Effectiveness and persistence of Vedolizumab in patients with inflammatory bowel disease : results from the Belgian REal-LIfe study with VEdolizumab (Be-RELIVE)

C. Reenaers[1], A. Cremer[2], O. Dewit[3], B. De Vroey[3,4], W. Van Moerkercke[5], P. Bossuyt[6], V. Muls[7], J. Imschoot[8], S. Block[8], A. Hantson[8], P. Van Hootegem[9]

(1) Centre Hospitalier Universitaire de Liège, Avenue de l'Hôpital 1, 4000 Liège, Belgium ; (2) Cliniques Universitaires de Bruxelles, Hôpital Erasme, Brussels, Belgium ; (3) Clinique Universitaire Saint-Luc, Brussels, Belgium ; (4) Centre Hospitalier Jolimont, Haine-Saint-Paul, Belgium ; (5) Algemeen Ziekenhuis Groeninge, Kortrijk, Belgium ; (6) Imelda GI Clinical Research Centre, Bonheiden, Belgium ; (7) Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium ; (8) Takeda Belgium, Zaventem, Belgium ; (9) Algemeen Ziekenhuis Sint-Lucas Brugge vzw, Brugge, Belgium.

Abstract

Background and study aims : **Vedolizumab (VDZ) is a gut-selective integrin inhibitor used to treat Crohn's disease (CD) and ulcerative colitis (UC). This retrospective study assessed effectiveness and treatment persistence of VDZ in a Belgian real-life cohort of CD and UC patients.**

Patients and methods : **CD and UC patients from 15 Belgian centers, who started VDZ between 01/09/2015 and 31/06/2016 and attended ≥1 visit after the first VDZ infusion, were included. Data were collected before first infusion, at week (W)10, W14 (CD patients only), month (M)6 and last follow-up. Treatment response and remission rates (changes in disease activity scores) and treatment persistence (Kaplan-Meier analysis) were assessed.**

Results : **Of the 348 patients receiving at least one dose of VDZ, 325 (202 CD, 45 biologic-naïve; and 123 UC, 42 biologic-naïve) patients were included in data analyses. At M6, 87.6% (176/201) of CD and 86.1% (105/122) of UC patients were still on VDZ treatment, 75.6% (34/45) and 83.9% (26/31) achieved clinical response, and 66.7% (44/66) and 42.9% (15/35) were in remission. At M6 remission rates was significantly higher while response rates tended to be higher among biologic-naïve versus biologic-failure CD patients.**

Conclusions : **VDZ offers an effective treatment option in real-life settings and treatment effectiveness appears higher in biologic-naïve versus biologic-failure CD patients.** (Acta gastroenterol. belg., **2020**, 83, **15-23**).

Keywords : vedolizumab, real-life, treatment persistence, effectiveness, treatment predictors, inflammatory bowel disease

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of inflammatory bowel disease (IBD), which is a collective term for chronic, idiopathic and relapsing inflammatory conditions of the gastrointestinal tract (1). Conventional treatment options for IBD encompass 5-aminosalicylic acid (5-ASA) compounds (for UC), steroids, immunomodulators and biologics (1). With the introduction of anti-tumor necrosis factor alpha (TNFα) antibodies, medical treatment options in IBD have improved dramatically over the last decades. However, refractory disease and loss of response over time remain major challenges. Primary non-response to anti-TNFα antibodies is observed in 20% to 30% of CD (2-8) and up to 40% of UC patients (9,10). Up to 46% of primary responders relapse, despite continued treatment or dose escalation, with anti-TNFα therapy discontinuation occurring in a substantial proportion of patients after one year in randomized-controlled trials (11,12).

Vedolizumab (VDZ) is a humanized monoclonal antibody that specifically recognizes the α4β7 heterodimer and selectively blocks gut lymphocyte trafficking. Previous real-life data from a Belgian study conducted in UC and CD patients refractory to anti-TNFα treatment demonstrated that VDZ administration resulted in a clinical response in up to 70% of patients 10 to 14 weeks (W) post-treatment initiation (13). Real-life evidence from a study in the United States (US) also demonstrated its effectiveness with a 12-month (M) cumulative remission rate of 35% and mucosal healing of 63% (14).

While most of the available real-life data with VDZ were obtained from patients who were previously treated with biologics (13-16), this retrospective study aimed to collect real-life evidence on the effectiveness, treatment persistence and safety of VDZ in biologic treatment-naïve patients as well as in patients who received prior anti-TNFα treatment. Evaluating treatment effectiveness and safety the real-life and identifying predictors of treatment response will help to determine the optimal positioning of VDZ in routine clinical practice.

Patients/materials and methods

Patient recruitment

We performed a retrospective, descriptive, longitudinal study in 15 Belgian hospitals including patients of 18 years or older, with moderately to severely active UC or CD, who initiated VDZ treatment between September 1st, 2015 and July 31st, 2016 (eligibility period) and who attended at least one visit after the first VDZ infusion. Both anti-TNF-naïve and anti-TNFα-treatment-failure

Correspondence to : C. Reenaers, Centre Hospitalier Universitaire de Liège, Avenue de l'Hôpital 1, 4000 Liège, Belgium.
E-mail : catherine.reenaers@chu.ulg.ac.be

Submission date : 07/03/2019
Acceptance date : 14/09/2019

CD and UC patients participated in the study. Patients were excluded if they received VDZ treatment as part of an interventional study or via a Medical Need Program.

Objectives

The primary objective of the study was to determine the effectiveness of VDZ in terms of clinical response and remission rates after induction (at W10 +/-2W for UC and W14 +/-2W for CD) and during maintenance (at M6), and treatment persistence rates at last follow-up visit in CD and UC patients who initiated VDZ during the eligibility period and with at least one visit after the first VDZ infusion.

