The Real-World Effectiveness and Safety of Vedolizumab for Moderate–Severe Crohn's Disease: Results From the US VICTORY Consortium

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OBJECTIVES: **We assessed the real-world effectiveness and safety of vedolizumab (VDZ) in moderate–severe Crohn's disease (CD).**

METHODS: **Retrospective cohort study of seven medical centers, from May 2014 to December 2015. Adults with moderate-severe CD treated with VDZ, with follow-up after initiation of therapy, were included. Using the multivariable Cox proportional hazard analyses, we identified independent predictors of clinical remission or mucosal healing with VDZ. Rates of serious infection (requiring antibiotics, resulting in discontinuation of VDZ, hospitalization or death) and serious adverse events (discontinuation of VDZ, hospitalization or death) were described quantitatively.**

RESULTS: **We included 212 patients with moderate–severe CD (median age 34 years; 40% male; 90% tumor necrosis factor (TNF)-antagonist exposed) with a median follow-up (IQR) of 39 weeks (25–53). Twelve-month cumulative rates of clinical remission, mucosal healing, and deep remission (clinical remission+mucosal healing) were 35%, 63%, and 26%, respectively. Individuals with prior TNF-antagonist exposure (hazard ratio (HR) 0.40; 95% confidence interval (CI): 0.20–0.81), smoking history (HR 0.47; 95% CI: 0.25–0.89), active perianal disease (HR 0.49; 95% CI: 0.27–0.88), and severe disease activity (HR 0.54; 95% CI: 0.31–0.95) were less likely to achieve clinical remission. Those with prior TNF-antagonist exposure (HR 0.29; 95% CI: 0.12–0.73), and severe disease activity (HR 0.54; 95% CI: 0.31–0.95) were less likely to achieve mucosal healing. During 160 patient years of follow-up (PYF) and 1,433 VDZ infusions, 5 patients developed infusion reactions (3.5 per 1,000 infusions), 21 developed serious infections (13 per 100 PYF), and 17 developed serious adverse events (10 per 100 PYF). A minority of adverse events required discontinuation of therapy (6 per 100 PYF).**

CONCLUSIONS: **VDZ is a safe and effective treatment option for moderate–severe CD in routine practice. Clinical remission and deep remission (clinical remission and mucosal healing) can be achieved in 1/3 of individuals, and a minority of individuals require discontinuation of therapy due to adverse events.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

The use of biologic agents, in particular tumor necrosis factor-antagonists (TNF-antagonists), has become the cornerstone of therapy for moderately to severely active Crohn's disease (CD). Considerable strides have been made towards understanding how best to utilize and monitor these agents, yet up to 30% of patients will fail to initially respond, and among those who do respond, nearly half will lose response over time (1). Furthermore, the use of these agents is not without risk, and treatment may be limited by adverse events (2–4). Newer agents with alternative mechanisms of action are needed.

Vedolizumab (VDZ), an anti-integrin antibody that selectively targets lymphocyte migration to the gut, was approved in 2014 for the treatment of moderately to severely active CD (5). Although the rates of clinical remission with VDZ are similar to those seen with TNF-antagonists (6–8), and its mechanism of action may suggest an improved safety profile, uncertainty remains regarding its real-world effectiveness and safety given the strict inclusion criteria employed in clinical trials (2,9–12). Thus, it remains unclear what the optimal positioning of this agent will be in routine clinical practice among currently approved biologics. Determining treatment effectiveness and safety in the real world, and identifying predictors of treatment response, is therefore of importance.

Through a multi-center consortium, we estimated the real-world effectiveness and safety of VDZ for moderately to severely active CD, and aimed to identify baseline clinical factors predictive of achieving clinical remission or mucosal healing. We anticipate these data will allow for an optimized approach to the integration of this biologic in routine practice.

METHODS

Study design

This study is reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (13). IRB approval for data collection and data sharing was obtained at each site to create the **V**edol**I**zumab for Health Ou**TC**omes in Inflammat**ORY** Bowel Diseases (VICTORY) Consortium. This consortium includes sites from across the United States: University of California at San Diego, Icahn School of Medicine at Mount Sinai, Mayo Clinic in Rochester Minnesota, Dartmouth-Hitchcock Medical Center, New York University (NYU), Montefiore Medical Center in New York, and Lenox Hill Medical Center in New York. Patients were identified at each site through electronic medical record searches, review of clinic records, and/or queries of infusion center records, and all patients receiving at least one dose of VDZ at the consortium site, or those being followed clinically while receiving VDZ infusions elsewhere, were included in the consortium. Data were collected retrospectively at each site, between May 2014 and December 2015, and transferred de-identified to the coordinating site (University of California, San Diego). Data collection was performed using a standardized data collection form using pre-specified definitions and criteria for coding. If a discrepancy or uncertainty arose regarding data coding, it was resolved through consensus between the study site and the coordinating site investigators.

