

Original Article

Ulcerative Colitis Patients Continue to Improve Over the First Six Months of Vedolizumab Treatment: 12-Month Clinical and Mucosal Healing Effectiveness

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Abstract

Background: Vedolizumab (VDZ) is a humanized monoclonal IgG1 antibody which inhibits leukocyte vascular adhesion and migration into the gastrointestinal tract through $\alpha 4\beta 7$ integrin blockade.

Aims: We retrospectively assessed the 12-month, real-world efficacy and safety of VDZ as induction and maintenance therapy in adult patients with ulcerative colitis (UC).

Methods: The rates of clinical remission (CR, partial Mayo score < 2), steroid-free clinical remission (SFCR), and mucosal healing were assessed with nonresponder imputation analysis. Baseline independent predictors of clinical remission were investigated, and adverse events were recorded.

Results: We analyzed outcomes in 74 patients; 32% were anti-TNF naïve, 68% had pancolitis, and 46% were on systemic steroids at baseline. At week six, week 14, six months and one year, the CR rates were 26%, 34%, 39% and 39% respectively, and the SFCR rates were 24%, 31%, 38% and 39%, respectively. Among patients not in CR after induction, the probability of remission at six months was 20%. Sustained SFCR between weeks 14 and 52 and between weeks 22 and 52 was found in 69% and 86% of the patients, respectively. Steroid-free clinical remission at 12 months was significantly associated with remission after the induction phase (OR = 30.4; 95% CI, 6 to 150; $P < 0.001$). Mucosal healing rate at one year was 39%. The most common side effect was headache (7%).

Conclusions: Increasing remission rates were observed over the first six months of VDZ treatment. One-fifth of patients not in remission post-induction achieved remission by six months of continued therapy. Mucosal healing was associated with higher rates of one-year steroid-free remission and VDZ treatment continuation.

Keywords: *Crohn's disease; mucosal healing; remission; steroid-free; ulcerative colitis; vedolizumab*

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract of unknown etiology characterized by a chronic relapsing-remitting course (1). Current treatment options include aminosalicylates, corticosteroids,

immunomodulators (IMMs; azathioprine, 6-mercaptopurine and methotrexate), biologics including anti-TNF agents (infliximab, adalimumab, certolizumab pegol and golimumab), anti-IL23 agents (ustekinumab) and anti-integrins (vedolizumab).

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Traditionally, biologics are used when conventional therapy with aminosalicylates, corticosteroids and immunomodulators has failed or is not tolerated. Anti-TNF agents have been widely used for almost 20 years in UC and CD, and they have provided a potent therapeutic option in the management of IBD patients. The advent of anti-TNF agents has dramatically changed the disease course and has improved patients' quality of life with fewer surgeries, less frequent hospitalizations, steroid sparing, and increased periods of disease remission (2, 3). However, as the experience with these agents is accumulating, a significant proportion of patients either initially do not respond to anti-TNF therapy (30% to 40%), lose their response over time (23% to 46%) or have to discontinue treatment due to side effects or intolerance (4-6).

Vedolizumab (VDZ) is a recombinant humanized monoclonal antibody (Ab) that blocks leukocyte trafficking into the intestinal mucosa by binding specifically to the leukocyte integrin $\alpha 4\beta 7$, which is the ligand for endothelial cell mucosal addressin cell adhesion molecule-1 (MAdCAM-1) involved in gut-selective trafficking (7). A phase 3 clinical trial program has demonstrated the clinical efficacy and safety of vedolizumab in patients with moderate to severe active UC and CD (8-11).

The lack of systemic immunosuppression due to its gut selectivity and the good tolerability profile combined with its clinical efficacy suggests that VDZ will be an important option for treatment for IBD patients, particularly those with anti-TNF treatment failure or intolerance, patients predisposed to infection or malignancy and those individuals with significant safety concerns (12).

In an observational retrospective study, we evaluated the short- and long-term effectiveness of VDZ as induction and maintenance therapy in a real-life cohort of UC patients. We also investigated predictors of response to VDZ treatment and the occurrence of adverse events.

MATERIALS AND METHODS

Patients

Adult patients with active ulcerative colitis with a total Mayo Clinic Score of 6 to 12 points (13) and moderately to severely active disease on colonoscopy (Mayo endoscopic subscore of at least two) who started on VDZ between May 2015 and December 2016 at the IBD centre in Mount Sinai Hospital, Toronto, Canada, were included in the study. Intravenous infusions of 300 mg of VDZ were administered at weeks zero, two, and six during the induction phase and every eight weeks afterward as maintenance. Eligible subjects for the retrospective analysis were (1) patients who completed 12 months of treatment and (2) patients who discontinued VDZ due to adverse events (AEs) during the 12-month period or for no response (NR) after the first three infusions. The study was approved by the Institutional Research Ethics Board.