Secondary objectives aimed to identify predictors of clinical remission, clinical response, mucosal healing and treatment discontinuation and to establish clinical characteristics of patients receiving VDZ. The following criteria were analyzed: patients characteristics (age, sex, gender, smoking status) disease characteristics (IBD type, disease duration, age at diagnosis, disease behavior and location), previous anti-TNF exposure, concomitant medications with CS or IS drugs, previous IBD surgery, extra-intestinal manifestations, HB or Mayo score at treatment initiation, CRP at treatment initiation.

Definitions and data collection

Anti-TNFα-failure patients included patients who had a primary non-response, loss of response or were intolerant to anti-TNFα. Disease activity in UC was determined using the full Mayo score, if available, or partial Mayo score (10,17) and in CD patients, using the Harvey-Bradshaw index (HBI) (18), and physician assessment. The full Mayo-score without endoscopic sub-score is understood as the partial Mayo-score (10). Clinical response was defined as a drop of at least one severity category for the relevant clinical score (HBI or full/partial Mayo score) and clinical remission as a Mayo score ≤2 and an HBI score ≤4. The presence of inflammatory mucosal lesions was evaluated at baseline, W10 or W14 and M6 using endoscopy. Mucosal healing was defined as an endoscopic sub-score ≤1. Mucosal healing was assessed for UC at W10 and M6. Treatment persistence was defined as the absence of an interruption of the treatment at different time points (W10, W14, M6 and/or last follow-up visit) and was expressed in percentage. The reasons for VDZ treatment initiation and discontinuation, the need for VDZ dose escalation (i.e., to every 4W [Q4W]), the rate of mucosal healing at W10 in UC patients and the identification of potential treatment outcome predictors were also analyzed.

Data were collected retrospectively in the patient dossier by site personnel using a web-based tool at baseline (before first infusion), W10, W14 (CD patients only), M6 and/or last follow-up visit. Last data points were collected up to January 31st, 2017.

The study was carried out in compliance with the protocol and the Sponsor's and the Contract Research Organization's standard operating procedures. Data privacy was maintained at all times during the study. As only anonymized data were collected, and aggregated data were returned for analysis, no informed consent of the patients was required. As per Belgian law, this retrospective study falls outside the scope of clinical trial legislation and therefore does not require approval by a medical institutional ethics committee or an institutional review board. However, a notification was submitted to the institutional ethics committee of the participating centers.

Safety assessment

Adverse events (AEs), serious (S)AEs and special situation reports (SSRs) were documented during the entire study period. SSR included events such as pregnancy, breast feeding, overdose, suspected transmission of an infectious agent, lack of efficacy of the medicinal product, occupational exposure, off-label use, use of falsified medicinal product and product quality issue.

Statistical analysis

For descriptive statistics, continuous variables were summarized by mean as central value and standard deviation and range (minimum – maximum) as measure of dispersion. Categorical variables were summarized by number of observations and percentages. Missing data were excluded of the base for calculating percentages of patients.

Treatment persistence in CD and UC patients was described by Kaplan-Meier curves and the median persistence times, together with the 95% confidence limits, were reported. Logistic regression and/or univariate COX regression analyses were used to identify potential predictive factors. The effect of each independent predictor was summarized by the p-value and/or by the odds ratio (OR) and its 95% confidence interval (CI). A predictor had a significant impact if the CI of the OR did not cover 1.

Statistical analyses were performed using SAS version 9.4 (SAS Inst. Inc., Cary, NC), the PROC LIFETEST for the Kaplan-Meier analysis and PROC PHREG for the Cox regression analysis.

Results

Study population

Out of the 348 patients who received at least one dose of VDZ, 325 (202 CD and 123 UC) patients were included in the effectiveness data analysis (effectiveness population); the remaining 23 patients were excluded from this analysis for not meeting all inclusion criteria. All 348 patients were included in the safety population (Figure 1). In total, 22.3% (45/202) of CD and 34.1%

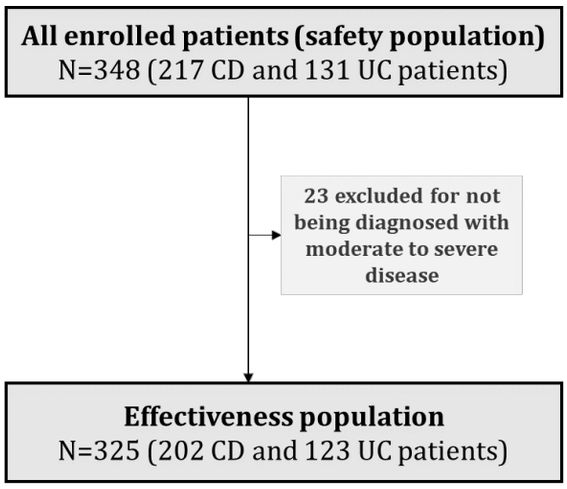

Fig. 1. — Flow Diagram
CD, Crohn's disease ; UC, ulcerative colitis ; N, number of patients.

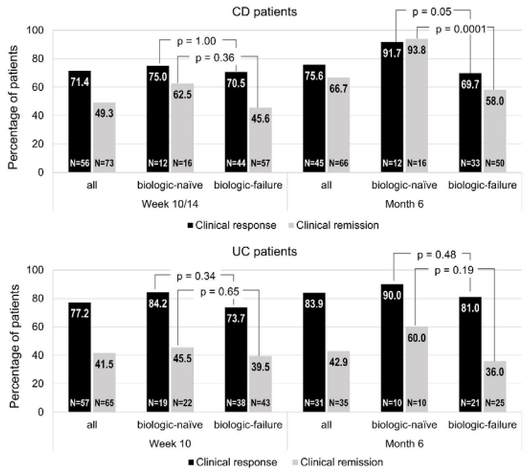

Fig. 2. — Clinical response and remission in CD and UC patients.
CD, Crohn's disease ; UC, ulcerative colitis ; N, number of patients with a known result.

