Effectiveness and Safety of Vedolizumab in Anti-TNF-Naïve Patients With Inflammatory Bowel Disease—A Multicenter Retrospective European Study

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Background: Vedolizumab (VDZ) is effective for treatment of ulcerative colitis (UC) and Crohn's disease (CD). In GEMINI trials, anti–tumor necrosis factor (anti-TNF)–naïve patients had a superior response compared with anti-TNF-exposed patients. In real-world experience (RWE), the number of included anti-TNF-naïve patients was low. We aimed to evaluate the effectiveness and safety of VDZ in anti-TNF-naïve patients in an RWE setting.

Methods: This retrospective multicenter European pooled cohort study included consecutive active anti-TNF-naïve IBD patients treated with VDZ. The primary end point was clinical response at week 14. Patients with follow-up beyond week 14 and those discontinuing VDZ at any time were included for maintenance outcomes analysis.

Results: Since January 2015, 184 anti-TNF-naïve patients from 23 centers initiated VDZ treatment (Crohn's disease [CD], 50; ulcerative colitis [UC], 134). In CD, 42/50 (82%) patients responded by week 14 and 32 (64%) were in clinical remission; 26/50 (52%) achieved corticosteroid-free remission (CSFR). At last follow-up (44 weeks; interquartile range [IQR], 30–52 weeks), 27/35 (77.1%) patients with available data responded to treatment; 24/35 (68.6%) were in clinical remission, 21/35 (60%) were in CSFR. For UC, 116/134 (79.1%) responded to treatment by week 14, including 53 (39.5%) in clinical remission; 49/134 (36.6%) achieved CSFR. At last follow-up (42.5 weeks; IQR, 30–52 weeks), 79/103 (76.7%) patients responded to treatment, 69/103 (67.0%) were in remission, and 61/103 (59.2%) were in CSFR. Adverse effects were reported in 20 (11%) of the patients, leading to treatment discontinuation in 6 (3.3%).

Conclusions: VDZ is similarly effective in ant-TNF-naïve CD and UC patients. The efficacy is higher than reported in anti-TNF-experienced patients and is comparable to that of anti-TNF biologics in this population.

Key Words: vedolizumab, Crohn's disease, ulcerative colitis, anti-TNF-naïve

INTRODUCTION

Vedolizumab (VDZ) is a humanized monoclonal antibody that targets the alpha 4 beta 7 integrin, characteristically expressed by gut-homing lymphocytes and recognized by mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1) on endothelial cells. VDZ decreases gut inflammation by limiting lymphocyte recruitment from the blood to the intestinal lamina propria. The efficacy of VDZ in patients with Crohn's disease (CD) and ulcerative colitis (UC) was demonstrated in the GEMINI trials.[1–4] In the GEMINI I study (UC), VDZ was more effective in anti–tumor necrosis factor (TNF)–naïve patients in comparison with anti-TNF-experienced patients at both week 6 (53.1% and 26.3%, respectively; $P < 0.05$) and week 52 (39.0% and 20.6%; $P < 0.05$).[5] In CD trials, the remission rates in VDZ arms were significantly higher compared with placebo in the GEMINI II study, which included a mix of anti-TNF-experienced and -naïve patients; however, in the GEMINI III study, which included only patients who failed anti-TNF treatment, the difference was significant only at week 10 and not week 6 (defined as the primary outcome).[3,4] Overall, the rate of remission in both CD studies was numerically higher in anti-TNF-naïve CD patients at week 6 (22.7 vs 13.3%, respectively), and also at week 52 (48.9% vs 27.7% in week 6 responders).[6]

Since the approval of VDZ by regulatory authorities, several real-world cohort studies describing the effectiveness and safety of VDZ, enrolling more than 1500 patients, have been published.[7–15] The effectiveness of VDZ in CD varied between 37% and 64% for response and 24% and 42% for remission at week 14, respectively; for UC, the rates of response and remission were 37%–57% and 24%–26%, respectively.[16] However, more than 90% of the patients included in these studies had previously failed at least 1, and in most cases 2, anti-TNF agents.[7,8,11–14,17–19] Therefore, the aim of our study was to evaluate the effectiveness and safety of VDZ as induction and maintenance treatment in a real-world cohort of anti-TNF-naïve patients with inflammatory bowel disease (IBD).

