohort IGIBD study (VE2TO-UC)[☆]

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[☆] The data underlying this article will be shared on reasonable request to the corresponding author.

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¹ To See the detail of VE2TO-UC study group [click here](#)

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ABSTRACT

Background and aims: Drug positioning in ulcerative colitis (UC) patients refractory to anti-tumor necrosis factor (TNF) is still debated. In a nationwide multicentre observational cohort, we aimed to compare the real-life effectiveness and safety of tofacitinib and vedolizumab as second-line for UC after anti-TNFs.

Methods: Disease activity was evaluated at weeks 8, 26, and 52 ± 4 . The primary outcome was to compare clinical remission (partial Mayo score (PMS) ≤ 2 with no subscore >1) at week 26. Secondary outcomes included comparative effectiveness for corticosteroid-free clinical remission (CFCR); biochemical, endoscopic, and histologic remission; combined corticosteroid-free clinical-objective remission; and treatment persistence. Inverse probability of treatment weighting was used for all comparisons.

Results: Overall, 134 tofacitinib- and 277 vedolizumab-treated UC patients were included. At week 26, no difference was observed between tofacitinib and vedolizumab for clinical remission (adjusted odds ratio [aOR]: 0.9; 95 % confidence interval [CI]: 0.6 – 1.6). At week 8, tofacitinib was more effective in achieving CFCR (aOR: 1.7; 95 % CI: 1.0 – 2.7). Clinical, biochemical, endoscopic, and histologic outcomes showed no difference between tofacitinib and vedolizumab at weeks 26 and 52. In patients with baseline PMS ≥ 2 , steroid use, or anti-TNF non-response no difference was found for clinical remission at week 26. Tofacitinib-treated patients were more likely to discontinue treatment (adjusted Hazard Ratio: 1.8; 95 % CI: 1.2 – 2.8). Safety was consistent with treatment profiles in UC.

Conclusions: Tofacitinib and vedolizumab were equally effective and safe as second-line therapy in anti-TNFs experienced UC patients. Tofacitinib showed greater efficacy in inducing CFCR at week 8, but carried higher discontinuation risk.

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1. Introduction

Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease (IBD) involving the rectum and a variable extent of the colon [1]. Despite the licensing of several novel advanced therapies, anti-tumour necrosis factor (TNF) dominates as first-line biologic therapy for moderate-to-severe UC [2]. Positioning different agents especially in patients with prior exposure to anti-TNF therapy is a key knowledge gap. A network meta-analysis of randomized controlled trials (RCT) of adults with moderate-to-severe UC treated with anti-TNF, vedolizumab, tofacitinib, or ustekinumab, as first-line or second-line agents showed the superior efficacy of ustekinumab and tofacitinib over vedolizumab as second-line agents in inducing clinical remission and endoscopic improvement in patients with prior exposure to TNF antagonists [3]. In this specific scenario, only a Dutch non-inferiority real-life observational study has been performed [4]. Therefore, the treatment of choice remains an open issue, based primarily on clinician's experience and expert opinion-based treatment algorithms [5]. This real-life observational multicentre cohort study aims to address this knowledge gap.

2. Methods

Study design and patients. This is a retrospective real-life observational multicentre cohort study involving 28 Italian IBD referral centres on behalf of the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD). Patients with a confirmed diagnosis of UC according to the European Crohn's and Colitis Organization (ECCO) guidelines, failure or intolerant to ≥ 1 anti-TNFs, receiving vedolizumab or tofacitinib treatment as a second advanced therapy according to clinical standard of care between 2015 and 2024, were considered for inclusion in the study. Patients with acute severe UC requiring hospitalization and IV steroids, bio-naïve to biological therapy, not treated with an anti-TNF as first-line biological therapy, or receiving tofacitinib for an indication different from UC were excluded.

Clinical conditions recorded at the start of either tofacitinib or vedolizumab were considered baseline conditions. Demographics data and disease-related were extracted from patients' clinical records. (Supplementary Methods) Study data were pseudo-

anonymized and managed using an electronic data capture tool hosted at IG-IBD (REDCap, Research Electronic Data Capture) [6,7].

At baseline, data on clinical disease activity, calculated by the Partial Mayo Score (PMS), and steroid and thiopurine use and their dosage, were recorded; data on biochemical disease activity as assessed by C-reactive protein (CRP), faecal calprotectin (FCP), on endoscopic disease activity as assessed by the Mayo endoscopic score (MES) within 3 months prior to tofacitinib or vedolizumab initiation and histologic disease activity as assessed by the presence or absence of neutrophils from superficial epithelium and lamina propria were also recorded, when available. At weeks 8, 26, and 52 (± 4 weeks) data on clinical disease activity, concurrent UC treatments and, when available, biochemical and endoscopic disease activity were recorded. A pre-specified list (supplementary methods) and any other side effects, adverse events, and causes of treatment discontinuation reported in the clinical records were also collected.