(42/123) of UC patients were anti-TNFα-naïve. Overall, 24% of CD patients were on immunosuppressants and 36.5% were on corticosteroids at baseline. For UC patients, the respective percentages were 33.3% and 58.5%. Extra-intestinal manifestations seemed more common in patients who had previously been treated with anti-TNFα (CD, 54.4% anti-TNFα-failure versus 25.8% anti-TNFα -naïve and UC, 31.1% versus 17.1%, respectively) (Table 1).

For CD, 39.1% of patients failed one anti-TNFα treatment, 32.7% failed two and 5.9% failed more than two anti-TNFα therapies. The respective percentages for UC patients were 43.9%, 19.5% and 2.4%. The main reasons of VDZ initiation treatment were failure or intolerance to previous conventional therapy including aminosalicylates, immunosuppressants and corticosteroids (Supplementary Table S1). The failure was reported by 61.8% (n=76, N=123) of patients with UC disease and 57.4% (n=116, N=202) of patients with CD. Other reasons of VDZ treatment initiation were failure or intolerance to previous biological agents therapy including among others infliximab, adalimumab and golimumab (Supplementary Table S1).

Patient baseline characteristics are detailed in Table 1. For 111 CD and 34 UC patients, baseline HBI or baseline total Mayo scores were not available, therefore, further analysis depending on these data (e.g., clinical response) could not be calculated for these patients.

Table 1. — **Baseline patient and disease characteristics (effectiveness population)**

	Biologic-naïve N=87				Biologic-failure N=238			
Characteristic	CD		UC		CD		UC	
	N'	N=45	N'	N=42	N'	N=157	N'	N=81
Sex: male, n (%)	45	24 (53.3)	42	23 (54.8)	47	47 (29.9)	43	43 (53.1)
Age: years, mean (SD)	45	46.80 (17.05)	42	45.38 (16.93)	47	41.48 (13.82)	43	43.31 (14.49)
HBI: moderate/severe[a], n (%)	17	14 (82.4)/ 0 (0.0)	-	-	74	50 (67.6)/ 8 (10.8)	-	-
Mayo-score: moderate/severe[b] n (%)	-	-	29	20 (69.0)/ 9 (31.0)	-	-	60	45 (75.0)/ 15 (25.0)
C-reactive protein, mean values in mg/l (SD)	32	16.11 (19.35)	28	19.61 (38.13)	130	12.50 (19.19)	65	11.15 (14.79)
Ongoing medication, n (%)								
Aminosalicylate	45	6 (13.3)	42	20 (47.6)	155	7 (4.5)	81	33 (40.7)
Immunosuppressants	45	16 (35.6)	42	14 (33.3)	155	32 (20.6)	81	27 (33.3)
Corticosteroids	45	15 (33.3)	42	26 (61.9)	155	58 (37.4)	81	46 (56.8)
History or presence of draining fistula, n (%)	41	9 (22.0)	-	-	152	42 (27.6)	-	-
History or presence of extra-intestinal manifestation, n (%)	31	8 (25.8)	35	6 (17.1)	136	74 (54.4)	74	23 (31.1)

CD, Crohn's disease ; UC, ulcerative colitis ; HBI, Harvey-Bradshaw index ; N, total number of patients ; N', number of patients with a known status ; n (%), number (percentage) of patients within a category ; SD, standard deviation ; [a] Moderate disease : HBI of 8-16/Severe disease : HBI >16 ; [b] Moderate disease : Mayo score 6-10/Severe disease : Mayo score >10.

Supplementary Table S1. — **Reasons for Vedolizumab initiation**

Statistics or Categories	**Global population (N UC=123) (N CD=202)**	**Biologic-naïve (N UC=42) (N CD=45)**	**Biologic-failure (N UC=81) (N CD=157)**
CD patients	n (%)	n (%)	n (%)
Failure/intolerance to previous medication - Conventional therapy	116 (57.4)	17 (37.8)	99 (63.1)
Failure/intolerance to previous medication - Biological agents - Adalimumab	90 (44.6)	0 (0.0)	90 (57.3)
Failure/intolerance to previous medication - Biological agents - Infliximab	89 (44.1)	0 (0.0)	89 (56.7)
Physician decision	58 (28.7)	19 (42.2)	39 (24.8)
Failure/intolerance to previous medication - Biological agents - Other	13 (6.4)	0 (0.0)	13 (8.3)
Vedolizumab safety profile	10 (5.0)	4 (8.9)	6 (3.8)
Failure/intolerance to previous medication	9 (4.5)	3 (6.7)	6 (3.8)
Contra-indication to other biologic agent	7 (3.5)	1 (2.2)	6 (3.8)
Other*	6 (3.0)	1 (2.2)	5 (3.2)
Failure/intolerance to previous medication - Biological agents - Golimumab	3 (1.5)	0 (0.0)	3 (1.9)
Patient preference for vedolizumab	2 (1.0)	2 (4.4)	0 (0.0)
Vedolizumab efficacy data in this indication	2 (1.0)	0 (0.0)	2 (1.3)
Vedolizumab mode of administration-IV	2 (1.0)	1 (2.2)	1 (0.6)
UC patients	n (%)	n (%)	n (%)
Failure/intolerance to previous medication - Conventional therapy	76 (61.8)	18 (42.9)	58 (71.6)
Failure/intolerance to previous medication - Biological agents - Infliximab	51 (41.5)	0 (0.0)	51 (63.0)
Physician decision	37 (30.1)	17 (40.5)	20 (24.7)
Failure/intolerance to previous medication - Biological agents - Adalimumab	31 (25.2)	0 (0.0)	31 (38.3)
Failure/intolerance to previous medication - Biological agents - Golimumab	10 (8.1)	0 (0.0)	10 (12.3)
Failure/intolerance to previous medication	6 (4.9)	5 (11.9)	1 (1.2)
Vedolizumab safety profile	5 (4.1)	4 (9.5)	1 (1.2)
Vedolizumab efficacy data in this indication	5 (4.1)	4 (9.5)	1 (1.2)
Failure/intolerance to previous medication - Biological agents - Other	1 (0.8)	0 (0.0)	1 (1.2)
Contra-indication to other biologic agent	1 (0.8)	0 (0.0)	1 (1.2)
Patient preference for vedolizumab	1 (0.8)	1 (2.4)	0 (0.0)
Other*	1 (0.8)	1 (2.4)	0 (0.0)
Vedolizumab mode of administration-IV	0 (0.0)	0 (0.0)	0 (0.0)