Variables

Data on variables of interest were collected for: patient characteristics (age at diagnosis, age at VDZ initiation, gender, smoking status), disease characteristics (prior hospitalizations, prior surgeries, disease-related complications or extra-intestinal manifestations, and phenotype classified according to Montreal sub-classifications (14)), and treatment history (steroids, immunomodulators and TNF-antagonists; duration of use; indication for discontinuation; and complications). Variables of interest specific to VDZ use were: baseline disease severity (endoscopic, radiographic, or clinical assessments), concomitant treatments (steroids and/or immunomodulators), infusions (dates, intervals, pre-medications), prescribing site and provider, and follow-up assessments (endoscopic, radiographic, or clinical assessments).

Participants

Individuals were included in the current analysis if they met the following criteria: (a) confirmed diagnosis of CD based on clinical and endoscopic, or radiographic data; (b) active clinical symptoms attributed to CD before starting VDZ; (c) graded as moderately to severely active disease before starting VDZ based on endoscopic or radiographic assessment (graded as moderate or severe by local site investigators), and/or clinical assessment (graded as moderate or severe based on Harvey–Bradshaw Index score of 8–16 or >16, respectively); (d) had at least one clinical and/or endoscopic follow-up after initiation of therapy. Patients started on VDZ for ulcerative colitis, indeterminate colitis, pouchitis or post-operative prophylaxis of CD, or those in clinical remission at time of starting VDZ (e.g., patients with CD transitioned from natalizumab to VDZ for safety) were excluded.

Outcomes

Our primary effectiveness outcomes of interest were the proportion of individuals achieving clinical remission or mucosal healing. Secondary effectiveness outcomes of interest included: deep remission (clinical remission and mucosal healing), clinical response, corticosteroid free response or remission, VDZ interval escalation for loss of response and/or remission, and progression to surgery or penetrating disease complications. Clinical assessments for response to therapy were performed based on physician global assessment, where response was defined as ≥50% reduction in CD-related symptom activity and/or severity, and remission was defined as complete resolution of all CD-related symptoms. The assessment of steroid-free response and remission (performed only in patients on prednisone or budesonide at time of initiation of VDZ) was defined as tapering off steroids completely, achieving response or remission, and no repeat steroid prescription within 4 weeks of tapering.

Endoscopic mucosal healing was defined as the absence of ulcers and/or erosions (10,15). Given the potential variability in endoscopic scoring (16), endoscopic categorization of mucosal

healing was done by local study investigators and was re-verified by a coordinating study investigator (P.S.D) using de-identified endoscopy reports. If a discrepancy or uncertainty arose regarding the categorization of mucosal healing, it was resolved through consensus between the study site and coordinating site investigators. Radiologic mucosal healing was defined according to the local site radiologist, and all of these individuals also had a baseline radiologic assessment demonstrating active disease as a reference. We were unable to consistently apply a radiologic scoring index to images for the categorization of mucosal healing, and a sensitivity analysis was therefore performed by excluding individuals who had an assessment for mucosal healing by radiology alone.

Our safety outcomes of interest were the proportion of individuals developing infusion reactions, serious infections or serious adverse events. Adverse events were graded as serious if they resulted in discontinuation of VDZ, hospitalization, or death. Infections were graded as serious if they required antibiotics, or they resulted in discontinuation of VDZ, hospitalization, or death.

Statistical analysis

Statistical analyses were performed using STATA statistical software (College Station, TX). Continuous variables were presented as means (and standard deviations (s.d.)), or as medians (and interquartile ranges (IQR)) if the distribution was skewed, and categorical or binary variables were presented as proportions or percentages. For the comparison of baseline continuous variables, we used the independent sample *t*-test (two group comparisons) or 1-way ANOVA with Bonferroni correction (three or more group comparisons), and for the comparison of baseline binary variables we used the Pearson χ^2 or Fisher's exact test. Primary and secondary effectiveness outcomes were described quantitatively with the Kaplan–Meier survival analyses, and log-rank statistics were performed to compare sub-groups of interest. Safety outcomes were described quantitatively.

The Cox proportional hazard regression analyses were performed to identify independent predictors of clinical remission or mucosal healing. Disease duration was assessed as a continuous variable, and it was converted into a binary variable (≥5 years) for ease of clinical interpretation according to the published literature demonstrating lower response rates to biologics with prolonged disease duration (17). An initial assessment for co-linearity between baseline variables was performed, and co-linearity was demonstrated for age at diagnosis (i.e., age diagnosis+disease duration=age at VDZ initiation), both when used as a continuous variable or categorical variable according to the Montreal subclassifications (14). Age at diagnosis was therefore removed before model selection (**Supplementary Table 1**).