METHODS

We performed a retrospective, observational pooled European multicenter study aiming to assess the effectiveness and safety of VDZ in anti-TNF-naïve patients with CD and UC. The study protocol was reviewed and approved by the Clinical Research Committee (ClinCom) of the European Crohn's and Colitis Organization (ECCO). The study call was advertised to all ECCO members. Only ECCO members who

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could provide a complete list of anti-TNF-naïve IBD patients who had started vedolizumab were eligible to participate.

Inclusion Criteria

All anti-TNF-naïve adult IBD patients with active disease who received at least 1 infusion of VDZ and were followed for at least 14 weeks were eligible for inclusion. Active disease was defined as any of the following: for CD: Harvey Bradshaw Index (HBI) >4, Crohn's disease activity index (CDAI) >150; for UC: Lichtiger score >4; simple clinical colitis activity index (SCCAI) >2, partial Mayo score ≥2. We assessed the clinical, laboratory, and endoscopic characteristics at baseline, week 14, week 30, and week 52.

Vedolizumab Dosing

VDZ was administered intravenously at a standard dosing regimen (300 mg at weeks 0, 2, and 6, followed by q8w maintenance dosing). Some of the participating centers administered an additional VDZ dose of 300 mg at week 10 in CD patients as standard practice. In addition, the interval between VDZ infusions could be shortened (to q4/q6 weeks) in some of the patients with primary or secondary nonresponse, per discretion of the treating physician and local reimbursement guidelines or availability of a medical need program.

Study Definitions

The clinical, endoscopic, and laboratory data for each timepoint were extracted from the patients' clinical charts and electronic records. As this was a retrospective multicenter study, there was a need to combine several clinical scores into a single clinical severity model. Baseline clinical severity was defined as follows: 0: clinical remission; 1: mild disease; 2: moderate disease; 3: severe disease using the appropriate definitions for each clinical score (Supplementary Table 1). Clinical severity was reassessed at week 14, week 30, and week 52 in patients reaching those time points, per availablity. Clinical response was defined as an improvement of at least 1 severity score category. Clinical remission for CD was defined as HBI ≤4, CDAI <150; for UC: Lichtiger score <4; SCCAI <2, partial Mayo score ≤1. Steroid-free remission was defined as clinical remission without systemic corticosteroid treatment. The authors did not request the individual components of the clinical scores from the investigators and used the reported calculated values. In absence of clinical scores, Physician's Global Assessment (PGA) could be used, provided that in the presence of bloody stools, the patient was regarded as nonresponse.

Induction outcomes were calculated at week 14. Maintenance outcomes were established per the last follow-up after week 14 (the latest of week 30/52); if the patient continued treatment after week 14 but no data for remote time points were available, we excluded that patient from the analysis of maintenance outcomes.

Secondary loss of response (LOR) was defined as clinical exacerbation after initial clinical response achieved by week 14 (induction). Need for surgery and initiation of corticosteroids or immunomodulators during the course of treatment were also considered loss of response. Dose adjustments for VDZ were not considered loss of response as long as other definitions of secondary loss of response were not met and the patient maintained clinical response at the next time point. Dose escalation was defined as a shortening of duration between VDZ infusions to less than 8 weeks; administration of a single additional dose at week 10 (available in some jurisdictions) was not considered dose escalation if the patient continued to receive VDZ q8w from week 14 onwards.

Endoscopic activity was assessed for UC using the endoscopic Mayo subscore. Mucosal healing was defined as an endoscopic Mayo score of 0 or 1; endoscopic response was defined as a drop of at least 1 point in the endoscopic Mayo subscore. For CD, we used the following scale; for baseline evaluation: 0, absence of ulcerations (mucosal healing); 1, presence of ulcerations; for follow-up endoscopy: mucosal healing was defined as the absence of ulcerations at follow-up endoscopy in patients who had ulcerations at baseline ileocolonoscopy; endoscopic response was defined as clear endoscopic improvement but with detectable ulcerations.[20]

Concomitant immunomodulator therapy was defined as co-treatment with a thiopurine or methotrexate during the induction of VDZ therapy.

Study Outcomes

Primary outcome was defined as clinical response at week 14. Main secondary outcomes included the following: clinical remission by week 14; steroid-free clinical remission at week 14; C-reative protein (CRP) normalization at week 14 in patients with elevated baseline CRP; clinical response, remission, steroid-free remission at the last follow-up; secondary loss of response; endoscopic response; and mucosal healing.