CD, Crohn's disease ; N, total number of patients; n (%), number (percentage) of patients ; UC, ulcerative colitis ; [a]Other : patient stopped treatment due to skin problems, inadequate disease control, to reduce immunosuppression induce by anti-TNF, loss of compliance, corticosteroid dependance, pseudolupusreaction.

Efficacy evaluation

About three quarters of the patients for whom data were available achieved clinical response at W10/W14 (CD, 40/56 [71.4%] and UC, 44/57 [77.2%]) that persisted up to M6 (CD, 34/45 [75.6%] and UC, 26/31 [83.9%]) (Figure 2). At M6, 44/66 (66.7%) CD patients and 15/35 (42.9%) UC patients were in clinical remission (Figure 2). In CD patients, clinical remission rates at M6 were higher among biologic-naïve versus biologic-failure patients (p = 0.0001). In line with the higher clinical remission rate in biologic-naïve patients, clinical response rates tended to be higher among biologic-naïve compared to biologic-failure CD patients at M6 (91.7% versus 69.7%; p = 0.0518). Biologic-naïve and biologic-failure UC patients had similar clinical response and remission rates at M6 (p = 0.4791 and p = 0.1879, respectively).

In all groups, CRP levels tended to decrease from baseline to M6. While biologic-naïve patients had CRP values around the normal value at M6 (<6 mg/l; decrease from 16 mg/l to 6.3 and from 20 mg/l to 4.6 mg/l for CD and UC patients, respectively), biologic-failure patients had higher CRP levels (decrease from 12.2 mg/l to 11.4 and from 11,mg/l to 7.6 mg/l for CD and UC patients, respectively) (Supplementary Figure S1). At M6, mucosal healing was achieved in 28.1% (9/32, biologic-failure) and 30.0% (3/10, biologic-naïve) of UC patients (Figure 3). In all groups, the percentage of patients who discontinued corticosteroid treatment since baseline tended to increase from W10/W14 to M6 (40% to 60% in CD biologic naïve, from 28.8% to 60% in CD biologic failure, from 58% to 69% in UC biologic-naïve, from 41% to 63% in UC biologic failure) (Figure 4).

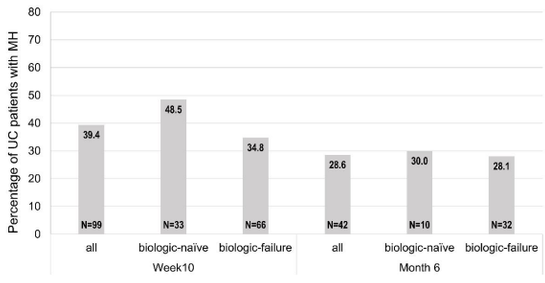

Fig. 3. — Percentage of UC patients with mucosal healing at week 10 and month 6

MH, mucosal healing ; N, total number of patient with a known result ; UC, ulcerative colitis.

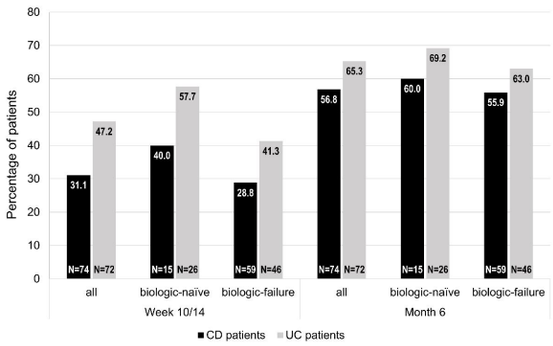

Fig. 4. — Corticosteroid discontinuation in CD and UC patients at week 10/14 and month 6

CD, Crohn's disease ; UC, ulcerative colitis ; N, total number of patients with a known result.

Table 2. — **Ongoing Vedolizumab treatment in CD and UC patients at week 10/14 and month 6**

		All N = 201	**Biologic-naïve N = 45**	**Biologic-failure N = 156**
CD, n (%)	**Week 14**	186 (93.0)	44 (97.8)	142 (91.6)
	Month 6	176 (87.6)	40 (88.9)	136 (87.2)
		All N = 123	**Biologic-naïve N = 42**	**Biologic-failure N = 81**
UC, n (%)	**Week 10**	113 (91.9)	39 (92.9)	74 (91.4)
	Month 6	105 (86.1)	37 (90.2)	68 (84.0)

CD, Crohn's disease ; N, maximum number of patients with a known status ; n (%), number (percentage) of patients with vedolizumab treatment ongoing ; UC, ulcerative colitis.