Outcomes. The primary outcome was to compare the two treatments' effectiveness at week 26 in terms of clinical remission, defined as PMS ≤ 2 with no subscore >1 . The secondary outcomes were to compare the two treatments' effectiveness in terms of clinical response (decrease ≥ 50 % rectal bleeding and stool frequency) at week 8; corticosteroid-free clinical remission (CFCR), biochemical remission (CRP ≤ 0.5 mg/dL or FCP level ≤ 250 μ g/g), endoscopic response (decrease in MES of ≥ 1 compared with baseline), endoscopic remission (MES ≤ 1), and histologic remission (absence of neutrophils) at weeks 8, 26 and 52; combined corticosteroid-free clinical-objective (biochemical or endoscopic) remission at weeks 26 and 52; and treatment persistence. Adverse events and severe adverse events leading to drug discontinuation were reported.

Statistics. Standard descriptive statistics were used to analyse patients' characteristics. Continuous variables were described as median and interquartile range (IQR). Categorical variables were described as the number of cases and proportions. Comparisons between variables were performed by chi-squared and Mann-Whitney U tests. To minimize the effect of confounding variables, propensity score with inverse probability of treatment weighting (IPTW) was used for the analysis of primary and secondary outcomes [8]. (Supplementary Methods) IPTW was independently calculated and applied for the entire cohort of analysed patients (*i.e.* all-patient cohort) to evaluate clinical outcomes at weeks 8, 26, and 52, and for the sub-cohort of patients who had baseline and

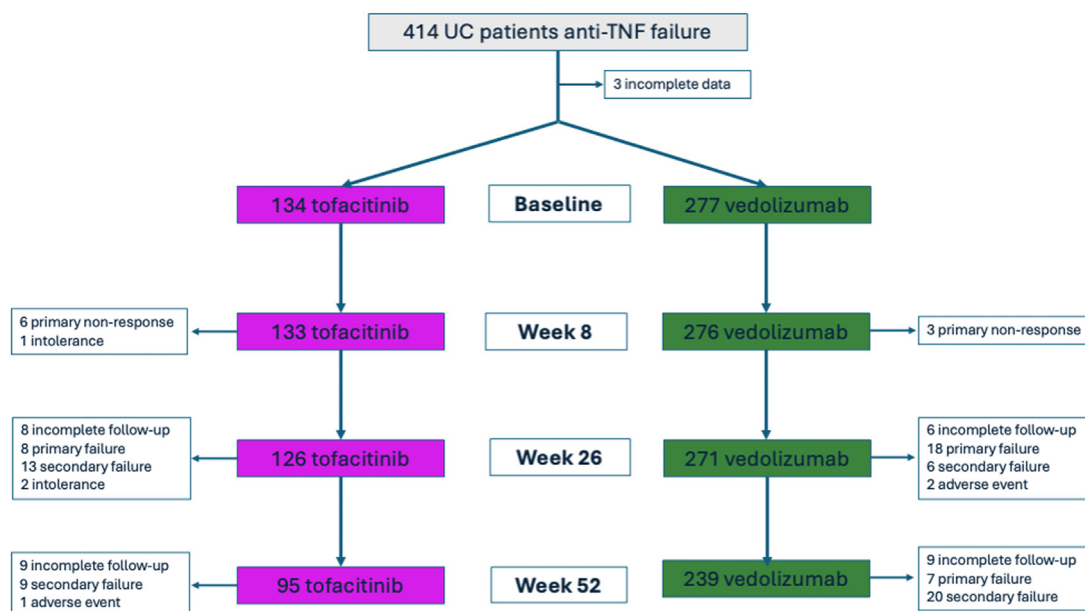


Fig. 1. Study profile.

endoscopic evaluation during maintenance to evaluate objective response and remission. E-values were used to assess the potential impact of unmeasured confounders [9]. In this study, the dataset exhibited a missing data rate of <10 %. Multiple imputation was done for missing data using Multivariate Imputations by Chained Equations algorithm which implies that missing values are distributed under the Missing At Random assumption. Diagnostic of the quality of the imputed values was done and all the generated imputed data were clinically plausible

Sample size. During the study design, based on two meta-analyses of real-world observational studies the expected rate of clinical remission was 24 % among patients treated with vedolizumab and 40 % among patients treated with tofacitinib [10,11]. To demonstrate an absolute difference of 16 % in favour of tofacitinib, in an observational study [12,13], 133 patients were required in each group to obtain a study power of 80 % and a two-sided type I error set at 5 %.

Ethical considerations. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The study was approved by the Ethics Committee of the coordinating center (Comitato Etico Milano Area 2: 161,704) and, thereafter, by all the participating centers.

3. Results

3.1. Baseline characteristics of the patients

All clinical records of patients with UC in a regular follow-up at 28 IBD centres from January 2015 to April 2024 were retrospectively reviewed. Overall, four hundred fourteen patients with UC previously exposed to TNF and treated with either tofacitinib or vedolizumab as second-line therapies were identified. Three patients were excluded due to incomplete data beyond baseline (Fig. 1) Four hundred-eleven patients met the inclusion criteria and were included. One hundred thirty-four patients (32.6 %) were treated with tofacitinib, whereas 277 patients (67.4 %) received vedolizumab. Baseline patient characteristics were similar between the 2 groups, except for age at baseline, age at UC onset, comorbidities, cardiovascular and venous thromboembolic events risk factors, and herpes zoster vaccination (Table 1) Other baseline

characteristics were balanced (Supplementary results and Table 1) After propensity score estimations, no difference between the 2 groups was observed, and the standardized difference was <0.1 for all variables included (Supplementary Figures 1–7) Fourteen patients – 8 in the tofacitinib and 6 in the vedolizumab group – were censored from the primary outcome analysis due to insufficient follow-up.