Safety Events

Adverse events were recorded, and safety data are reported from the safety population (patients who received at least 1 dose of vedolizumab). The results are expressed using Medical Dictionary of Regulatory Activities (MedDRA) 18.1 terminology.[21]

Statistical Analysis

Descriptive statistics are presented as means ± standard deviations for parametric variables and medians with interquartile ranges (IQRs) for nonparametric continuous variables, and percentages for categorical variables. Categorical variables were analyzed by chi-square/Fisher exact test and continuous variables by *t* test/Mann-Whitney test, as appropriate. A 2-tailed *P* value <0.05 was considered statistically significant.

We constructed a multivariate logistic regression model to identify the independent predictors of week 14 response. Variables with significance level <0.1 on univariate analysis were included in the multivariate model. To investigate the effect of the variables on VDZ discontinuation, we performed a survival analysis using a Cox multivariate proportional hazard model. The model included variables with a significance level <0.1 on univariate analysis. The analysis was performed using IBM SPSS (version 20.0; Armonk, NY, USA).

RESULTS

Study Population

A total of 184 consecutive IBD patients (CD: 50, 27.2%; UC: 134, 72.8%) from 23 centers in 9 countries (Belgium, Finland, France, Greece, Germany, Italy, Israel, Switzerland, United Kingdom) who initiated VDZ treatment between January 2015 and March 2017 were included. The median duration of follow-up (IQR) was 30 (14–48) weeks. The clinical and demographic characteristics of the included patients are detailed in Tables 1 and 2. Eighty (43.4%) patients had a relative contraindication to anti-TNF therapy or a safety concern that led to selection of a non-anti-TNF biologic agent (35 [19%]: history of malignancy or premalignant condition; 5 [2.7%]: latent tuberculosis or history of active tuberculosis; 10 [5.4%]: other major infections in the past under immunosuppressive treatment; 7 [3.8%]: history of demyelinative disease; 10 [5.4%]: advanced age; 12 [5.4%]: congestive heart failure or ischemic heart disease, 1 [0.5%]: severe chronic obstructive pulmonary disease). The study flow is described in Figure 1. Baseline clinical scores were available for all patients, week 14 clinical scores for 175/184 (95.4%) and at last follow-up for 132/138 (95.6%) patients (PGA was used for the remaining patients).

TABLE 1: Clinical Characteristics of the Included Crohn's Disease Patients

Characteristic		n = 50
Median (IQR) age, y		49 (33–67)
Median (IQR) age at disease onset, y		32 (23–50)
Sex	Male, No. (%)	27 (54)
	Female, No. (%)	23 (46)
CD location	Ileal, No. (%)	14 (28)
	Colonic, No. (%)	12 (24)
	Ileocolonic, No. (%)	24 (48)
CD behavior	Nonstricturing nonpenetrating, No. (%)	32 (64)
	Structuring, No. (%)	12 (24)
	Penetrating, No. (%)	6 (12)
Perianal disease, No. (%)		6 (12)
Prior surgery for Crohn's disease, No. (%)		18 (36)
Smoking status	Never, No. (%)	29 (58)
	Current, No. (%)	6 (12)
	Past, No. (%)	15 (30)
Disease severity	Mild, No. (%)	19 (38)
	Moderate, No. (%)	21 (42)
	Severe, No. (%)	10 (20)
Elevated CRP, No. (%)		30/47 (67)
Systemic corticosteroids at treatment onset, No. (%)		18 (36)
Concomitant immunomodulators at treatment onset, No. (%)		7 (10.5)

Clinical Outcomes

Crohn's disease

Induction outcomes. Forty-two (84%) patients responded by week 14, and 32 (64%) were in clinical remission; 26/50 (52%) achieved corticosteroid-free remission, including 7/18 (38.9%) patients treated with systemic corticosteroids at baseline (Fig. 2). An additional week 10 dose was administered in 22 (44%) patients. The response rate by week 14 in patients who received an additional week 10 dose was 21/22 (94.5%) vs 21/28 (75%; $P = 0.064$)

CRP values at weeks 0 and 14 were available for 36 patients and normalized in 9/26 (36.1%) patients with elevated baseline CRP levels. None of the clinical or demographic parameters were significantly associated with the likelihood of response (Table 3).