At M6, 88.9% of biologic-naïve and 87.2% of biologic-failure CD patients were still on VDZ treatment. The percentage for biologic-naïve and biologic-failure UC patients were 90.2% and 84.0%, respectively (Table 2). Failure of or intolerance to previous anti-TNFα agents did not have a significant impact on VDZ treatment discontinuation. However, persistence tended to be better among biologic-naïve CD patients (p=0.0832) (Figure 5). At M6, VDZ dose escalation to Q4W was reported for 7.3% CD patients in overall, 5.1% in biologic-naive and 8.0% in biologic-failure groups . The percentages for UC

Table 3. — **Vedolizumab dose escalation to every 4 weeks and re-escalation to every 8 weeks at month 6**

Statistics or Categories	**All (N CD=164) (N UC=104)**	**Biologic-naïve (N CD=39) (N UC=35)**	**Biologic-failure (N CD=125) (N UC=69)**
CD patients	n (%)	n (%)	n (%)
Q8W (Re-escalation or not)	151 (92.1)	37 (94.9)	114 (91.2)
Patients with vedolizumab dose escalation to Q4W	12 (7.3)	2 (5.1)	10 (8.0)
Patients with vedolizumab dose escalation different from Q4W (i.e. Q6W)	1 (0.6)	0 (0.0)	1 (0.8)
UC patients	n (%)	n (%)	n (%)
Q8W (Re-escalation or not)	94 (90.4)	33 (94.3)	61 (88.4)
Patients with vedolizumab dose escalation to Q4W	8 (7.7)	2 (5.7)	6 (8.7)
Patients with vedolizumab dose escalation different from Q4W (i.e. Q6W)	2 (1.9)	0 (0.0)	2 (2.9)

patients were 7.7% in overall, 5.7% in biologic-naïve and 8.7% in biologic-failure groups (Table 3). Reasons for dose escalation are described in Supplementary Table S2.

Predictive factors for treatment outcomes

Predictive factors for clinical remission, clinical response, mucosal healing, and treatment discontinuation in CD and UC patients at different time points are detailed in Table 4.

For CD patients, being biological-naïve was predictive of clinical remission only after M6 of treatment follow-up, while absence of immunosuppressive therapy and presence of inflammatory lesions during endoscopy at baseline were predictive factors of clinical response after W10- and M6-treatment follow-up, respectively.

For UC patients, moderate (versus severe) disease activity at baseline was a predictive factor for clinical remission after M6 of treatment follow-up. While a

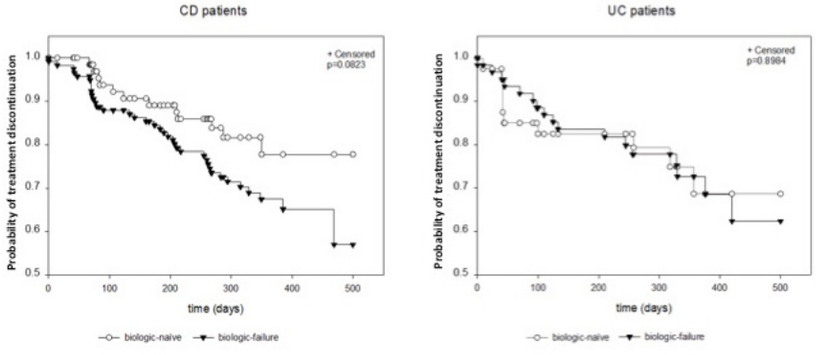

Fig. 5. — Treatment persistence in CD and UC patients

CD, Crohn's disease; UC, ulcerative colitis.

Supplementary Table S2. — **Reason for dose escalation to every 4 weeks at month** 6

Disease	**Statistics or Categories**	**All (N CD=11[a]) (N UC=8)**	**Biologic-naïve (N CD=2) (N UC=2)**	**Biologic-failure (N CD=9[a]) (N UC=6)**
	CD patients	n (%)	n (%)	n (%)
CD, (n, %)	Loss of response	9 (81.8)	2 (100.0)	7 (77.8)
CD, (n, %)	Low vedolizumab through level	0 (0.0)	0 (0.0)	0 (0.0)
CD, (n, %)	Other[b]	2 (18.2)	0 (0.0)	2 (22.2)
	UC patients	n (%)	n (%)	n (%)
UC, (n, %)	Loss of response	5 (62.5)	1 (50.0)	4 (66.7)
UC, (n, %)	Low vedolizumab through level	1 (12.5)	0 (0.0)	1 (16.7)
UC, (n, %)	Other[b]	2 (25.0)	1 (50.0)	1 (16.7)

CD, Crohn's disease ; N, total number of patients with a known status ; n, (%), number (percentage) of patients; UC, ulcerative colitis ; [a]Does not include one patient with unknown result ; [b]Other: Better response, endoscopic finding mayo 2, insufficient disease control.

Table 4. — **Predictive factors of responders**

Predictors of clinical remission, clinical response, mucosal healing and discontinuation			**OR (95% CI); p-value**
CD patients (W14)	Remission	No predictive factor	-
	Response	Previous immunosuppressant medication not ongoing (versus ongoing)	OR= 4.86 (1.10; 21.52); p= 0.03
UC patients (W10)	Remission	No predictive factor	
	Response	Baseline CRP ≤5 mg/l (versus >5 mg/l)	OR cannot be estimated[c]; p=0.03
	MH	Baseline Mayo endoscopic score of 2 (versus 3)	OR=2.57 (1.01; 6.54); p=0.01
		Baseline CRP≤5 mg/l (versus >5)	OR=0.20 (0.07; 0.58); p=0.002
CD patients (M6)	Remission	Previous anti-TNFα treatment (versus biologic-naïve) at baseline	OR=0.09 (0.01; 0.75); p=0.01
	Response	Inflammatory lesions (yes versus no) at baseline	OR cannot be estimated[d]; p=0.05
	Treatment discontinuation	Inflammatory lesions (yes versus no) at baseline	OR=0.05 (0.01; 0.46) for biologic naïve
		Baseline physician assessment evaluated as moderate (versus severe) disease	OR=0.41 (0.21; 0.79); p=0.01 OR=0.19 (0.05; 0.77) for biologic-naïve
		Baseline HBI score moderate (versus severe)[a]	OR=0.25 (0.09; 0.72); p=0.01
UC patients (M6)	Remission	Baseline Mayo endoscopic score of 2 (versus 3)	OR=6.00 (1.11; 32.55); p=0.04
	Response	No predictive factor	-
	MH	Baseline total Mayo score of moderate (versus severe) disease[b]	OR cannot be estimated[e]; p=0.01
	Treatment discontinuation	No predictive factor	-