3.2. Crude and propensity-weighted comparisons of clinical and biochemical effectiveness at week 8

The crude rate of clinical response, clinical remission, and CFCR at week 8 were 23.4 vs. 16.3 % ($p = 0.1$), 54 vs. 49.6 % ($p = 0.5$), 48.4 vs. 36.8 % ($p = 0.04$) in patients treated with tofacitinib and vedolizumab, respectively. The rate of biochemical remission was 69.8 % in patients treated with tofacitinib and 67.6 % vedolizumab ($p = 0.8$). After IPTW analysis, tofacitinib was more effective than vedolizumab in achieving CFCR with an adjusted odds ratio (aOR) of 1.7 (1.0 – 2.7). However, no difference between tofacitinib- and vedolizumab-treated patients in terms of clinical response aOR 1.4 (0.8 – 2.5), clinical remission aOR 1.3 (0.8 – 2.1), and biochemical remission aOR 1 (0.6 – 1.9) was observed. (Fig. 2)

3.3. Crude and propensity-weighted comparisons of clinical and biochemical effectiveness at week 26

In 126 patients in treatment with tofacitinib, 23.8 % (30/126) and 20.6 % (26/126) were still on induction dose (10 mg b.i.d.) at weeks 16 and 26, respectively. An additional off label infusion at week 10 was performed in six patients while 23.9 % (65/271) received dose-optimized 300 mg every 4 weeks at week 26. The rate of clinical remission and CFCR were similar between the 2 groups - tofacitinib vs vedolizumab 54.8 % vs. 56.8 % ($p = 0.8$) and 51.6 % vs. 53.5 % ($p = 0.8$). The rate of biochemical remission was 80.2 % in patients treated with tofacitinib and 76.7 % vedolizumab ($p = 0.6$). After IPTW analysis, no difference between tofacitinib- and vedolizumab-treated patients in terms of clinical remission aOR 0.9 (0.6 – 1.6), CFCR aOR 1.0 (0.6 – 1.6), biochemical remission aOR 1.4 (0.7 – 2.7) was observed. (Fig. 2)

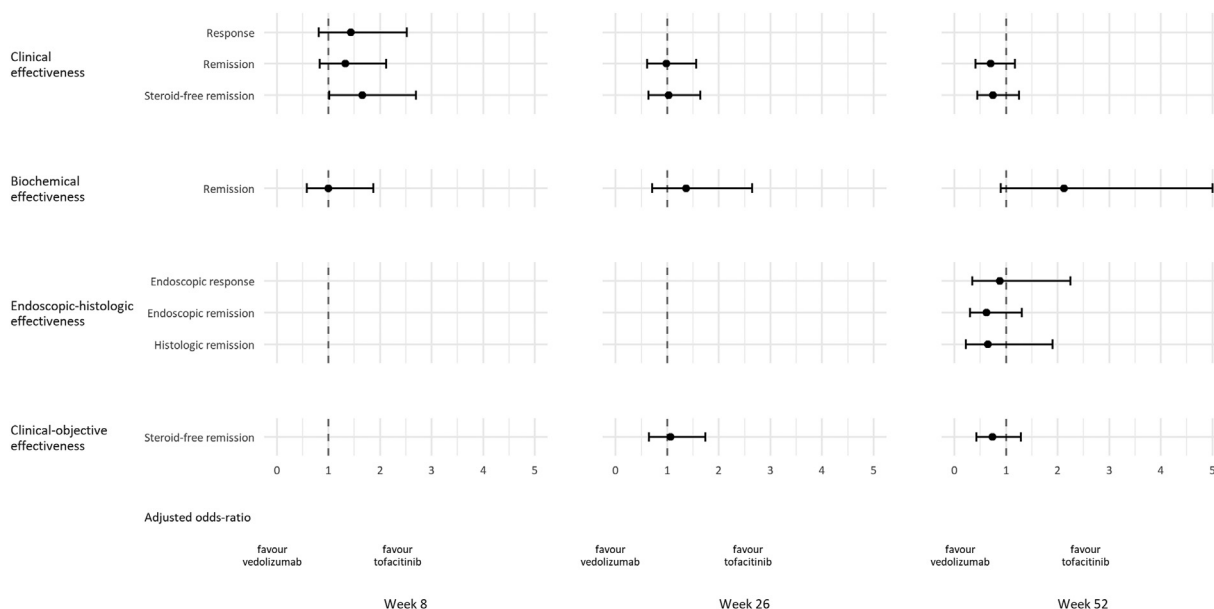


Fig. 2. Propensity-matched comparisons of clinical, biochemical, endoscopic, histologic, and corticosteroid-free clinical-objective effectiveness of tofacitinib and vedolizumab at weeks 8, 26, and 52.