Data Collection Methods

Demographic, clinical and laboratory data were collected by chart review of each clinic visit or endoscopy visit. Baseline

demographic, clinical and laboratory data collected included age, sex, disease duration, disease extent, smoking status, concomitant medications, prior or current immunomodulators or biologics, and serum C-reactive protein (CRP) levels.

Baseline clinical activity was measured with the partial Mayo score (14) for UC (remission 0 to 1 with bleeding subscore zero, mild activity 2 to 4, moderate activity 5 to 6, severe activity 7 to 9). The most recent colonoscopy, which was performed within three months before starting VDZ, was used to evaluate the baseline endoscopic activity of the disease and to calculate the endoscopic Mayo score (inactive disease score of zero, mild disease score of one, moderate disease score of two and severe disease score of three) (13).

Follow-up data were collected after VDZ infusions at weeks six, 14, 22 and 52. These included clinical response according to changes in partial Mayo score, CRP levels, concomitant medications, changes in medications, intolerance to VDZ infusions, adverse events, hospitalizations and surgeries. Endoscopic outcomes were recorded in those patients who had colonoscopy for disease activity assessment any time between week 14 and week 52. Decisions regarding the timing of clinical and endoscopic follow-up assessments, use of concomitant corticosteroids or immunomodulators, steroid tapering schedules, and changes in treatment and disease management were at the discretion of the attending physician.

Definitions of Outcome Measures

Clinical partial response (PR), clinical complete remission (CR) and steroid-free complete clinical remission (SFCR) at weeks 22 and 52 were considered as the primary outcomes of VDZ long-term effectiveness.

The secondary outcomes for short-term VDZ effectiveness included CR and PR at weeks six and 14. Mucosal healing, prednisone use reduction, CRP level reduction, hospitalizations, surgeries and adverse events were also analyzed. Finally, demographic, clinical and laboratory predictors of response were also investigated.

Clinical remission was defined as a partial Mayo score <2 with bleeding subscore of zero, and clinical partial response was defined as a decrease of at least two points of the partial Mayo score from baseline with a change in activity severity grade but without remission (15). Steroid-free remission was defined as the absence of use of oral or topical steroids. Mucosal healing was defined as an endoscopic Mayo score of zero or one (16).

Statistical Analysis

All statistical analyses were performed by using IBM SPSS statistical software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Continuous variables were summarized as median values along with interquartile ranges (IQR). The nonresponder imputation (NRI) method was used to calculate the response and remission rates. Patients who discontinued VDZ during the observation period were considered nonresponders (NR), and this status was carried forward for

the outcomes analyses. For continuous variables, the Mann-Whitney U test or the Kruskal-Wallis test were used when appropriate. For paired sample comparisons, the Wilcoxon signed-rank test or Friedman test were used. Categorical variables were expressed as proportions, and statistical comparisons were performed by the chi square test or the Fisher exact test when appropriate. Changes in remission status or steroid use between two or more time points were assessed with the Cochran Q test for matched samples. Pairwise comparisons were performed using the Dunn procedure. Adjusted P values are presented. Logistic regression analysis was performed to identify baseline characteristics as predictors of steroid-free remission at 12 months. Multivariable analysis, including the most significant variables observed in the univariable analysis, was performed. A binomial logistic regression was performed to ascertain the effects of gender, disease extent, disease duration, prior treatment with IMMs or biologics, baseline use of steroids or IMMs, baseline CRP levels, baseline disease severity, and clinical Remission status after three or four VDZ infusions on the likelihood that patients will have steroid-free remission after one year of VDZ treatment. The selection of variables was based in the literature from similar studies on VDZ or other biologics. A binomial logistic regression was also performed to investigate factors related to late response in patients without remission after the induction phase. All analyses were two-tailed, and P values less than 0.05 were considered significant.

RESULTS

Patient Baseline Characteristics

A total of 74 UC patients treated with VDZ were eligible for retrospective analysis in December 2017. Baseline demographics and clinical characteristics of the patients are summarized in Table 1.

Patients had a median age of 32 years (IQR 26 to 41), and 64% were male. The median disease duration was six years (IQR 3 to 11). Most of the patients had pancolitis (68%), and 19% had been diagnosed with extraintestinal manifestations. Prior thiopurine or methotrexate use was reported in 54% of the patients. Prior exposure to treatment with anti-TNF agents had 68% (50 of 74) of the patients, and one-third of them (14 of 50; 28%) had previous treatment failures with two or more anti-TNFs. The main reasons for the anti-TNF failures were primary nonresponse (PNR) or secondary loss of response (LOR) (Table 1).