CI, confidence interval ; CD, Crohn's disease ; CRP, C-reactive protein ; HBI, Harvey-Bradshaw index ; MH, mucosal healing ; M, month ; OR, odd ratio ; TNFα, tumor necrosis factor alpha ; W, week; UC, ulcerative colitis ; [a]Moderate disease : HBI of 8-16/Severe disease : HBI >16 ; [b]Moderate disease : Mayo score 6-10/Severe disease : Mayo score >10 ; [c]OR cannot be estimated for baseline CRP, but a clinical response is significantly more likely if the baseline CRP is >5 ; [d]OR cannot be estimated for presence of inflammatory lesions, but a clinical response is significantly more likely if there are inflammatory lesions at baseline ; [e]OR cannot be estimated for the total Mayo score, but the mucosal healing is significantly more likely if the total Mayo score is moderate compared to severe.

baseline CRP >5 mg/l was predictive of a response at W10 for UC patients, no predictive factor for treatment response could be identified at M6. Moderate (versus severe) disease activity at baseline was predictive of mucosal healing after M6- treatment follow-up and disease activity evaluated by a Mayo endoscopic sub-score of 2 (versus 3) was a predictive factor of mucosal healing after both W10- and M6-treatment follow-up.

Safety results

During the entire safety follow-up, a total number of 418 AEs (84 in the biologic-naïve and 334 in the biologic-failure group) were reported among 348 patients who received at least one infusion of VDZ. Overall, 90 (41.5%) patients treated for CD reported AEs, of whom 14 (30.4%) were biologic-naïve and 76 (44.4%) biologic-failure patients. At least one SAE was reported by 4.3% (2/46) and 14.0% (24/171) of CD patients within biologic-naïve and biologic-failure groups, respectively. Similar results were observed for patients treated for UC. Overall, 38 (29.0%) UC patients reported AEs during the entire safety follow-up, 16 (36.4%) of whom were biologic-naïve and 22 (25.3%) biologic-failure. At least one SAE was reported by 4.5% (2/44) and 14.9% (13/87) of UC patients within biologic-naïve and biologic-failure groups, respectively. The most common AEs were arthralgia (3.8%), fatigue (3.6%), skin eruption (3.1%), headache (2.9%) and gastroenteritis (2.6%). The number of patients with at least one (S)AE are listed in Table 5.

During the M6 safety follow-up post-VDZ treatment initiation, 19.6% (82/418), 26.2% (22/84) and 18.0%

Table 5. — **Summary of adverse events in biologic-naïve and biologic-failure UC and CD patients**

	All (N UC=131) (N CD=217)	**Biologic-naïve (N UC=44) (N CD=46)**	**Biologic-failure (N UC=87) (N CD=171)**
Number of participants with at least one AE, n (%)			
CD patients	90 (41.5)	14 (30.4)	76 (44.4)
UC patients	38 (29.0)	16 (36.4)	22 (25.3)
Number of participants with at least one SAE, n (%)			
CD patients	26 (12.0)	2 (4.3)	24 (14.0)
UC patients	15 (11.5)	2 (4.5)	13 (14.9)
Most common adverse events, n (%)	N'=418	N'=84	N'=334
Arthralgia	16 (3.8)	4 (4.8)	12 (3.6)
Fatigue	15 (3.6)	2 (2.4)	13 (3.9)
Skin eruption	13 (3.1)	5 (6.0)	8 (2.4)
Headache	12 (2.9)	1 (1.2)	11 (3.3)
Gastroenteritis	11 (2.6)	3 (3.6)	8 (2.4)
Number of infectious AEs based on number of AEs, n (%)	**N'=418**	**N'=84**	**N'=334**
Infection	82 (19.6)	22 (26.2)	60 (18.0)

CD, Crohn's disease ; (S)AE, (serious) adverse event ; N, total number of participants ; N', total number of reported AEs ; n (%), number (percentage) of reported adverse events or number (percentage) of participants with at least one AE ; UC, ulcerative colitis.

(60/334) of the reported AEs were infectious AEs in the overall, biologic-naïve and biologic-failure groups, respectively (Table 5).

Discussion

This study provides real-life information on the effectiveness and safety of VDZ for the treatment of CD and UC patients. VDZ induced and maintained clinical response, clinical remission and mucosal healing in patients with moderate to severe CD and UC as previously shown in the Phase III GEMINI clinical trial program (19-21).

As compared to results from our study, results from a study conducted in 8 Israeli centers showed lower clinical response (53.1%) and remission (34.6%) for CD patients at W14 (22). For UC patients, 43.2% responded to treatment and 28.4% achieved clinical remission in the study conducted in Israel (22). Likewise, data from real-life cohorts in the US or France demonstrated lower remission and response rates at W14 than in the current study (23,24). Caution should be used when comparing this study with other real-life experiences due to the non-uniform definitions for clinical response/remission and differences in patient's treatment history across the studies. For instance, in the study conducted in Israel, only a small fraction of patients 15/204 were biologic-naïve and in the French study only 4/294 patients had no TNFα treatment history (22,24).