TABLE 2: Clinical Characteristics of the Included Ulcerative Colitis Patients

Characteristic		n = 134
Median (IQR) age, y		45 (34–63)
Median (IQR) age at disease onset, y		34 (26–53)
Sex	Male, No. (%)	73 (54.5)
	Female, No. (%)	61 (45.5)
UC location	Rectum, No. (%)	8 (6)
	Left-sided, No. (%)	42 (31.6)
	Extensive, No. (%)	83 (62.4)
Smoking status	Never, No. (%)	94 (70.1)
	Current, No. (%)	5 (3.7)
	Past, No. (%)	35 (26.1)
Disease severity	Mild, No. (%)	43 (32.1)
	Moderate, No. (%)	71 (53.0)
	Severe, No. (%)	20 (14.9)
Elevated CRP, No. (%)		72 (56.3)
Median (IQR) CRP, mg/L		…
Systemic corticosteroids at treatment onset, No. (%)		63 (47)
Concomitant immunomodulators at treatment onset, No. (%)		33 (23.9)

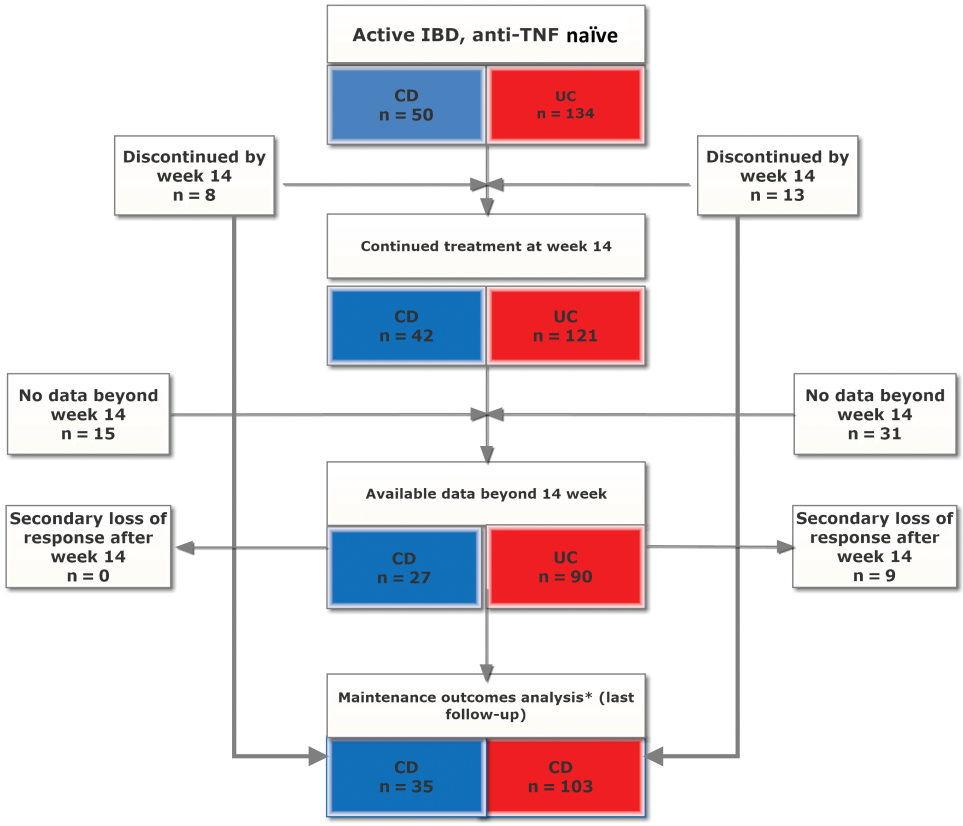

FIGURE 1. Study flow.

VDZ was continued in 42/50 (86%) patients after week 14. Treatment was discontinued in 8 patients (6 primary failure, 2 due to adverse events [1 arthralgia and 1 neutropenia]).

Maintenance outcomes. Maintenance data were available for 35/50 (70%) patients (median duration of follow-up [IQR], 44 [30–52] weeks). At last follow-up, 27/35 (77.1%) responded to treatment; 24/35 (68.6%) were in clinical remission; 21/35 (60%) were in corticosteroid-free remission, including 9/13 (69.2%) patients on baseline corticosteroids. CRP levels were available in 26 patients and were normal in 17 (65.4%); CRP normalized in 3/10 (30%) patients with elevated baseline and available last follow-up CRP levels. VDZ was discontinued in 2 patients due to adverse events (relapse of sarcoidosis and arthralgia) at week 30. All other patients continued treatment at last follow-up. Two patients received escalated VDZ dosing starting with week 10 (q4w); both continued VDZ at their last follow-up. Overall, VDZ was discontinued in 10/50 (20%) CD patients.

Ulcerative colitis. One hundred thirty-four patients were included. One hundred and six patients (79.1%) responded to treatment by week 14, including 53 patients (39.5%) in clinical remission. Steroid-free remission was achieved in 49/134 (36.6%) patients, including 20/63 (31.7%) patients on corticosteroids at baseline.