At baseline, the median total Mayo Clinic score was nine (IQR 8 to 11). The median baseline partial Mayo score was seven (IQR 6 to 8), and the median baseline endoscopic Mayo score was two (IQR 2 to 3). At baseline, the median serum CRP was 6.2mg/L (IQR 2 to 17).

Almost one-half of the patients (47%) were started on VDZ monotherapy at baseline, while 19% were on concomitant

Table 1. Baseline demographic and clinical characteristics of UC patients treated with vedolizumab

	UC (n = 74)	
Male gender, n (%)	47	64
Age, median (IQR), years	32	26–41
Duration of disease, median (IQR), years	6	3–11
Current smoker, n (%)	3	4
Disease extent, n (%)		
Ulcerative proctitis (E1)	1	1
Left-sided colitis (E2)	23	31
Extensive colitis/Pancolitis (E3)	50	68
Extraintestinal manifestations, n (%)	14	19
Prior treatments, n (%)		
Immunomodulators	40	54
Anti-TNF naïve	24	32
Anti-TNFs		
1	36	49
2	12	16
3	2	3
Infliximab	43	
Adalimumab	18	
Golimumab	5	
PNR	29	
LOR	33	
SEs	4	
Baseline treatment, n (%)		
VDZ monotherapy	35	47
CS at induction	34	46
Concomitant IMMs	14	19
Concomitant CS and IMMs	8	11
Baseline activity scores, median (IQR)		
Clinical Mayo Score (pMayo)	7	6–8
Endoscopic Mayo score	2	2–3
CRP mg/L	6.2	2–17

Abbreviations: VDZ: vedolizumab, CS: corticosteroids, IMMs: immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), PNR: primary no response, LOR: loss of response, SEs: side effects

therapy with IMMs, 46% were on systemic steroids, and 11% were on combination treatment with steroids and IMMs at the time of VDZ commencement (Table 1).

Vedolizumab Infusions

All 74 patients completed three VDZ infusions, 71 patients completed four infusions, 64 patients completed five infusions, and 55 (74%) patients completed 52 weeks of VDZ treatment (Figure 1).

Clinical Outcomes

Clinical partial response (PR) rates at weeks six, 14, 22 and 52 were 54%, 64%, 61% and 58%, respectively (Figure 2). Clinical remission rates at weeks six, 14, 22 and 52 were 26%, 34%, 39%

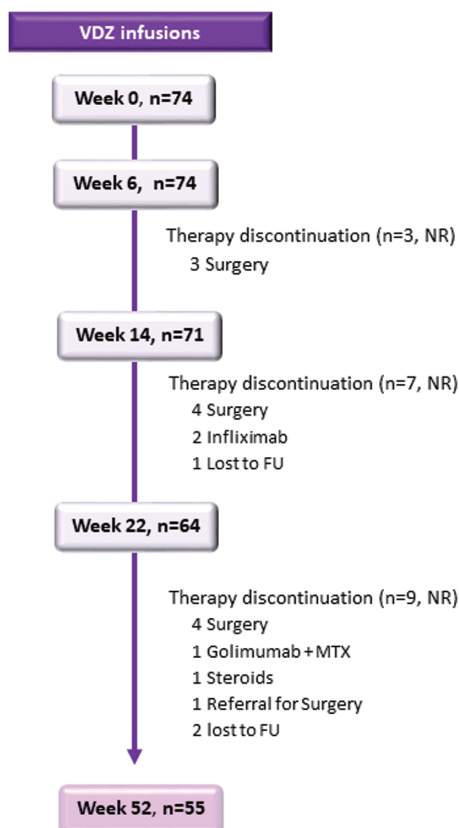


Figure 1. Flow chart diagram showing the UC patients treated with vedolizumab (VDZ) for 12 months, including those who discontinued treatment. NRI: nonresponder imputation; D/C: discontinued; NR: non-responder; Sx: surgery; Rx: treatment

and 39%, respectively. Steroid-free remission rates at weeks six, 14, 22 and 52 were 24%, 31%, 38% and 39%, respectively. There was a significant increase in CR and SFCR rates between week six and week 22 (adjusted $P = 0.011$ and adjusted $P = 0.011$, respectively) (Figure 2). Out of 55 patients without remission after the induction phase, 11 (20%) achieved CR at six months. In contrast, 14 out of 55 (25%) of the patients without remission after the induction phase had discontinued VDZ at six months due to lack of response.