3.4. Crude and propensity-weighted comparisons of clinical, biochemical effectiveness at week 52

In the tofacitinib group 14.7 % (14/95) of the patients were still on 10 mg b.i.d., while 25.1 % (60/239) in the vedolizumab group were receiving dose-optimized 300 mg every 4 weeks at week 52. The rate of clinical remission and CFCR were 56.6 % vs. 65.7 % ($p = 0.1$) 55.7 % vs. 63.6 % ($p = 0.2$) in patients treated with tofacitinib and vedolizumab, respectively. The rate of biochemical remission was 87.3 % in patients treated with tofacitinib and 79 % vedolizumab ($p = 0.2$). After IPTW analysis, no difference between tofacitinib- and vedolizumab-treated patients in terms of clinical remission aOR 0.7 (0.4 – 1.2), CFCR aOR 0.8 (0.4 – 1.3), and biochemical remission aOR 2.1 (0.9 – 5.0) was observed. (Fig. 2)

3.5. Crude and propensity-weighted comparisons of endoscopic and histologic effectiveness

Given that endoscopic re-evaluation in clinical practice is usually performed only once during maintenance within the end of the first year of therapy, this analysis included data from weeks 26 onward. Among 113 patients with moderate-to-severe endoscopic activity at baseline and an endoscopic re-evaluation during maintenance, the crude rate of endoscopic response was 64.7 % and 69.6 % ($p = 0.6$) in patients treated with tofacitinib and vedolizumab, respectively. Among 173 patients with endoscopic evaluation during maintenance, the crude rate of endoscopic remission was 45.8 % and 52.8 % ($p = 0.5$) in patients treated with tofacitinib and vedolizumab, respectively. Among 119 patients with histologic evaluation during maintenance, the rate of histologic remission was 23.3 % and 38.2 % ($p = 0.2$) in patients treated with tofacitinib and vedolizumab, respectively. After IPTW analysis, no difference between tofacitinib- and vedolizumab-treated patients in terms of endoscopic response aOR 0.9 (0.4 – 2.4), endoscopic remission aOR 0.6 (0.3 – 1.3), and histologic remission aOR 0.7 (0.2 – 1.9) was observed. (Fig. 2)

3.6. Crude and propensity-weighted comparisons of combined corticosteroid-free clinical-objective remission at weeks 26 and 52

The crude rate of combined corticosteroid-free clinical-objective remission in tofacitinib- and vedolizumab-treated patients at weeks 26 and 52 were 43.9 % vs. 43.9 % ($p = 1$) and 47.4 % vs. 54.5 % ($p = 0.3$), respectively. After IPTW analysis, no difference between tofacitinib- and vedolizumab-treated patients at weeks 26 aOR 1.1 (0.7 – 1.7) and 52 aOR 0.7 (0.4 – 1.3) was observed. (Fig. 2)

3.7. Treatment discontinuation

Therapy was stopped in 29.9 % (40/134) and 20.6 % (57/277) ($p = 0.05$) of the tofacitinib- and vedolizumab-treated patients after a median treatment duration of 22.4 (12.8 – 26.6) weeks and 26.9 (21.9 – 33.1) weeks ($p = 0.05$). The most common reason for treatment discontinuation in the tofacitinib group was secondary non-response, while primary and secondary loss of response were equal in the vedolizumab group (Table 2). Non-response was predominantly based on objective measures of disease activity—such as biochemical and/or endoscopic findings—alongside clinical data with no difference between the two groups ($p = 0.3$) (Supplementary Table 4) After IPTW analysis, tofacitinib-treated patients were more likely to discontinue treatment before 52 weeks of treatment with an adjusted hazard ratio of 1.8 (1.2 – 2.8). (Fig. 3)

3.8. Subgroup and sensitivity analyses

In the 340 patients with a baseline PMS ≥ 2 (Supplementary Table 1), the crude rate of clinical remission and CFCR at week 26 were 50.5 % vs. 53.6 % ($p = 0.7$) 47.7 % vs. 49.8 % ($p = 0.8$) in patients treated with tofacitinib and vedolizumab, respectively. After IPTW analysis, no difference between tofacitinib- and vedolizumab-treated patients in terms of clinical remission aOR 0.9 (0.6 – 1.5) and CFCR aOR 0.9 (0.6 – 1.6) was observed at week 26. In addition, in the subgroup of patients with prednisone ≥ 20 mg at baseline no difference in terms of clinical remission aOR 1.3 (0.4 – 3.6) was observed in the two groups at week 26. No difference between tofacitinib- and vedolizumab-treated patients

Table 1
Demographic and disease characteristics of the population.