Baseline variables were then fitted and a backward model selection technique was used where variables were selected out according to the Akaike's Information Criterion. Model assumption was checked on each attribute using the cox.zph test, and results showed that none of the included variables for either model violated proportional assumptions ($P>0.05$ for all variables). We then performed a stepwise model selection using the Akaike's Information Criterion for interaction terms (e.g., DiseaseSeverity:AntiTNFuse), and retained the same model for both clinical remission and mucosal healing (**Supplementary Table 2**). Hazard ratios (HR) with 95% confidence interval (CI) were presented for independent predictors where a HR<1 indicated a predictor was associated with a reduced probability for achieving the outcome (clinical remission or mucosal healing) and a HR >1 indicated a predictor was associated with an increased probability for achieving the outcome (clinical remission or mucosal healing).

RESULTS

Demographics

A total of 212 patients (median age (IQR), 34 years (24–45); 40% male; 90% TNF-antagonist exposed) with moderately to severely active CD started VDZ at one of the seven sites and were included in the current analysis, with a median clinical follow-up of 39 weeks (25–53) (**Tables 1** and **2**). A minimum of 6 and 12 months of follow-up were available in 133 and 44 individuals, respectively. The reason for TNF-antagonist discontinuation before VDZ initiation was: primary non-response in 41 (22.5%), loss of response without optimization (dose escalation or interval decrease) in 28 (15.4%), loss of response despite optimization in 64 (35.2%), and intolerance in 49 (26.9%). Concomitant immunosuppressive agents were used in the majority of individuals (*n*=156, 73.6%) and these included: steroids (prednisone or budesonide) alone (*n*=71, 45.2%), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) alone (*n*=36, 22.9%), or steroids+immunomodulators in combination (*n*=49, 31.2%).

Clinical remission or mucosal healing

At week 6, clinical remission with VDZ induction therapy was achieved in 10.9% (*n*=23/212), and cumulative rates of clinical remission after 6 and 12 months of maintenance therapy were 18 and 35%, respectively. At 18 months the cumulative rate of clinical remission was 54%. Among individuals achieving clinical remission, the median time to achieving clinical remission was 25 weeks (14–35).

A total of 141 individuals had at least one follow-up assessment for mucosal healing, with the majority of them having an endoscopic follow-up (*n*=121, 85.8%). An endoscopic assessment for mucosal healing could not be performed in the remaining 20 who had an assessment by radiology (magnetic resonance or computerized tomography enterography) alone due to stricturing disease complications (*n*=15) or isolated small bowel disease beyond the reach of ileocolonoscopy (*n*=5). Cumulative rates of mucosal healing after 6 and 12 months of maintenance therapy were 20% and 63%, respectively. Cumulative rates of deep remission (clinical remission and mucosal healing) after 6 and 12 months were 14% and 26%, respectively. When limiting this to the 121 individuals who had an endoscopic assessment for mucosal healing, cumulative rates of mucosal healing after 6 and 12 months of maintenance therapy were 21 and 67%, and respective cumulative rates of deep remission (clinical remission and mucosal healing) were 14 and 29%. Among individuals achieving mucosal healing, the median time to achieving mucosal healing was 33 weeks (21–41).

Table 1. Demographics of study patients

	Crohn's disease (*n*=212)
Median age, years (IQR)	34 (24–45)
Median disease duration, years (IQR)	11 (5–19)
Male gender, *n* (%)	85 (40%)
Smoking status, n *(%)*	
Never	148 (69.8%)
Former	35 (16.5%)
Current	29 (13.7%)
Disease phenotype, n *(%)*	
Isolated small bowel disease	29 (13.7%)
Isolated colonic disease	50 (23.6%)
Ileocolonic disease	133 (62.7%)
Non-stricturing and non-penetrating	94 (44.3%)
Stricturing or penetrating	118 (55.7%)
Perianal disease	77 (36.3%)
Active fistulizing disease	84 (39.6%)
Extra-intestinal manifestations, *n* (%)	70 (33.3%)
Severe disease, *n* (%)	80 (37.7%)
Prior Crohn's hospitalization	
Never, *n* (%)	53 (25%)
Yes within past year, *n* (%)	55 (26%)
Yes but not within past year, *n* (%)	104 (49%)
Prior Crohn's surgery	
Never, *n* (%)	95 (45.3%)
Yes within past year, *n* (%)	38 (17.9%)
Yes but not within past year, *n* (%)	76 (36.8%)
Prior TNF-antagonist, *n* (%)	193 (91%)
Qualified GEMINI trial, *n* (%)	89 (42%)

IQR, interquartile range; TNF-antagonist, tumor necrosis factor-antagonist.