CRP values at weeks 0 and 14 were available for 122 patients, and they normalized in 32/72 (44.4%) of those with an elevated CRP at baseline. The only clinical parameter significantly associated with the likelihood of response at week 14 was baseline disease severity (Table 4).

VDZ was continued in 121/134 (90.3%) after week 14. Treatment was discontinued in 13 patients for primary nonresponse (n = 9), adverse events (n = 2, tinnitus and cholestasis, respectively), or administrative reasons (n = 1). One patient (82 years old with a history of ischemic and valvular heart disease) died from acute myocardial infarction that was deemed unrelated to therapy 18 weeks after his first VDZ infusion; week 14 outcome was not documented. An additional patient (89 years old with preexisting ischemic and valvular heart disease) died from exacerbation of ischemic heart disease deemed unrelated to treatment.

Maintenance data were available for 103/134 (median duration of follow-up [IQR], 42.5 [30–52] weeks); 103 patients were included for analysis of maintenance outcomes. At last follow-up, 79 (76.7%) patients responded to treatment, 69 (67.0%) were in remission; 61 (59.2%) were in corticosteroid-free remission, including 25/48 (52.1%) patients on corticosteroids at baseline. CRP was normal in 61/91 (67%) patients with available CRP levels at last follow-up, including 29/53

TABLE 3: Clinical Variables Associated With Clinical Response at Week 14, Crohn's Disease

Characteristic		Nonresponse (n = 8), No. (%)	Response (n = 42), No. (%)	*P*
Sex	Male	6 (75)	21 (50)	0.7
	Female	2 (25)	21 (50)	
CD location	Ileal	0 (0.0)	14 (33.3)	0.15
	Colonic	3 (37.5)	9 (21.4)	
	Ileocolonic	5 (62.5)	19 (45.2)	
CD behavior	Nonstricturing nonpenetrating	4 (50.0)	27 (65.9)	0.47
	Stricturing	2 (25.0)	10 (24.4)	
	Penetrating	2 (25.0)	4 (9.8)	
Perianal disease		2 (25.0)	4 (9.8)	0.22
Prior surgery for Crohn's disease		2 (25.0)	38 (90.5)	0.42
Smoking status	Never	4 (50.0)	25 (59.5)	0.86
	Current	1 (12.5)	5 (11.9)	
	Past	3 (37.5)	12 (28.6)	
Disease severity	Mild	2 (25.0)	16 (38.1)	0.52
	Moderate	5 (62.5)	17 (40.5)	
	Severe	1 (12.5)	9 (21.4)	
Active ulcerations on endoscopy		4/5 (80.0)	28 (96.6)	0.15
Elevated CRP		6 (75.0)	24 (61.5)	0.47
Systemic corticosteroids at treatment onset		2 (25.0)	16 (38.1)	0.48
Concomitant immunomodulators at treatment onset		1 (12.5)	4 (9.5)	0.81
Additional week 10 VDZ dose		1 (12.5)	21 (50)	0.06

TABLE 4: Clinical Variables Associated With Clinical Response at Week 14, Ulcerative Colitis

Characteristic		Nonresponse (n = 28), No. (%)	Response (n = 106), No. (%)	*P*
Sex	Male	15 (53.6)	58 (54.7)	1.00
	Female	13 (46.4)	48 (45.3)	
UC location	Rectum	1 (3.6)	7 (6.7)	0.55
	Left-sided	11 (39.3)	32 (29.5)	
	Extensive	16 (57.1)	67 (63.8)	
Smoking status	Never	23 (82.1)	71 (67.0)	0.27
	Current	0 (0.0)	5 (4.7)	
	Past	5 (17.9)	30 (28.3)	
Disease severity	Mild	15 (53.6)	28 (26.4)	0.02
	Moderate	11 (39.3)	60 (56.6)	
	Severe	2 (7.1)	18 (17.0)	
Mayo subscore on index endoscopy	0	0 (0.0)	2 (2.1)	0.46
	1	0 (0.0)	6 (6.2)	
	2	11 (55)	39 (40.6)	
	3	9 (45)	49 (51.4)	
Elevated CRP		16 (64.0)	56 (54.4)	0.38
Systemic corticosteroids at treatment onset		13 (46.4)	50 (47.2)	0.94
Concomitant immunomodulators at treatment onset		6 (21.5)	26 (24.5)	0.52
Additional week 10 VDZ dose		0 (0)	11 (10.4)	0.12