Steroid Use

The percentage of patients on corticosteroids decreased gradually from 46% (34 of 74) at baseline to 35% (26 of 74), 27% (20 of 74), 27% (20 of 74) and 19% (14 of 74) at weeks six, 14, 22 and 52, respectively. The reduction in steroid use was most prominent at week 14 and week 52 compared with baseline (adjusted $P = 0.003$ and $P < 0.001$, respectively) (Figure 3).

At 12 months, all patients in remission ($n = 29$) were steroid-free. Sixty-nine percent and 86% of the patients showed sustained SFCR between week 14 and 52 and between week 22 and 52 respectively. Furthermore, the SFCR rates in the patients on corticosteroids at baseline were 24% (8 of 34), 27%

(9 of 34), 32% (11 of 34) and 41% (14 of 34) at weeks 6, 14, 22 and 52 respectively.

Clinical Scores and Markers of Inflammation

Changes in partial Mayo score were observed in the cohort and were more prominent in patients who achieved SFCR at 12 months (Figure 4). Significant and persistent decline in median CRP serum levels was observed only in patients who were in SFCR at 12 months (Figure 5).

Predictors of Steroid-Free Remission at 12 Months

Univariable analysis (Table 2) revealed that patients without pancolitis had three times higher odds of achieving steroid-free remission at 12 months compared with those with pancolitis (OR = 3.24; 95% CI, 1.2 to 9; $P = 0.022$). Patients in remission after the induction phase (week six) had 30 times higher odds of being in steroid-free remission at 12 months (OR = 30.4; 95% CI, 6 to 150; $P < 0.001$). Multivariable analysis, including the most significant variables observed in the univariable analysis, was performed and revealed that patients with left-sided colitis had three times higher odds of achieving SFCR at 12 months compared with those with pancolitis (OR = 3.4; 95% CI, 1.2 to 9.4; $P = 0.019$).

Univariable and multivariable logistic regression analysis was performed to investigate factors related to late response in patients without remission after the induction phase. Covariates of interest included disease extent, disease duration, prior treatment with IMMs or biologics, baseline use of steroids or IMMs, baseline CRP levels, baseline disease severity, delta CRP (weeks zero to six) and delta pMayo score (weeks zero to six). Patients without remission after three VDZ doses with moderate baseline disease (partial Mayo score of 5 to 6) had six times higher odds of achieving CR at six months compared with those with severe baseline disease (OR = 5.8; 95% CI, 1.1 to 32; $P = 0.045$). Patients without remission after three VDZ infusions but with improvement of the partial Mayo score between baseline and week six had two times higher odds of achieving CR at six months (OR = 1.7; 95% CI, 0.2 to 9.5; $P = 0.038$).

Mucosal Healing

Colonoscopies were performed in 36 patients during the first 12 months at a median time of 38 weeks (IQR 27 to 54) after initiation of VDZ. Mucosal healing was observed in 47% (17 of 36) of patients. Patients who achieved mucosal healing had higher SFCR rate at week 52 compared with those who did not achieve mucosal healing (88% versus 0%, respectively, $P < 0.001$). All patients who achieved mucosal healing continued treatment at week 52, while four of 19 patients who did not achieve mucosal healing discontinued VDZ.

The NRI corrected proportion of patients with mucosal healing, after adding the eight patients who had colectomy without