Clinical response and steroid tapering

At week 6, a clinical response to VDZ induction therapy was achieved in 40.6% (*n*=86/212), steroid-free response in 22% (*n*=26/117), and steroid-free remission in 8.6% (*n*=10/117). Cumulative rates of response, steroid-free response, and steroid-free remission after 6 months of maintenance therapy were 32%, 26%, and 18%, respectively. The corresponding cumulative rates after 12 months of maintenance therapy were 58%, 51%, and 34%, respectively. Among individuals achieving a clinical response, the median time to achieve a clinical response was 19 weeks (10–38); and among individuals on steroids at baseline who were able to taper off during maintenance therapy, the median time to steroid tapering was 30 weeks (17–51).

VDZ loss of response and dose escalation

In total, 21 individuals underwent escalation of VDZ maintenance intervals to Q4 weeks (*n*=18) or Q6 weeks (*n*=3) for: lack of response (*n*=3), sub-optimal response (*n*=10), loss of response (*n*=6), or loss of remission (*n*=2). Among the 13 individuals who underwent interval escalation for lack of response or sub-optimal response, clinical response was achieved in 4 (30.8%) and clinical remission was achieved in 1 (7.7%). Interval escalation for loss of response or remission occurred between 6 and 12 months after VDZ initiation, and among these 8 individuals a clinical response was regained in 3 (37.5%) and clinical remission was regained in 1 (12.5%).

Progression to surgery or penetrating disease complications

Cumulative rates of progression to surgery after 6 and 12 months of maintenance therapy were 10% and 23%, respectively, with the following procedures being performed: total proctocolectomy with end ileostomy for refractory disease (*n*=13); subtotal colectomy for colonic stricture (*n*=3); ileocolonic resection for persistent disease activity with a fistula or phlegmon (*n*=10); segmental small bowel resection for adhesions (*n*=2); strictures (*n*=2); or small bowel perforation (*n*=1); and temporary diverting loop ileostomy for persistent distal disease activity (*n*=4).

Another 3 individuals developed new fistulizing disease that did not require surgery. This occurred despite having completely healed mucosa endoscopically throughout the examined ileum and colon. Two of these were perianal fistulas with communication to the rectum, and the other individual developed an enteroenteric fistula from the small bowel to the colon. All three of these patients had prior treatment with TNF-antagonists but none of them had a history of fistulizing disease complications.

Predictors of clinical remission or mucosal healing

On univariable and multivariable Cox proportional hazards regression analysis, individuals with baseline severe disease activity (vs. moderate disease activity: HR 0.54; 95% CI: 0.31–0.95), baseline active perianal disease (vs. no baseline perianal disease: HR 0.49; 95% CI: 0.27–0.88), previous or current smoker status (vs. never smokers: HR 0.47; 95% CI: 0.25–0.89), and previous TNF-antagonist use (vs. TNF-antagonist naive: HR 0.40; 95% CI: 0.20–0.81) were less likely to achieve clinical remission. Individuals with baseline severe disease activity (HR 0.54; 95% CI: 0.31–0.93) and previous TNF-antagonist use (HR 0.29; 95% CI; 0.12–0.73) were less likely to achieve mucosal healing (**Figure 1**).

Compared to those who were TNF-antagonist-naive, individuals with prior TNF-antagonist exposure had lower rates of clinical response (*P*=0.011), steroid-free response (*P*=0.020), and steroid-free remission (*P*=0.050), and they had higher rates of progression to surgery (*P*=0.051). This was incremental according to the number of TNF-antagonists they had been exposed to (**Supplementary Figure 1**), but it was similar when stratified by the reason for failure of the TNF-antagonist used (**Supplementary Figure 2**), and whether an individual ever had a primary non-response to a TNF-antagonist (**Supplementary Figure 3**). Individuals with active perianal disease at baseline had lower rates of clinical response (*P*=0.011), steroid-free response (*P*=0.009), and steroid-free remission (*P*=0.034), but rates of mucosal healing (*P*=0.246) and