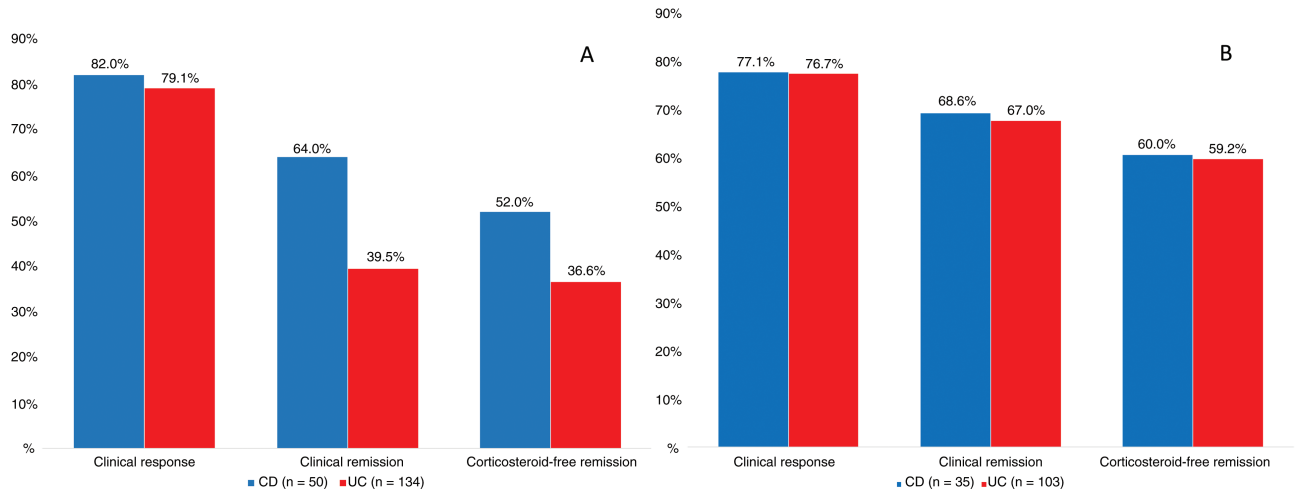

FIGURE 2. Efficacy of vedolizumab in Crohn's disease and ulcerative colitis. A, Week 14. B, Last follow-up.

(54.7%) patients with elevated baseline CRP. Treatment was discontinued in 9 (8.7%) after week 14 (median time to discontinuation [IQR], 30 [20–39] weeks). Seventy out of 90 patients (18.9%) were receiving escalated VDZ dosing after week 14 (15, q4w; 2, q6w). Among patients who continued treatment and had available follow-up data beyond week 14, secondary loss of response was developed in 9/90 (10%). Four patients responded to dose escalation (infusion every 4 weeks), and treatment was discontinued in 5 additional patients. Overall, VDZ was discontinued in 18/124 (14.5%) patients for the entire duration of follow-up.

On Cox proportional hazard analysis, the only variable that was correlated with drug discontinuation was disease severity >1 at week 14 (hazard ratio [HR], 0.12, 95% CI, 0.26–0.69, $P = 0.009$) (Fig. 3A) Dose escalation was not significantly associated with the risk of VDZ discontinuation (HR, 50.1; 95% CI, 0.3–82; $P = 0.15$)

The overall drug discontinuation rates for UC and CD did not differ significantly ($P = 0.33$) and are depicted in Figure 3B.

Endoscopic Outcomes

Crohn's disease

Baseline endoscopy was available for 34/50 (68%) patients (median [IQR], 4.5 [2–9] weeks before treatment onset) and demonstrated active ulcerations in all. Follow-up