	Tofacitinib (n = 134)	Vedolizumab (n = 277)	p-value
Age at baseline, y	38 (29 – 48)	45 (32 – 57)	<0.001
Female	48 (36 %)	108 (39 %)	0.53
Disease duration, m	83.2 (32.5 – 174)	82.5 (37.9 – 174.7)	0.73
Age at onset			<0.001
- <16 years	21 (16 %)	18 (6.5 %)	
- 17 – 40 years	91 (68 %)	165 (60 %)	
- > 40 years	22 (16 %)	94 (34 %)	
Disease extension			0.79
- Proctitis	1 (0.8 %)	2 (0.7 %)	
- Left-side	56 (42 %)	107 (39 %)	
- Extensive	76 (57 %)	167 (61 %)	
BMI	23.5 (21.9 – 25.4)	24.1 (22 – 26.4)	0.32
Family history of IBD	18 (15 %)	21 (8.6 %)	0.051
Appendectomy	2 (1.9 %)	13 (5.6 %)	0.19
Smoking			0.51
- never	74 (63 %)	157 (67 %)	
- former	35 (30 %)	57 (24 %)	
- active	9 (7.6 %)	22 (9.3 %)	
Systemic steroids cycles	4.1 ± 5.6	3.6 ± 3.9	0.64
Failed azathioprine (Imuran)	41 (32 %)	103 (38 %)	0.22
First anti-TNF failed			
- infliximab	100 (75 %)	188 (68 %)	0.16
- adalimumab	26 (19 %)	59 (21 %)	0.66
- golimumab	8 (6 %)	37 (13 %)	0.03
Second anti-TNF failed			
- infliximab	6 (4.5 %)	12 (4.3 %)	0.95
- adalimumab	4 (3 %)	16 (5.8 %)	0.22
- golimumab	7 (5.2 %)	5 (1.8 %)	0.06
Reason for anti-TNF discontinuation:			0.10
- Primary non-response	32 (23.9 %)	88 (31.8 %)	
- Secondary non-response	82 (61.2 %)	130 (46.9 %)	
- Intolerance	4 (2.9 %)	7 (2.5 %)	
- Adverse event	15 (11.2 %)	41 (14.8 %)	
Concomitant steroids			0.21
- Dose, mg	51 (39 %)	123 (46 %)	0.34
Concomitant azathioprine (Imuran)	4 (3 %)	18 (6.6 %)	0.14
Partial Mayo Score	5 (4 – 6)	5 (3 – 6)	0.37
C-reactive protein, mg/dL	4.1 ± 10.2	3.2 ± 6.8	0.90
Feecal calprotectin, µg/g	1038 ± 1,1357	1160 ± 1,1434	0.13
Mayo Endoscopic Subscore			0.66
- 0	2 (2 %)	1 (0.6 %)	
- 1	6 (5.9 %)	8 (4.5 %)	
- 2	40 (39 %)	70 (39 %)	
- 3	54 (53 %)	100 (56 %)	
Extraintestinal manifestations	16 (12 %)	37 (14 %)	0.64

(continued on next page)

Table 1 (continued)

	Tofacitinib (n = 134)	Vedolizumab (n = 277)	p-value
Presence of comorbidities	26 (19 %)	106 (39 %)	<0.01
Venous thromboembolism risk factors	2 (1.5 %)	16 (6.2 %)	0.04
Cardiovascular risk factor	17 (13 %)	68 (25 %)	<0.01
Varicella zoster virus status			0.21
- naive	26 (35 %)	24 (26 %)	
- experienced	49 (65 %)	69 (74 %)	
Herpes zoster vaccination	38(43 %)	16 (13 %)	<0.01

Data are presented as number (%) or median (IQR) or mean ± standard deviation.

Table 2
Discontinuation Within 52 Weeks of Treatment.

	Tofacitinib (n = 134)	Vedolizumab (n = 277)
Treatment discontinuation, w	22.4 (12.8 – 26.6)	26.9 (21.9 – 33.1)
Reason for discontinuation		
- Primary non-response	14 (10.4 %)	27 (9.7 %)
-Secondary non-response	22 (16.4 %)	27 (9.7 %)
-Adverse event	1	2
-Intolerance	3 (2 %)	0

Data are presented as number (%) or median (IQR).

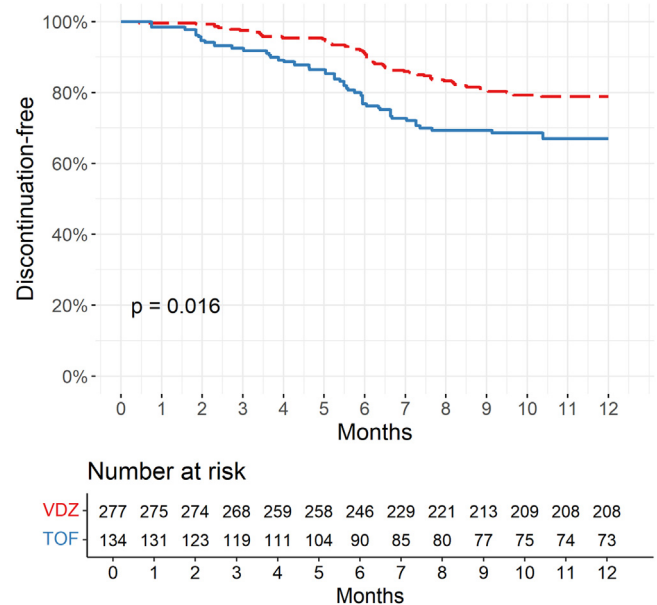


Fig. 3. IPTW-adjusted Kaplan–Meier curves comparing treatment discontinuation-free survival between tofacitinib and vedolizumab.