Table 2. Demographics stratified by prior TNF-antagonist use

	TNF-antagonist naïve, *n*=19	1 prior TNF-antagonist, *n*=49	2 prior TNF-antagonists, *n*=80	3 prior TNF-antagonists, *n*=64
Median age at Vedo, years (IQR)	34 (24–57)	36 (25–58)	34.5 (26–44)	33 (24–43)
Median disease duration, years (IQR)	6 (3–17)	10 (3–24)	11 (6–17)	12.5 (8–19)
Male gender, *n* (%)	6 (31.6%)	26 (53.1%)	32 (40%)	21 (32.8%)
Smoking status, n *(%)*				
Never smoker	11 (57.9%)	34 (69.4%)	57 (71.3%)	46 (71.9%)
Prior smoker	6 (31.6%)	7 (14.3%)	11 (13.8%)	11 (17.2%)
Current smoker	2 (10.5%)	8 (16.3%)	12 (15%)	7 (10.9%)
Disease phenotype, n *(%)*				
Isolated small bowel	3 (15.8%)	3 (6.1%)	16 (20%)	17 (26.6%)
Isolated colonic	3 (15.8%)	18 (36.7%	15 (18.8%)	14 (21.9%)
Ileocolonic	13 (68.4%)	28 (57.2%)	49 (61.2%)	33 (51.5%)
Stricturing/penetrating	5 (26.3%)	19 (38.8%)	48 (60%)	46 (71.9%)
Perianal disease	3 (15.8%)	10 (20.4%)	31 (38.8%)	33 (51.6%)
Active fistulizing disease	5 (26.3%)	14 (28.6%)	28 (35%)	23 (35.9%)
Extra-intestinal manifestations, *n* (%)	5 (26.3%)	11 (22.4%)	38 (47.5%)	30 (46.9%)
Severe disease, *n* (%)	6 (31.6%)	12 (24.5%)	31 (38.8%)	31 (48.4%)
Prior ustekinumab, *n* (%)	—	1 (2.1%)	12 (15.2%)	14 (21.9%)
Prior natalizumab, *n* (%)	—	1 (2.1%)	4 (5.1%)	6 (9.4%)

IQR, interquartile range.

progression to surgery (P=0.815) were similar (**Supplementary Figure 4**). Outcomes were similar when stratified by concomitant immunosuppressive agent(s) (**Supplementary Figure 5**), and by whether an individual had stricturing or penetrating disease complications, with the exception of patients with stricturing or penetrating disease complications having higher rates of progression to surgery (P=0.037) (**Supplementary Figure 6**).

Safety

The 212 patients included in our analysis received a total of 1,433 infusions over 160 patient years of follow-up. There were a total of five infusion reactions (3.5 per 1,000 infusions), only one of which required discontinuation of VDZ therapy (0.7 per 1,000 infusions). Rates of serious adverse events and serious infections were 10 and 13 per 100 patient years follow-up, respectively. The majority of serious infections were enteric or sinopulmonary in origin (**Table 3**). Five patients developed a severe musculoskeletal syndrome after the first or second dose of VDZ, which was characterized by diffuse myalgias, arthralgias, and severe headaches requiring discontinuation of therapy.

The single case of optic neuritis was in a female patient who had previously failed TNF-antagonist and natalizumab therapy. She was on azathioprine when she began VDZ therapy, and after the second dose of VDZ she developed sudden painless left eye blindness. She was eventually started on plasmapheresis after non-response to steroids, with gradual improvement in her vision. She had a previous episode of optic neuritis after golimumab therapy but had not been exposed to a TNF-antagonist in >6 months preceding initiation of VDZ and had not had any neurological complications with prior exposure to natalizumab.

The single death observed was in a 39-year-old female patient with no other co-morbid conditions, who developed post-operative septic shock. Her ileocolonic CD had previously been complicated by perianal fistulas, small bowel strictures, and internal fistulas with abscess formation, that had required multiple prior surgeries and resections, including a diverting ostomy. She had previously failed infliximab, adalimumab, certolizumab, azathioprine, and prednisone, and had failed seven doses of VDZ monotherapy, before undergoing another surgical resection of a small bowel stricture 4 weeks after her last VDZ dose. Two days post-operatively she developed an acute abdomen, underwent an exploratory laparotomy, and was found to have an anastomotic leak, which was repaired. During the following 3 days, she developed worsening sepsis and shock, and subsequently died from multi-organ dysfunction.

DISCUSSION

In this multi-center consortium, we were able to make several key observations about the real-world experience with VDZ for