Our results are comparable with data from a recent retrospective cohort of anti-TNF-naïve patients treated with VDZ showing 82% and 79.1% of the CD and UC patient respectively achieved clinical response at W14 and at last FU visit 68.6% and 67.0% of the CD and UC patient respectively achieved clinical remission.

At M6, 66.7% and 75.6% of CD patients showed clinical remission and response, respectively. The percentages were slightly higher in our study when compared to a Finnish study, in which 41.8% of CD patients were in clinical remission and 47.6% showed a clinical response at M6 (25). For UC patients in the current study, clinical response was higher (83.9% versus 63.3%) but clinical remission was lower (42.9% versus 73.3%) at M6 as compared to data obtained in the Finnish study. Of note, the definition for clinical remission for UC patient differed between the two studies (partial mayo score <3 plus a combined stool frequency and rectal bleeding subscore ≤1 versus a Mayo score ≤2 in the current study) (25).

Dose escalation to Q4W was performed only for 12/164 (7.3%) CD patients and 8/104 (7.7%) UC patients; adaptation to other than Q4W (i.e., Q6W) was initiated for 1/164 (0.6%) CD and 2/104 (1.9%) UC patients. Dose escalation to Q4W or Q6W dosing has previously been shown to allow patients to regain VDZ treatment response in case of loss of response to previous Q8W dosing (26,27).

While for anti-TNF treatment-naïve UC and CD patients elevated baseline CRP levels declined to normal levels (<6 mg/l) at M6, CRP levels for anti-TNF treatment-failure UC and CD patients remained above the normal level at M6. At W10/14, CRP levels were above the normal level in all groups. This is in line with reports from a multicenter study in the US, which demonstrated a non-significant decline in CRP level up to W14 following VDZ treatment (23). However, in the US

study, patients were not grouped based on their previous treatment history and the resulting heterogeneity in response may hinder comparison to our results. In the US study, elevated CRP level at baseline (8 mg/l) reduced the likelihood of response at in both UC and CD patients (23). Moreover, early response at W6 was a significant predictor of W14 response/remission in UC patients and showed a trend towards significance in CD patients. In the current study, baseline CRP >5 mg/l were predictive for W10 clinical response in UC patients, while no predictive factor for remission could be identified in UC patients at W14 and for remission in CD patients. Several predictive factors for clinical response, remission and mucosal healing were identified in this study. Due to the retrospective collection of data some initial parameters like HB index or Mayo score are missing which might have influence the analysis and represents a limitation of our study. Comparison with predictive factors identified in other real-life studies is limited by the non-uniform use of clinical parameters. For instance, in the US study, they assessed a composite response and remission outcome (23), while remission and response were evaluated separately in our study. While the clinical assessments performed in this study may have revealed potential predictive factors to identify patients who are suitable for VDZ treatment, a comparison to other settings should be performed on the basis of the above-mentioned limitation.

VDZ treatment benefit was dependent on treatment duration with higher benefits observed after M6 as compared to W10 or W14. At M6, treatment persistence, an indicator of effectiveness and tolerability, was reported in at least 86.1% of patients. No significant statistical differences between biologic-naïve and biologic-failure groups have been identified for treatment discontinuation suggesting that failure or intolerance to previous anti-TNFα agents did not have an impact on VDZ treatment discontinuation. In other studies, persistence was evaluated at a later time point after treatment initiation, for instance in a Swedish study the median follow-up was at 17 months and in a German study assessment was also performed at W30 and W54 (16,28).

No new safety concerns were raised. All safety signals were in line with what has been observed in the GEMINI clinical trial program (20,21,29).

The study had several limitations including the retrospective design, which resulted in a high number of clinical variables that were found to be unexpectedly missing. Moreover, the small sample size of biologic-naïve patients did not allow generalization of the study's effectiveness and limited the identification of potential predictive factors of treatment persistence. However, compared with other studies the number of anti-TNF naïve patients was relatively high (22,24).

Conclusion

VDZ treatment of CD and UC patients is effective and safe in a Belgian real-life setting. The identification of potential predictive factors for clinical response, remission and treatment persistence might support physicians to identify IBD patients who would benefit the most from VDZ treatment.

Acknowledgements

The authors would like to thank all study participants, investigators and study nurses at the participating centers (AZ Delta, Roeselare; AZ Groeninge, Kortrijk ; AZ Sint Lucas, Brugge ; AZ S int Maarten, Campus Rooienberg Duffel ; Imelda Ziekenhuis, Bonheiden ; OLV, Aalst ; ZOL, Genk ; Hopitaux Iris Sud (HIS) Molière Longchamp, Brussels ; CHU Saint Pierre, Brussels ; ULB Erasme, Brussels ; CHU Sart Tilman, Liège ; Centre Hospitalier Jolimont, La Louvière ; CHR Citadelle, Liège ; UCL, Brussels ; Centre Hospitalier Chrétien (CHC) Saint Joseph, Liège). The authors would further like to thank Anne-Theres Henze from XPE Pharma & Science, Waver, Belgium for writing services.

Funding

Takeda provided funding for the development of this study, for statistical analysis and writing support necessary to develop this manuscript.