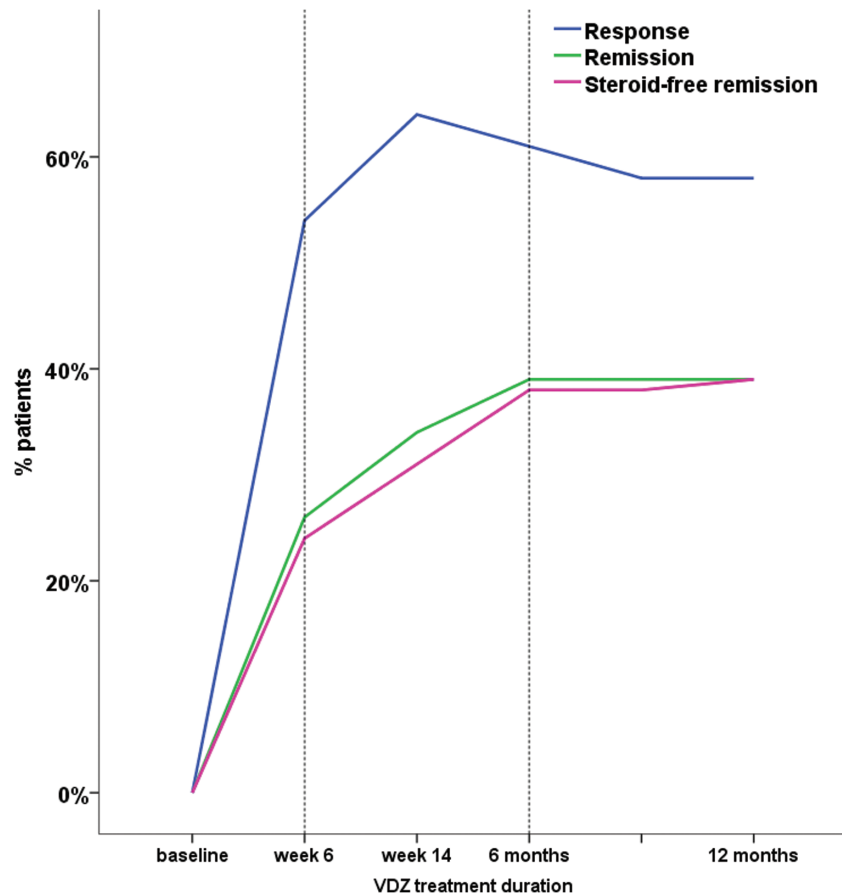


Figure 2. Clinical response, remission and steroid-free remission rates in UC patients during the 1st year of vedolizumab (VDZ) treatment, based on non-responder imputation analysis. * $P = 0.011$, CR and ** $P = 0.011$, SFCR; 6 months versus week 6; Cochran's Q test

follow-up endoscopy, was 39% (17 of 44). Subanalyses did not reveal associations between prior anti-TNF exposure and mucosal healing, while early remission at week 14 was associated with increased odds of mucosal healing (OR = 37; 95% CI, 4 to 340; $P = 0.001$).

VDZ Optimization

Vedolizumab treatment was escalated at a dose of 300 mg every four weeks in eight patients due to active disease (four NR and four PR), in two after week 14, and in six after week 22. At 12 months, three of them had discontinued VDZ due to no response, one was NR, three were PR, and one achieved CR.

Disease Course

Nineteen patients (26%) discontinued VDZ (16 for lack of response and three who were lost to follow-up) between week six and 52 (Figure 1). Three patients discontinued VDZ after week six due to lack of response and were operated with elective colectomy. Six patients discontinued VDZ after week 14 due to lack of response (four underwent elective colectomy, and two were started on infliximab). Seven more patients discontinued VDZ after the first six months (four underwent elective colectomy, one was referred for elective colectomy, one was

started on golimumab plus methotrexate, and one elected to be retreated with steroids).

All 19 UC patients who discontinued VDZ were nonresponders and were characterized by pancolitis (68%), prior exposure to anti-TNFs (74%), moderate/severe baseline disease (100%), baseline CRP over 5 mg/L (68%) and no response to treatment after three infusions (100%).

Overall, 14 (19%) patients were hospitalized during the 12-month period—11 for surgery and three for disease flare.

Safety

In general, vedolizumab treatment was well tolerated. There was no VDZ treatment discontinuation due to infusion reactions or due to serious adverse events during the first 12 months. In total, adverse events occurred in 19% (14 of 74) of the patients. Adverse events included headache/migraine ($n = 5$), insomnia ($n = 1$), gastroenteritis ($n = 2$), perianal abscess ($n = 1$), rash ($n = 2$), joint pain ($n = 2$) and pruritus ($n = 1$).

DISCUSSION

In this retrospective, observational study in a single-tertiary IBD centre, we found increasing response, remission and