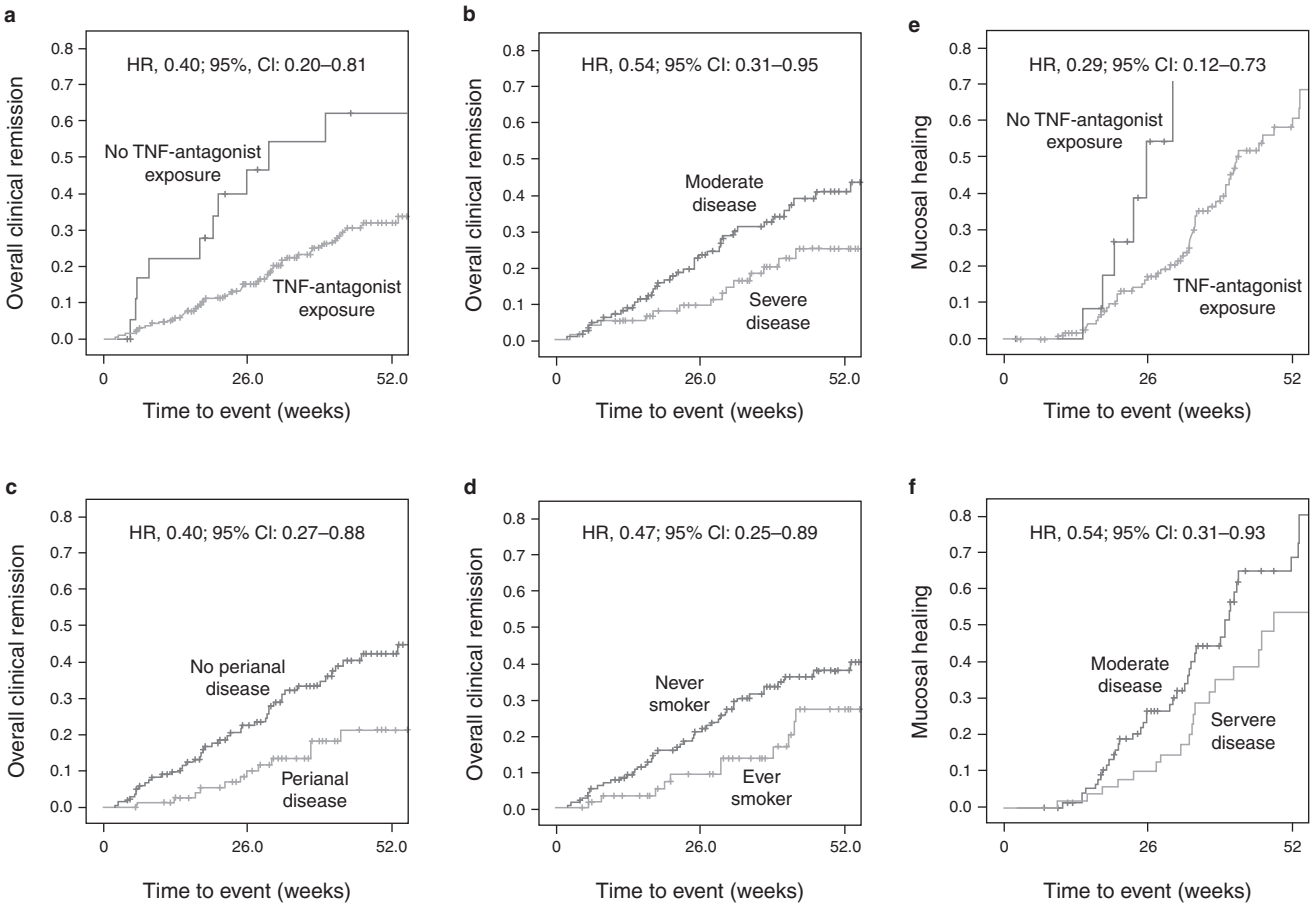

Figure 1. Cumulative rate of clinical remission and mucosal healing for clinical predictors. (**a**–**d**) Clinical remission during VDZ maintenance therapy stratified by (**a**) prior exposure to TNF-antagonists (yes vs. no); (**b**) baseline disease severity (moderate vs. severe); (**c**) baseline perianal disease (yes vs. no); and (**d**) smoking status (ever smoker vs. never smoker). (**e**,**f**) Mucosal healing during VDZ maintenance therapy stratified by (**e**) prior exposure to TNF-antagonists (yes vs. no) and (**f**) baseline disease severity (moderate vs. severe). HR, hazard ratio; 95% CI, 95% confidence interval; TNF-antagonist, tumor necrosis factor antagonist; VDZ, vedolizumab.

over 200 patients with moderately to severely active CD. First, clinical remission or mucosal healing were achieved in a substantial proportion of individuals, and treatment effectiveness was time dependent with the greatest benefit being observed after 6 months of therapy. Second, disease severity at time of VDZ initiation, active perianal disease, smoking status, and prior exposure to TNF-antagonists were associated with a reduction in treatment effectiveness, and the impact on outcomes was incremental according to the number of risk factors present. Finally, serious adverse events or serious infections occurred in 8–10% of CD patients initiating VDZ therapy, but the majority of these could be readily managed without discontinuation of therapy.