was identified with regard to clinical remission at week 26 in the subgroups of patients initiating either therapy after the prescriptive availability of tofacitinib aOR 0.9 (0.5 – 1.6), those exposed to a single anti-TNF aOR 0.9 (0.5 – 1.5), those exposed to infliximab as first-line aOR 0.9 (0.5 – 1.7), or those who discontinued anti-TNF for non-response aOR 1.1 (0.7 – 1.9). No difference between tofacitinib- and vedolizumab-treated patients was identified with regard to clinical remission at week 26 in the subgroups of patients with left-side colitis aOR 0.7 (0.3 – 1.5) or those with extensive colitis aOR 1.1 (0.6 – 2.0). In the subgroup of patients with EIM (Supplementary Table 2) at baseline (active disease activity in 11/16 in the tofacitinib group and 23/34 in the vedolizumab group) a nu-

Table 3

Overview of adverse events in the safety analysis population.

	Tofacitinib (n = 134; 94.7 person-years)		Vedolizumab (n = 277; 231.7 person-years)		Incidence risk ratio	p-value
	n	Events per 1000 person-years	n	Events per 1000 person-years		
Any adverse events	19	200.6	20	86.3	2.3	<0.01
Venous thromboembolism	0	–	1	4.3	0	0.52
Herpes zoster reactivation	3	31.7	2	8.6	3.7	0.13
Major cardiovascular adverse event	0	–	0	–	–	–
Severe lymphopenia	0	–	1	4.3	0	0.52
Cholesterol-lowering drug	11	116.2	2	8.6	13.5	<0.001
UC-related hospitalization	3	31.7	6	25.9	1.2	0.78
Clostridium difficile infection	0	–	1	4.3	0	0.52
UC-related surgery	1	10.6	4	17.3	0.6	0.66
Dysplasia or colorectal carcinoma	0	–	1	4.3	0	0.52
Creatine phosphokinase above upper normal limit	1	10.6	0	–	–	0.12
Uterine fibroma	0	–	1	4.3	0	0.52
Pancreatic Intraepithelial Neoplasia	0	–	1	4.3	0	0.52
Death	0	–	0	–	–	–

merically higher proportion of tofacitinib-treated patients achieved EIM remission at week 26 compared to vedolizumab (5/8 vs 15/30) ($p = 0.5$). Among various IPTW-adjusted models fitted, only the use assessing CFCR at Week 8 showed a significant association with the drug used (OR 1.66, 95 % CI 1.02–2.70). Sensitivity analysis using E-values indicates that this association could be explained by an unmeasured confounder with a risk ratio of at least 1.90 for both the drug used and the outcome (Supplementary Table 3) Nevertheless, considering that known potential confounders were included in the IPTW model, the sensitivity to unmeasured confounding remains moderate.

3.9. Safety

Patients were treated with tofacitinib and vedolizumab for 94.7 and 231.7 patient-years, respectively. The list of AEs is reported in Table 3. AEs were recorded in 19 and 20 patients in the tofacitinib group and vedolizumab group, respectively, with an incidence risk ratio of 2.3 for tofacitinib. Of note, eleven patients in the tofacitinib group initiated or escalated cholesterol-lowering drugs accounting for most AEs in this group. Herpes zoster reactivation occurred in 5 patients (3 in the tofacitinib and 2 in the vedolizumab group, one patient treated with tofacitinib had received a zoster vaccination), one venous thromboembolism event was recorded in the vedolizumab group. No major adverse cardiovascular events or death were recorded in both groups of treatment.

4. Discussion

In the open issue of positioning different agents in anti-TNF experienced patients with UC, this nationwide multicentre cohort study provided the largest data on the real-life effectiveness and safety of tofacitinib and vedolizumab as second-line. Our IPTW-adjusted results showed that tofacitinib and vedolizumab were equally effective as second-line therapy in anti-TNFs experienced UC patients in achieving clinical, biochemical, endoscopic, and histological remission up to 52 weeks. Tofacitinib showed greater efficacy in inducing CFCR at week 8, but carried higher discontinuation risk during maintenance. Safety was consistent with known tofacitinib and vedolizumab profiles in UC.

Reliance on real-world evidence (RWE) from observational studies is increasingly valuable to fill knowledge gaps not directly answered in RCT, informing healthcare decisions and guiding healthcare policy. In this specific scenario, only a Dutch observational study has been performed although limited by a non-inferiority

study design with a small sample size. Two additional studies have been conducted, but their validity is somewhat limited by the use of administrative data and treatment persistence as the outcome measure [14,15].