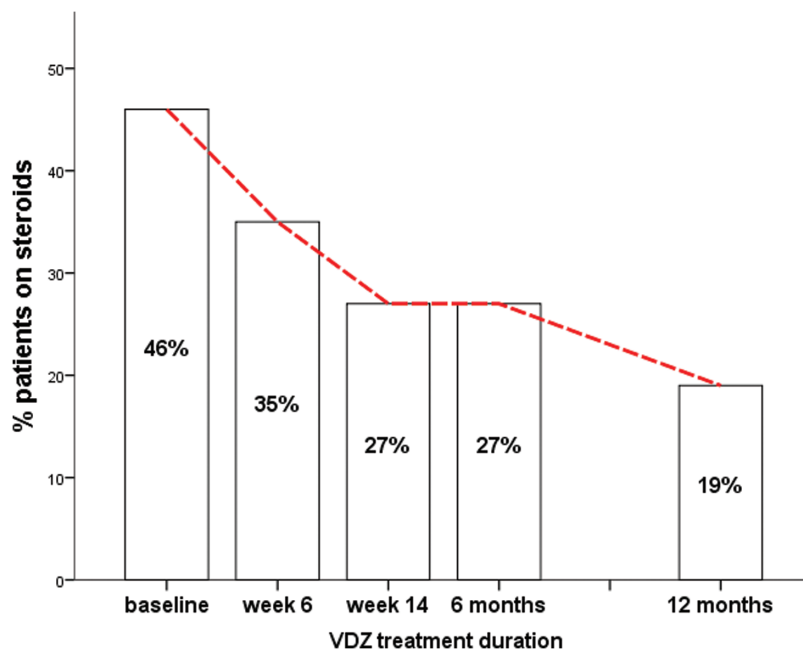


Figure 3. Steroid use during the 1st year of vedolizumab (VDZ) treatment in UC patients. * $P = 0.003$, week 14 versus baseline and ** $P < 0.001$, 12 months versus baseline, Cochran's Q test

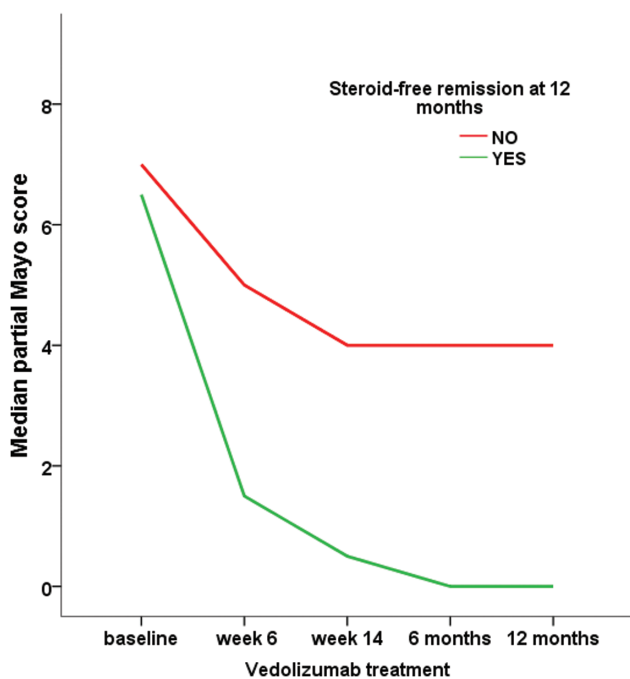


Figure 4. Changes in partial Mayo clinical activity score in UC patients treated with vedolizumab (VDZ) according to 1st year outcomes (remission or no remission). * $P < 0.001$, for SFCR patients at 12 months, Related samples Friedman's two-way ANOVA by ranks

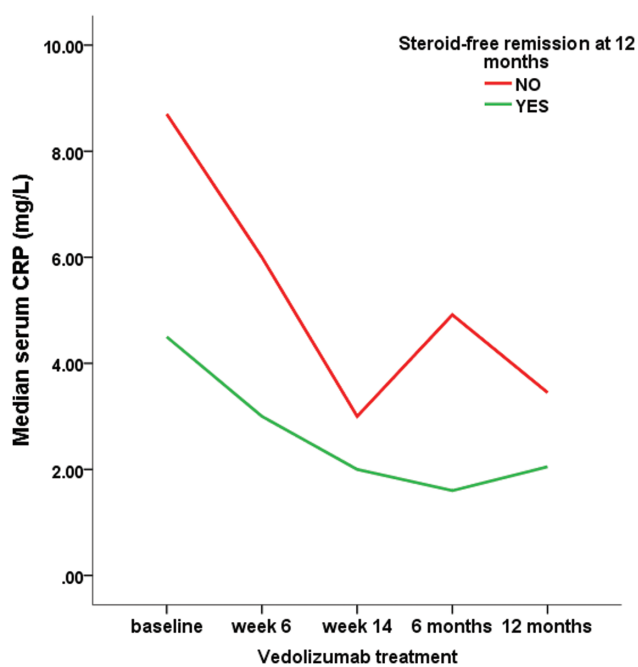


Figure 5. Changes in median CRP levels in UC patients treated with vedolizumab (VDZ) according to 1st year outcomes (remission or no remission). * $P = 0.04$, for SFCR patients at 12 months, related samples Friedman's two-way ANOVA by ranks

steroid-free remission rates during the first year of continuous vedolizumab treatment. We also observed substantial improvement after the induction phase during the early maintenance phase at six months. Among patients without remission after

the induction phase, the probability of achieving CR or SFCR with continuation of VDZ treatment for six months was 20%. Sustained remission and steroid-free remission rates were observed between six months and 12 months of treatment. Mucosal healing in interval follow endoscopy was associated

Table 2. Univariable analysis of predictors of steroid-free remission at 12 months