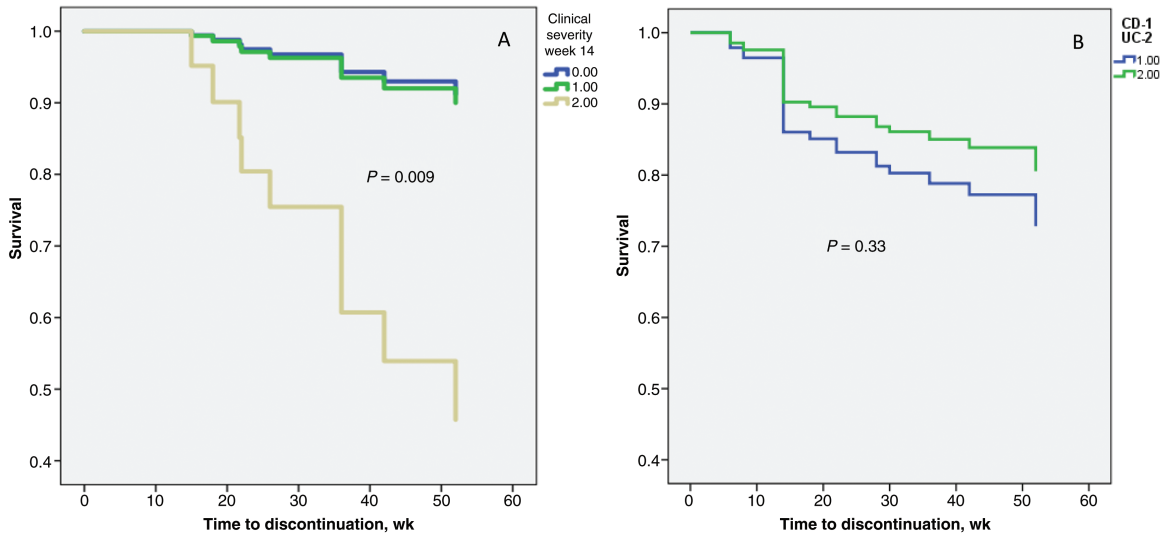

FIGURE 3. Survival analysis for discontinuation of vedolizumab. A, Cox proportional hazard analysis for vedolizumab discontinuation after week 14 (UC; clinical remission; 1: mild severity; 2: moderate severity). B, Cox proportional hazard analysis for vedolizumab discontinuation for the duration of the treatment (CD and UC).

endoscopy was available in 11 patients after 26 (IQR, 14–32) weeks. Endoscopic improvement was achieved in 8/11 (63.7%) patients with available data; mucosal healing was achieved in 5/11 (45.5%) patients.

Ulcerative colitis

Endoscopic Mayo subscore >1 was detected in 108 patients at baseline endoscopy (1 week before treatment onset; IQR, 1–5 weeks). A follow-up endoscopy (performed after 14 weeks from initiation of treatment; IQR, 10–23 weeks) was available in 55 (51%) patients with active ulcerations at baseline. Mucosal healing was achieved in 31 (58.5%) patients.

Safety

The adverse events that were documented during the entire follow-up period are listed in Table 5. Overall, 20 (11%) patients reported adverse events. VDZ was discontinued in 6 patients (2 arthralgia, 1 neutropenia, 1 sarcoidosis flare-up, 1 tinnitus, 1 cholestasis). Two CD patients required surgical intervention (1 ileocolonic resection, 1 perianal abscess drainage); 5 UC patients underwent total colectomy, and 1 required liver transplantation for known PSC. Two patients with preexisting severe heart disease died.

DISCUSSION

This large multicenter study demonstrates the effectiveness of vedolizumab as a firstline biologic in IBD in a real-world setting. At week 14, 82% of CD and 79.1% of UC anti-TNF-naïve patients responded to treatment. At last follow-up, 77.1% of CD and 76.7% of UC patients responded to VDZ. In the GEMINI studies, VDZ seemed to be substantially more effective in both UC and CD in anti-TNF-naïve patients compared with patients who previously failed anti-TNFs. Since the approval of VDZ, several real-world experience (RWE) series with VDZ have been published, demonstrating response rates of 37%–64% for CD and 37%–57% for UC at week 14, respectively. However, the number of anti-TNF-naïve patients in these studies was quite small (<10%), and as a consequence, none of them addressed anti-TNF-naïve patients as a separate subgroup. Moreover, VDZ was a third biologic in most of these patients. Although our study was not comparative (we excluded anti-TNF-experienced patients), it seems that the rates of response and remission are substantially higher in biologic-naïve patients in comparison with previous series. Similarly, RWE studies with anti-TNF biologics demonstrated decreasing effectiveness with each previous agent failure.[22, 23]

In recent RWE series, the response rate to infliximab for biologic-naïve patients approximated 89%,[24, 25] with sustained long-term response in >60%.[26] In UC, initial response was reported in 68%, and two-thirds of these experienced long-term benefit.[27] In CD, initial response to adalimumab was achieved in 89% of anti-TNF-naïve patients.[25] In a recent Spanish cohort study, adalimumab therapy was associated with a response rate of 61% in anti-TNF-naïve and 47% in anti-TNF-experienced UC patients.[28] For golimumab, response rates were 75% as first anti-TNF, 70% as second anti-TNF, and 50% as third anti-TNF.[22] Our results are well in line with the response rates of anti-TNF biologics in the biologic-naïve patients reported. Interestingly, even though VDZ was less effective in CD than UC in the GEMINI studies, particularly in anti-TNF failures, this is not the case in RWE studies, including the current one, where the response rates are quite similar.[8, 10, 12, 13, 29]