The VE2TO-UC study included a large multicentre cohort of anti-TNF experienced UC patients designed with an adequate sample size to investigate the superior effectiveness of one treatment over the other. At baseline, the two groups had similar characteristics for almost all variables, including those concerning disease activity. Notwithstanding, we used an IPTW approach for all comparisons – primary and secondary outcomes as well as subgroup and sensitivity analyses – to balance baseline patient characteristics and obtain estimates adjusted for confounders. Our results showing the greater effectiveness of tofacitinib over vedolizumab in the short-term, particularly in terms of CFCR, are consistent with real-world evidence and network meta-analyses of RCT [3,4,16]. However, it is worth noting that the superiority in our cohort is smaller than in the Dutch cohort (aOR 1.7 vs 6.3) although direct comparison is limited by different scores used (PMS vs Simple Clinical Colitis Activity Index) and time of disease activity evaluation (8 vs 12 weeks) [4]. A possible explanation could be the differing physician approaches to the expected onset of treatment effect and option for drug discontinuation. In our cohort, nearly all patients remained on therapy until the end of induction, whereas only 80–90 % of patients in the Dutch cohort continued treatment – aligning also with the lower rate of PNR observed in our cohort [4].

During maintenance, in our cohort the effectiveness increased slightly in the tofacitinib group and markedly in the vedolizumab group, but neither showed superiority at weeks 26 and 52. This result was consistent across all disease activity levels (clinical, biochemical, endoscopic, and histological). Although our clinical results differ from that of the Dutch cohort, they are consistent with also their non-superiority findings for objective (biochemical and endoscopic) disease activity as well as network meta-analysis clinical comparisons of the maintenance phase of RCT[3]. Of note, in our cohort more than half of patients achieved CFCR at week 52 in both treatment groups. Our results align with the CFCR effectiveness in almost half of the patients for both treatments as reported in a meta-analysis of vedolizumab observational studies and other tofacitinib cohorts, despite heterogeneity in patient cohort characteristics [11,17]. Likewise, this may be partly attributed to the high rates of optimized therapy, especially in the vedolizumab group, although a recent RCT did not show greater efficacy for this strategy in UC patients with PNR to vedolizumab [18]. In our cohort, treatment with vedolizumab showed higher treatment persistence.

Although this finding differs from the Dutch study, the one-year vedolizumab superiority aligns with an administrative cohort in anti-TNF experienced patients and a meta-analysis of observational studies where vedolizumab ranked first at one-year persistence in UC [19,20]. Moreover, the discontinuation-free rates observed in our cohort are consistent with those reported in a large real-world UK cohort of patients with ulcerative colitis treated with anti-TNF therapy [21]. Since discontinuation rates could have influenced long-term outcomes and the interpretation of treatment effectiveness, an intention-to-treat approach was adopted. Any treatment discontinuation—whether due to AEs, LOR, or loss to follow-up—was considered a treatment failure from that point onward. This approach ensured that all patients were included in the analysis, minimizing bias associated with discontinuation rates and better reflecting the challenges of clinical practice.

Despite having similar baseline characteristics for almost all variables in both groups and using IPTW for all comparisons, other potential factors such as disease burden, the number types reason for discontinuation of previous anti-TNF drugs [22], and prescribing availability could have influenced the results. To confirm the reliability of our results, we carried out targeted subgroup and sensitivity analyses to address these potential additional confounders. In patients with active disease at baseline, steroid use, anti-TNF non-response as reason for discontinuation, exposure to infliximab or a single anti-TNF, and those treated after tofacitinib prescription availability no difference was observed between tofacitinib and vedolizumab with consistent results with the entire study population.

Our results confirm that tofacitinib and vedolizumab are both overall safe treatment options for patients with UC over a 12-month period. Notably, no cardiovascular or thromboembolic events were observed in the tofacitinib group. Baseline characteristics suggest a marked preference towards vedolizumab in case of cardiovascular or thromboembolism risk factors, reflecting current European Medical Agency and Italian recommendations [23]. Surprisingly, no difference in zoster reactivation was observed between the two groups. This lack of increased risk in the tofacitinib group could likely be due to the Herpes Zoster vaccination received by approximately half of this group. Of note, eleven (8.2 %) patients in the tofacitinib group initiated or escalated cholesterol-lowering drugs, which is in line with the RCT long-term extension cohort (6.3 %) [24].

Concerning drug positioning in UC patients refractory to TNF our results can be interpreted as both positive and negative. While a clear superiority might have endorsed a one-size-fits-all strategy in this scenario, the effectiveness of both treatments once again underscores the need for a personalized approach. In a shared decision-making process between patient and healthcare provider, the patient's perspective regarding the speed of action, the potential risk of loss of remission, the presence of EIM or comorbidities, and potential adverse events should be taken into account in the preference of tofacitinib or vedolizumab after anti-TNF. For instance, patients requiring a rapid induction of remission may benefit more from tofacitinib whereas vedolizumab may be more suitable for those prioritizing long-term treatment persistence, particularly in the presence of comorbidities.

This study comes with limitations of retrospective observational studies and some that should be acknowledged. Patients were included in both academic and non-academic hospitals. Although it may increase clinical management heterogeneity, this methodologic choice allowed to recruit the largest patient population and to be assimilated into a nationwide cohort reflecting real-world practice. Endoscopic assessment was only performed at the discretion of the treating physician. However, endoscopic results were consistent with other disease activity variables. Additional covariates might have affected treatment selection or outcomes that we

have not adjusted for. Nevertheless, IPTW was used not only for the primary outcome but for all comparisons.