Variable	Odds ratio (OR)	95% CI	P
Male gender	0.9	0.34–2.37	0.83
Left sided colitis	3.26	1.2–9	0.022
Disease duration <10 years	0.64	0.21	1.91
Anti-TNF naive	1.54	0.55–4	0.418
No prior IMMs	1.46	0.57–3.74	0.424
Baseline CS	1.27	0.5–3.2	0.6
IMMs baseline	0.58	0.18–1.86	0.36
Baseline CRP <5mg/L	2.23	0.84–5.88	0.105
Baseline moderate disease	1.53	0.59–3.95	0.37
Clinical Remission post 3 rd infusion	30.4	6–150	<0.001
Clinical Remission post 4 th infusion	26.9	7–100	<0.001

IMMs: immunomodulators (azathioprine, 6-mercaptopurine, methotrexate); CS: corticosteroids
 UC of moderate activity: partial Mayo score of 5–6

with higher rates of one-year steroid-free remission and VDZ treatment continuation.

Recent real-world observational studies reported similar results. In these studies, the reported post-induction rates were 53% to 59% for clinical response, 23% to 39% for clinical remission, and 19% to 36% for steroid-free clinical remission (17–20). Although the GEMINI 1 trial reported lower clinical response and remission rates of 47% and 17% respectively, these results were achieved by the first two VDZ infusions, whereas most real-world observational studies report induction results after the three infusions. (8) These real world studies have clearly shown that VDZ response increases substantially after the completion of the 3rd induction dose at week six (17–20).

Furthermore, real-world studies focusing on the long-term outcomes of VDZ treatment in UC patients reported increasing clinical benefit during maintenance at six or 12 months. Samaan et al., in a small cohort of 23 UC patients, reported an increase in remission rates from 30% at week six to 50% at week 30 (21). Stallmach et al. reported one-year outcomes in 60 UC patients with 38% clinical response, 25% clinical remission and 22% steroid-free clinical remission. They found that lack of clinical response after three infusions (at week 14) was associated with approximately a 10% likelihood of clinical remission at week 54 (22). The US VICTORY consortium study of 180 UC patients treated with VDZ reported cumulative rates of 53% clinical response, 37% remission and 27% steroid-free remission at six months and 73%, 51% and 49%, respectively at 12 months (23). Amiot et al., in a multicentre, prospective cohort study of 121 UC patients, reported steroid free remission rates of 36%, 39%, 42% and 40% at weeks 14, 22, 30 and 54, respectively (24). A recent meta-analysis of real-world effectiveness of VDZ over one year in IBD suggested increasing remission rates over 12 months of therapy (25).

An important finding in our study is that 20% of the patients not in remission after the first three VDZ infusions achieved remission after having two more standard maintenance infusions. No further significant changes in remission rates were found after the first six months of VDZ treatment. Regression analysis in this subgroup revealed that patients with moderate baseline disease and improvement of the partial Mayo score after the induction phase had higher odds of achieving remission at six months. These data are in contrast with the findings of Stallmach et al. (22) and the suggestion to discontinue VDZ treatment in UC patients not achieving clinical remission at week 14. We believe that there is still opportunity for improvement in those patients not responding following three VDZ infusions by administering two additional VDZ infusions at weeks 14 and 22. Moreover, in this cohort, there was a significant reduction in steroids use during VDZ therapy. The steroid-sparing effect of VDZ was significantly overt after the 4th infusion and even more so at six months. Patients not responding after six months of VDZ treatment should be considered for discontinuation.

Altogether, these data, including those of this study, indicate that VDZ efficacy is clinically apparent and substantial after the induction phase and continues to increase gradually in UC patients who remain on long-term maintenance with VDZ. The treating physicians should be patient and allow enough time—at least three months and perhaps even six months—for VDZ to demonstrate its benefit. These findings support the suggestion of assessment for initial response to VDZ after the 3rd infusion. The 2015 Toronto Consensus guidelines for the medical management of nonhospitalized UC patients recommend that UC patients on VDZ should be evaluated for lack of symptomatic response to induction therapy in eight to 14 weeks to determine the need to modify therapy (26). Nonresponders could be evaluated with endoscopic reassessment, and VDZ dose escalation could be tried before making

a final decision to discontinue the treatment. Amiot et al. reported that the optimization of VDZ therapy (300 mg every four weeks) in IBD patients with nonresponse or inadequate response was effective to induce or restore clinical response in 40% of these patients (24). In our cohort, VDZ dose escalation was observed in eight patients, but the response was not favorable. Perhaps early escalation soon after the induction phase would be more effective. Therapeutic drug monitoring by measuring VDZ trough levels may be helpful in making the decision to escalate or discontinue the treatment. The GEMINI 1 trial has demonstrated that VDZ drug levels were positively associated with clinical response at week six and endoscopic improvement in UC patients (8). Furthermore in a prospective study of IBD patients, Willet et al. showed that low VDZ trough levels at week six (<19.0 mg/mL) were associated with the need for dose escalation (every four weeks) within the first six months, which resulted in achieving clinical response (27).