Within the GEMINI clinical trials 39% of patients achieved clinical remission and 32% achieved steroid-free clinical remission by 12 months (5). Although data on the real-world effectiveness of VDZ for CD is now available, follow-up within these studies is limited, and the long-term effectiveness of VDZ over 6–12 months remains to be established (18–21). We have addressed this gap and observed that in a refractory population of moderate–severe CD patients, 90% of whom had failed TNF-antagonist therapy, clinical remission and steroid-free remission were achieved in ~35% of individuals by 12 months. Similar to recent observations from the GEMINI trial, we also observed that the effectiveness of VDZ was time dependent, and the greatest benefit appeared to be after 6 months of therapy (5,22). Furthermore, similar to TNF-antagonists, the majority of the risk for loss of response was within the 6–12-month window after VDZ initiation (1), and interval shortening allowed for re-capturing of response or remission in some cases.

Our study further expanded on the available literature by presenting the first report of mucosal healing and deep remission rates with VDZ. When considering TNF-antagonists, mucosal healing rates at 12 months with adalimumab and certolizumab have been reported to be in the range of 20–25%, with endoscopic remission being achieved in up to 50% of patients (23,24). With infliximab, ~30% of individuals achieved mucosal healing by 6 months with rates increasing to 45% when using concomitant immunosuppressive therapy (4,25). Deep remission can be achieved in

Table 3. Serious adverse events and serious infections

Adverse event	Event rate per 100 PYF	Comment
Enteric infections (*n*=8)	5 per 100 PYF	Seven of these were *Clostridium difficile* (44 per 1,000 PYF) and of these, three required hospitalization and FMT. The other case was CMV duodenitis. All were able to continue therapy after treatment.
Sinopulmonary infections (*n*=7)	4.4 per 100 PYF	One case of sinusitis after escalating to Q4 week dosing. Continued VDZ therapy.
Severe arthralgia (*n*=5)	3.1 per 100 PYF	Severe arthralgias and myalgias requiring discontinuation of therapy
Urogenital infection (*n*=4)	2.5 per 100 PYF	UTI, labial abscess, fungal rash, anogenital HSV infection. Continued VDZ therapy.
Autoimmune hepatitis (*n*=1)	0.6 per 100 PYF	Transaminitis with positive ANA, and improvement after stopping VDZ
Optic neuritis (*n*=1)	0.6 per 100 PYF	Optic neuritis after second dose of VDZ. Prior episode of optic neuritis after golimumab. Unclear if optic neuritis was TNF-antagonist-induced as had tolerated infliximab and adalimumab. Stopped VDZ.
Bowel perforation (*n*=1)	0.6 per 100 PYF	Worsening bowel obstruction and perforation requiring surgery. Stopped VDZ therapy.
Meningitis (*n*=1)	0.6 per 100 PYF	Previously reported (11) and stopped VDZ therapy.
Septic shock and death (*n*=1)	0.6 per 100 PYF	Exploratory laparotomy for anastomosis leak. Developed sepsis, shock, and death 72 h later.

ANA, anti-nuclear antibody; CMV, cytomegalovirus; PYF, patient years of follow-up; Q4, every 4; UTI, urinary tract infection; VDZ, vedolizumab.

over 50% of individuals treated with infliximab at 6 months, but these rates drop considerably (33%) when looking at individuals with a more aggressive phenotype and prior disease-related complications (e.g., bowel resection) (26). Our observed rates for mucosal healing are in keeping with mucosal healing rates seen with TNF-antagonists, and although our observed rates for deep remission with VDZ are lower than those with TNF-antagonists, the majority of individuals included in our cohort were refractory to prior TNF-antagonists and a substantial proportion had a history of disease-related complications. Given only a sub-set of individuals underwent an assessment for mucosal healing, and clinical remission rates increased to over 50% by 18 months for the entire cohort, it's possible that rates of deep remission with VDZ will more closely approximate those seen with TNF-antagonists when examining a larger cohort of less refractory individuals over an extended duration of time.

Within our cohort, we observed that the effectiveness of VDZ was significantly influenced by prior TNF-antagonist exposure. This is in keeping with the GEMINI trial, which demonstrated a reduction in clinical remission rates at 12 months (29%) among individuals with prior TNF-antagonist exposure, but we expanded upon this through two key observations. The impact of prior TNF-antagonist failure on the effectiveness of VDZ was consistent across all outcomes, including mucosal healing and progressing to surgery, and it appeared to be incremental according to the number of TNF-antagonists an individual had been exposed to. One potential hypothesis for this may be that these patients simply had a more aggressive phenotype and inherent resistance to biologic therapy (27). This may help to explain why other features known to be associated with a more aggressive natural disease course, such as disease severity, smoking status and active perianal disease, were identified to be independent predictors of failing to achieve clinical remission or mucosal healing (28–30). It does not entirely explain these findings, however, given several other factors like prior stricturing or penetrating disease complications, bowel resection, and disease duration or age at diagnosis, were not associated with a reduction in treatment effectiveness. An alternative hypothesis is that these risk factors portend a worse prognosis through alternations in lymphocyte proliferation, chemokine and cytokine expression, and/or variations in adhesion molecule expression (29–32). This second hypothesis will need to be explored further, as relative alterations in adhesion molecule expression may be important when attempting to identify which individuals may be more likely to respond to biologics that selectively target various leukocyte endothelial cell interactions (33,34).