In conclusion, tofacitinib and vedolizumab are equally effective as second-line therapy in anti-TNF experienced UC patients in terms of clinical, biochemical, endoscopic, and histological remission up to week 52. Tofacitinib shows greater efficacy in inducing CFCR at week 8, but carries higher discontinuation risk during maintenance. Safety was consistent with known tofacitinib and vedolizumab profiles in UC.

Key Messages

- What is already known?
 - Drug positioning in ulcerative colitis patients refractory to anti-TNF is still debated with limited real-life evidence
- What is new here?
 - This study provides real-life comparative evidence demonstrating that in a nationwide cohort tofacitinib and vedolizumab are equally effective and safe as second-line therapies after anti-TNF
- How can this study help patient care?
 - This study supports a personalized treatment strategy instead of a one-size-fits-all strategy in this scenario

Authorship statement

Guarantor of the article: Prof. Flavio Caprioli

Conflict of Interest

DN received unrestricted research grants from Pfizer, consulting fees from Abbvie and Dr. Falk, and lecturer fees from Alfasigma and Ferring.

WF received an educational grant from Pfizer and served as advisory board member for Takeda, Janssen, Abbvie, and Galapagos.

AO Consulting/advisory board fees from AbbVie, Alfa-Sigma, Biogen, Eli-Lilly, Ferring, Galapagos, Giuliani, Janssen, Johnson & Johnson, Lionhealth, MSD, Nestlé, Pfizer, Samsung Bioepis, Sandoz, Takeda. Speaker's fees from AbbVie, Alfa-Sigma, Biogen, Celltrion, Eli-Lilly, Ferring, Fresenius Kabi, Galapagos, Janssen, Lionhealth, MSD, Pfizer, Samsung Bioepis, Sandoz, Takeda. Research grants from Takeda and Pfizer

CB served as a consultant or received lecture fees from AbbVie, Alfasigma, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, Lionhealth, Johnson & Johnson, MSD, Pfizer, and Takeda.

F.Casti Lecture fees and advisory board: AbbVie, Biogen, Pfizer, Takeda, Janssen, Galapagos, Giuliani, Cadigroup, Johnson and Johnson, Celltrion, Sandoz

EVS has served as speaker for Abbvie, Abivax, Agave, AG-Pharma, Alfasigma, Apoteca, Biosline, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Galapagos, Johnson&Johnson, JB Pharmaceuticals, Innovamedica/Adacyte, Eli Lilly, Malesci, Mayo Biohealth, Montefarco, Novartis, Omega Pharma, Pfizer, Rafa, Reckitt Benckiser, Sandoz, Sanofi/Regeneron, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Dr. Falk, Eli Lilly, Fenix Pharma, Ferring, Giuliani, Grunenthal, Johnson&Johnson, JB Pharmaceuticals, Merck & Co, Nestlé, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Sofar, Takeda, Unifarco; he received research support from Bonollo, Difass, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Sofar, Unifarco, Zeta Farmaceutici

DGR served as consultant to Abbvie, Takeda, Johnson & Johnson, Alfasigma, Pfizer, Celltrion, Sandoz.

SF Advisory board member and/or consultancy fees for: Pfizer, Galapagos, Johnson & Johnson, Abbvie

PB Lecture fees and advisory board: AbbVie, Eli Lilly, Takeda, Janssen, Galapagos

SS Consultancy, lecture fees, and advisory board for AbbVie, Arena, Ferring, Galapagos, Gilead, Janssen, MSD, Pfizer, and Takeda.

AA - Consulting/advisory board fees from AbbVie, Alfa-Sigma, Astra Zeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Giuliani, Janssen, Lionhealth, Merck & Co, Nestlé, Pfizer, Protagonist Therapeutics, Roche, Sanofi, Samsung Bioepis, Sandoz, Takeda, Tillots Pharma. Speaker's fees from AbbVie, AG Pharma, Alfa-Sigma, Biogen, Bristol-Myers Squibb, Celltrion, Dr Falk, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, Lionhealth, Merck & Co, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Teva Pharmaceuticals. Research grants from MSD, Takeda, Pfizer, Biogen

MaV received consulting/advisory board fees from Abbvie, MSD, Takeda, Janssen, Bristol-Meyers Squibb, Giuliani, NTC Pharma, Galapagos, Pfizer, Mundipharma, Biogen, received lecture fees from Abbvie, Ferring, Takeda, Janssen, Pfizer, Biogen, and unrestricted research grants from AGPharma, Giuliani, Sofar, Takeda.

FC served as consultant to Abbvie, MSD, Takeda, Janssen, Roche, Celgene, Bristol-Meyers Squibb, Galapagos, Gilead, Pfizer, Mundipharma, Galapagos, Biogen, received lecture fees from Abbvie, Ferring, Takeda, Allergy Therapeutics, Janssen, Pfizer, Biogen, and unrestricted research grants from Pfizer, Giuliani, Sofar, MSD, Takeda, Abbvie.

Summary

Drug positioning in ulcerative colitis patients refractory to anti-TNF is still debated with limited real-life evidence. In a nationwide cohort tofacitinib and vedolizumab were equally effective and safe as second-line therapies.

VE2TO-UC study group

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Supplementary materials

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