Conflict of interest

SB, AH and JI are employees of Takeda Belgium. AC received a lecture fee from Ferring and a consultancy fee from Takeda Belgium. PB obtained lecture fees from AbbVie, Dr. Falk Pharma, Takeda Belgium and a consultancy fee from Dr. Falk Benelux, Janssen, MSD, Takeda, Pfizer and Mundipharma. PH received a consultancy and speakers fee from Takeda Belgium. OD received a lecture and consultancy fee from Takeda, MSD, AbbVie and Janssen Pharmaceutical. CR received lectures fees and consultancy fees from AbbVie, Takeda Belgium, Janssen, Pfizer, MSD, Celgene. WVM, VM and BDV declared that there is no conflict of interest.

References

1. HARLAN WR, MEYER A, FISHER J. Inflammatory Bowel Disease: Epidemiology, Evaluation, Treatment, and Health Maintenance. *N C Med J*, 2016, **77** : 198-201.
2. HANAUER SB, FEAGAN BG, LICHTENSTEIN GR, *et al*. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*, 2002, **359** : 1541-1549.
3. COLOMBEL JF, SANDBORN WJ, RUTGEERTS P, *et al*. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*, 2007, **132** : 52-65.
4. HANAUER SB, SANDBORN WJ, RUTGEERTS P, *et al*. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*, 2006, **130** : 323-333; quiz 591.
5. SANDBORN WJ, FEAGAN BG, STOINOV S, *et al*. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*, 2007, **357** : 228-238.
6. SCHREIBER S, KHALIQ-KAREEMI M, LAWRANCE IC, *et al*. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med*, 2007, **357**: 239-250.

7. Schreiber S, Rutgeerts P, Fedorak RN, *et al*. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology,* 2005, **129** : 807-818.
8. SANDBORN WJ, HANAUER SB, RUTGEERTS P, *et al*. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*, 2007, **56** : 1232-1239.
9. YANAI H AND HANAUER SB. Assessing response and loss of response to biological therapies in IBD. *Am J Gastroenterol,* 2011, **106** : 685-698.
10. RUTGEERTS P, SANDBORN WJ, FEAGAN BG, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med,* 2005, **353** : 2462-2476.
11. BEN-HORIN S. Loss of response to anti-tumor necrosis factors: what is the next step? *Dig Dis,* 2014, **32** : 384-388.
12. RODA G, JHARAP B, NEERAJ N, *et al*. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol,* 2016, **7** : e135.
13. DE VOS M, DHOOGHE B, VERMEIRE S, *et al*. Efficacy of vedolizumab for induction of clinical response and remission in patients with moderate to severe inflammatory bowel disease who failed at least two TNF antagonists. *United European Gastroenterol J,* 2018, **6** : 439-445.
14. DULAI PS, SINGH S, JIANG X, *et al*. The Real-World Effectiveness and Safety of Vedolizumab for Moderate-Severe Crohn's Disease: Results From the US VICTORY Consortium. *Am J Gastroenterol,* 2016, **111** : 1147-1155.
15. BAUMGART DC, BOKEMEYER B, DRABIK A, *et al*. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice – a nationwide consecutive German cohort study. *Aliment Pharmacol Ther,* 2016, **43** : 1090-1102.
16. ERIKSSON C, MARSAL J, BERGEMALM D, *et al*. Long-term effectiveness of vedolizumab in inflammatory bowel disease: a national study based on the Swedish National Quality Registry for Inflammatory Bowel Disease (SWIBREG). *Scand J Gastroenterol,* 2017, **52** : 722-729.
17. SCHROEDER KW, TREMAINE WJ, ILSTRUP DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*, 1987, **317** : 1625-1629.
18. HARVEY RF, BRADSHAW JM. A simple index of Crohn's-disease activity. *Lancet,* 1980, **1** : 514.
19. FEAGAN BG, RUTGEERTS P, SANDS BE, *et al*. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med,* 2013, **369** : 699-710.
20. SANDBORN WJ, FEAGAN BG, RUTGEERTS P, *et al*. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med,* 2013, **369** : 711-721.
21. SANDS BE, FEAGAN BG, RUTGEERTS P, *et al*. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology,* 2014, **147** : 618-627 e613.
22. KOPYLOV U, RON Y, AVNI-BIRON I, *et al*. Efficacy and Safety of Vedolizumab for Induction of Remission in Inflammatory Bowel Disease-the Israeli Real-World Experience. *Inflamm Bowel Dis,* 2017, **23** : 404-408.
23. SHELTON E, ALLEGRETTI JR, STEVENS B, *et al*. Efficacy of Vedolizumab as Induction Therapy in Refractory IBD Patients: A Multicenter Cohort. *Inflamm Bowel Dis,* 2015, **21** : 2879-2885.
24. AMIOT A, GRIMAUD JC, PEYRIN-BIROULET L, *et al*. Effectiveness and Safety of Vedolizumab Induction Therapy for Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol,* 2016, **14** : 1593-1601 e1592.
25. YLISAUKKO-OJA T, AALTONEN J, NUUTINEN H, *et al*. High treatment persistence rate and significant endoscopic healing among real-life patients treated with vedolizumab – a Finnish Nationwide Inflammatory Bowel Disease Cohort Study (FINVEDO). *Scand J Gastroenterol,* 2018, **53** : 158-167.
26. SHIVASHANKAR R, MENDOZA LADD AH, GRACE R, *et al*. Effect of Vedolizumab Dose Escalation on Recapturing Response in Patients with Inflammatory Bowel Disease. *Gastroenterology,* 2017, **152** : S77.
27. SIERRA MORALES M, BIRDI S, SAMAAN MA, *et al*. P673 Vedolizumab dose escalation as a way of recapturing response in patients with inflammatory bowel disease. *Journal of Crohn's and Colitis,* 2018, **12** : S451-S452.
28. STALLMACH A, LANGBEIN 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.
29. FEAGAN BG, RUBIN DT, DANESE S, *et al*. Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. *Clin Gastroenterol Hepatol*, 2017, **15** : 229-239 e225.