The rapidity of response to vedolizumab is still a matter of concern in the IBD community. However, a recent post hoc analysis from GEMINI 1 demonstrated that a substantial improvement in stool frequency and rectal bleeding can be detected as early as week 2 and is more robust at week 6; the effect was more solid in anti-TNF-naïve patients.[30] In recent real-world evidence studies that included <10% of anti-TNF-naïve patients, clinical response was achieved in up to 43%, and remission in up to 25% of UC patients by week 6.[7–9, 11, 16] In our

TABLE 5: Adverse Effects During Vedolizumab Treatment Using MedDRA 18.1 Terminology

Preferred Term	System Organ/Class	CD	UC
Arthralgia	Musculoskeletal and connective tissue disorders	2	4
Nasopharyngitis	Infections and infestations	2	1
Headaches	Nervous system disorders		2
Clostridium difficile colitis	Infections and infestations		1
Cholestasis	Hepatic disorder		1
Herpes zoster	Infections and infestations		1
Neutropenia	Hematopoetic neutropenia	1	
Pleurisy	Pleural infections and inflammations		1
Pneumonia	Infections and infestations	1	
Sarcoidosis flare-up	Interstitial lung disease	1	
Tinnitus	Hearing impairment		1

study, we were not able to access the rapidity of response due to the limitations of the study format.

Generally, the efficacy in retrospective RWE series seems to be higher than in corresponding randomized controlled studies. The main reasons for that include less stringent definitions of response and remission (such as utilization of PGA instead of clinical scores), missing laboratory and endoscopic data, and in some cases persistence of not clearly beneficial treatment in the face of a lack of alternatives (with some patients indeed benefitting from the treatment at a later phase). We tried to avoid those pitfalls by using validated clinical scores as much as possible (in more than 95% of our patients); CRP levels were available for at least 70% of the patients at week 14.

In addition, RWE studies commonly utilize more remote time points to define response and remission. In the GEMINI studies, response and remission were evaluated at week 6 (in GEMINI II, also at week 10 as a secondary outcome), whereas most RWE series including ours extended the duration until week 14. Currently, there is no clear definition as to what constitutes primary nonresponse to biologics; for practical matters, it is pertinent to evaluate the response after completion of full induction for anti-TNF agents.[31] With the mostly similar dosing schedules for VDZ and infliximab, we applied the same definition in our study as well.

The safety profile of VDZ in our study was very favorable and consistent with the data from randomized controlled trials and other RWE series. Only 3.3% of the patients in our study had to discontinue treatment due to adverse effects. No new safety signals were identified in this multicenter cohort.

Our study has several limitations, mostly attributed to its retrospective multicenter design. In such setting, we can expect significant heterogeneity in treatment strategies and patient management and assessment policy; moreover, endoscopic and laboratory data were not universally available. Minor adverse events could have been underreported due to a potential recall bias. These limitations are not unique to our study and are similar to all multicenter RWE series. An additional limitation is the noncomparative design of our study; we did not include anti-TNF-experienced patients to avoid reproduction of RWE series that provided a multitude of data on these patients. We also did not include comparator arms of patients treated with other biologics. In addition, vedolizumab levels were not available to most of the centers in our study. Lack of data pertaining to response of extraintestinal manifestations to VDZ is another limitation of this study.

Our results suggest that vedolizumab is at least as effective and safe as anti-TNF biologics in biologic-naïve patients and that it can be used very effectively in these patients. The possibly slower onset of the effect is a potential drawback; however, this was not explored in the current study. The efficacy seems to be diminished in anti-TNF-exposed patients; however, this is not unique to VDZ, and a similar trend can be detected with all biologics. As vedolizumab is a relatively new drug, it is still mostly used in patients who previously failed anti-TNF biologics; nevertheless, the excellent safety profile and at least comparable efficacy challenge this predisposition.

With the recent addition of ustekinumab and the pending dawn of the era of small molecules, our therapeutic arsenal in IBD is rapidly expanding. One of the major challenges of the coming years is the creation of an individualized treatment approach using integrative models that utilize clinical pharmacological, genetic, serologic, and microbial data to predict susceptibility to targeting of specific molecular pathways and medications. Such studies, which are urgently needed, are likely to override our current treatment paradigm and provide individualized treatment algorithms for our patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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