Data on mucosal healing during VDZ treatment are scarce. In the phase 3 GEMINI 1 study, 56% of the patients with moderately to severely active UC receiving VDZ every 8 weeks achieved mucosal healing at week 52 (8). Observational studies have reported widely varying mucosal healing rates of between 30% and 77% (23, 28, 29). In our cohort, we observed mucosal healing in almost half of the patients during VDZ maintenance therapy over a median follow-up period of approximately 10 months. Mucosal healing was associated with steroid-free remission and VDZ treatment continuation. Subanalyses did not reveal associations between prior anti-TNF exposure and achievement of mucosal healing, while remission after the 3rd VDZ infusion was associated with increased odds of mucosal healing.

Regression analysis revealed that left-sided colitis and remission after induction were factors associated with steroid-free remission at 12 months. We did not find associations between remission and other disease characteristics including concomitant IMMs, concomitant steroid use, prior anti-TNF exposure or CRP elevation. Allegretti et al. reported on predictors of remission at one year in IBD patients treated with VDZ (30). There were no significant predictors of clinical response or remission in the UC cohort, although the need for hospitalization was associated with decreased odds of remission. Amiot et al. reported that the absence of concomitant steroid use, Mayo Clinic score <9 and clinical response at week six were associated with steroid-free clinical remission at 12 months (24). In a recent study, Waljee et al. applied machine learning tools to data from the GEMINI 1 clinical trial to develop and validate predictive models of corticosteroid-free endoscopic remission in response to VDZ in UC. They found that prior use of anti-TNF therapy, use of immunomodulators or use of corticosteroids at baseline were weak predictors of SFCR at 52 weeks

(31). Furthermore, Singh et al. found that there was no difference in response to VDZ in patients with prior PNR or LOR to anti-TNF agents (32).

VDZ therapy was well tolerated in our cohort with no infusion reactions, serious adverse events or infections, including no observed cases of progressive multifocal leukoencephalopathy. Although our observations regarding the safety profile of VDZ are in keeping with most previous reports, larger long-term studies are needed to rule out the possibility of rare or long-term adverse effects.

Our study has limitations which should be noted. This is a single-centre, retrospective, observational study of open-label real-life VDZ treatment in UC patients. Disease management, including timing of clinical follow-up visits, changes in treatment, and timing of endoscopic evaluation were at the attending physician's discretion. The use of corticosteroids was not uniform in this study, and this could have an impact on the outcomes. The number of UC patients included in this study is less than most of the other real-life studies which were multicentre or national. The number of patients in our study did not allow for more extended subgroups analysis; however, this study represents the real-world experience on VDZ effectiveness and safety in a large Canadian tertiary IBD centre.

In summary, this study showed that in a refractory cohort of UC patients with nearly two-thirds exposed to prior anti-TNF agents, VDZ was an effective, safe and well-tolerated treatment both as induction and maintenance treatment. It was also demonstrated that interval mucosal healing was associated with steroid-free remission and VDZ treatment continuation. The important message emerging from this study is that clinical benefit of VDZ treatment may be delayed and may become more apparent in the early maintenance period. The patients should have regular follow-up during the first six months of treatment, and patients with suboptimal clinical response can potentially have VDZ continued beyond the induction period with the expectation that some of them will achieve further improvement over time with or without dose optimization. Further studies are needed to more precisely determine the kinetics of clinical and endoscopic response to vedolizumab therapy and to develop strategies to identify those patients who are likely to have further improvement following induction therapy.

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drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Conflicts of Interest: PZ received Honoraria fee for Educational Event Presentations from Abbvie, Takeda, Pfizer, and Merck & Co. AVW served as a speaker and served on advisory boards for Janssen, Abbvie, Takeda and Ferring. NN received research support and consulting fees from Janssen, Abbvie, Takeda, Ferring and Pfizer. KC received educational grants from Janssen, Abbvie and Takeda and has served on advisory boards for Abbvie, Janssen and Takeda. AHS received research grants from Abbvie, Amgen and Pfizer and Millennium Honoraria for Educational Event Presentations from Abbvie, Janssen and Takeda and has served on advisory boards for Abbvie, Actavis, Janssen, Takeda, Pharmascience and Shire. MSS receives research support and consulting fees from Janssen, Abbvie, Takeda and Prometheus. The remaining authors disclose no conflicts of interest.

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