Our rates for serious adverse events and serious infections were similar to those seen in the GEMINI trial and other population based cohort studies (12,20,21), and we again observed that the majority of infections were enteric or sinopulmonary in origin, and individuals could safely continue therapy with only a minority requiring discontinuation. Although a single case of optic neuritis was observed, it is unclear if this is truly related to VDZ therapy given the prior correlation with TNF-antagonist therapy and the lack of symptoms with prior natalizumab exposure. Within the GEMINI trial dataset there were no reported cases of demyelination (12). Population based cohort studies have observed paresthesias when initiating VDZ (20,21), but neurological evaluation and imaging were unremarkable for demyelination in these individuals. Similarly, a single death was observed but this was related to an anastomotic leak in an individual who had undergone multiple prior surgeries and resection, making it unclear if this is truly related to VDZ or rather technical difficulties from prior surgeries and adhesions.

Our study has some important limitations. Patient identification and data collection was performed retrospectively, and all of the sites included in this consortium are referral centers within their respective regions. We have tried to overcome these limitations by creating uniform outcome assessments, and by using more objective measures of treatment response, but biases inherent to a study of this design may have influenced our results and the external validity of our observations when incorporating these findings into clinical practice. The majority of individuals reported within this study were biologic experienced, with a substantial proportion of individuals have been exposed to 2 or more biologic agents.

This may impact the validity of our findings when considering biologic-naive individuals, but given the restrictions being placed by third party payers on the use of VDZ before TNF-antagonists, our results will remain of importance when determining which individuals should transition to VDZ or an alternative biologic after failing the first or second TNF-antagonist. A selection bias may also be present for clinical outcomes given the variability in follow-up intervals and assessment for mucosal healing. We have attempted to address this by using the Kaplan–Meier statistics, which accounts for drop-out and loss to follow-up, but it is possible that heavy censoring or a lack of independence of censoring and events could have influenced our estimates. Furthermore, a detailed assessment of perianal disease activity, and response to VDZ over time for these patients, could not be assessed due to variations in assessments across sites and within patients. Long-term prospective studies using well-described and validated scoring indices are therefore needed to fully understand the effectiveness of VDZ.

In summary, VDZ is a safe and effective treatment option for moderate–severe CD in clinical practice and a substantial proportion of individuals are able to achieve clinical remission, steroid-free remission, mucosal healing, and deep remission. We have identified several clinical factors that should be taken into consideration when discussing with patients the optimal positioning and use of VDZ among currently approved biologic therapies, and providers should allow a minimum of 6 months to determine treatment response. Among high risk individuals or those failing to achieve an adequate response, interval escalation can be considered in an effort to optimize treatment outcomes, recognizing that high quality data supporting this approach is still needed.

CONFLICT OF INTEREST

Guarantor of the article: Parambir S. Dulai, MD.

Author contributions: Study concept and design: P.S.D. Acquisition of data: P.S.D., S.S., F.P., N.N., K.C., D.W., D.H., D.L., A.S., and E.S. Analysis and interpretation of data: P.S.D., S.S., X.J., and S.W. Drafting of the manuscript: P.S.D. and S.S. Critical revision of the manuscript for important intellectual content: B.S.B., J.T.C., S.K., C.A.S., E.V.L., W.J.S., B.E.S., and J.-F.C. Approval of the final manuscript: All authors. Study supervision: C.A.S., E.V.L., W.J.S., and J.-F.C.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Vedolizumab (VDZ) is an effective treatment option for moderately to severely active Crohn's disease (CD).
- ✓ The safety and effectiveness of VDZ in routine practice is not well-characterized, and the optimal positioning and use of this agent is unclear.

WHAT IS NEW HERE

- ✓ In routine practice, clinical remission, steroid-free remission, and deep remission (clinical remission and mucosal healing), can be achieved in 1/3 of individuals.
- ✓ Disease severity, active perianal disease, smoking status, and prior exposure to tumor necrosis factor (TNF)-antagonists were associated with a reduction in treatment effectiveness.
- ✓ VDZ is well-tolerated and only a minority of individuals require discontinuation of therapy due to adverse events or intolerance.

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