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Vedolizumab for Ulcerative Colitis: Treatment Outcomes from the VICTORY Consortium

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OBJECTIVES: **We aimed to quantify the safety and effectiveness of vedolizumab (VDZ) when used for UC, and to identify predictors of response to treatment.**

METHODS: **Retrospective review (May 2014–December 2016) of VICTORY Consortium data. Adults with follow-up after starting VDZ for clinically active UC were included. Primary effectiveness outcomes were cumulative rates of clinical remission (resolution of all UC-related symptoms) and endoscopic remission (Mayo endoscopic sub-score 0). Key secondary effectiveness outcomes included cumulative rates of corticosteroid-free remission and deep remission (clinical remission and endoscopic remission). Cox proportional hazard analyses were used to identify independent predictors of treatment effectiveness. Non-response imputation (NRI) sensitivity analyses were performed for effectiveness outcomes. Key safety outcomes were rates of serious infection, serious adverse events, and colectomy.**

RESULTS: **We included 321 UC patients (71% prior TNFα antagonist exposure, median follow-up 10 months). The 12-month cumulative rates of clinical remission and endoscopic remission were 51% and 41%, respectively. Corresponding rates for corticosteroid-free remission and deep remission were 37% and 30%, respectively. Using NRI, 12-month rates were 20% ($n=64/321$) for clinical remission, 17% ($n=35/203$) for endoscopic remission, 15% ($n=30/195$) for corticosteroid-free remission, and 14% ($n=28/203$) for deep remission. A majority of the patients without adequate follow-up at 12 months who were deemed non-responders using NRI had already achieved clinical remission ($n=70$) or a significant clinical response ($n=36$) prior to 12 months. VDZ discontinuation prior to 12 months was observed in 91 patients, for lack of response ($n=56$), need for surgery ($n=29$), or adverse event ($n=6$). On multivariable analyses, prior exposure to a TNFα antagonist was associated with a reduced probability of achieving clinical remission (HR 0.53, 95% CI 0.38–0.75) and endoscopic remission (HR 0.51, 95% CI 0.29–0.88). Serious adverse events and serious infections were reported in 6% and 4% of patients, respectively. Overall cumulative rates of colectomy over 12 months were 13%, with lower rates observed in patients naive to TNFα antagonist therapy (2%) than those who had been exposed to TNFα antagonists (19%).**

CONCLUSION: **In this large real-world cohort we observed that VDZ was well tolerated and effective in achieving key clinical outcomes.**

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon, characterized by bloody diarrhea, urgency, and abdominal pain. For patients with moderate-to-severe disease activity, or those not responding adequately to other immunosuppressive agents (i.e., thiopurines and/or steroids), treatment with tumor necrosis factor-α (TNFα) antagonists results in improved clinical disease activity, tapering off steroids, and endoscopic remission [1]. Up to two-thirds of patients however may either fail to respond or lose response over the 1st year following initiation of TNFα antagonist therapy. Furthermore, TNFα antagonists can be associated with serious adverse events including opportunistic infections and malignancies [2].

Vedolizumab (VDZ), a novel humanized monoclonal antibody, selectively inhibits the migration of gut-homing memory T cells into the gastrointestinal submucosa by antagonizing the interaction of α4β7 integrin with its ligand MAdCAM-1 (mucosal vascular addressin cell adhesion molecule-1). The GEMINI 1 study was a randomized controlled trial (RCT) that established the efficacy and safety of VDZ induction and maintenance therapy in UC [3]. Although this trial demonstrated a statistically significant improvement in clinical remission, steroid-free remission, and endoscopic remission with VDZ, compared to placebo, clinical trial data are limited by the restrictive inclusion criteria often used in phase 3 trials and therefore may not readily translate to clinical practice [4]. Real-world studies are therefore useful to provide additional information regarding how biologics perform in clinical practice. In a previous publication, we reported on treatment outcomes in Crohn's disease patients treated with VDZ in the real-world setting [5]. The current study aims to report on treatment outcomes in UC patients receiving treatment with VDZ and to identify predictors of treatment outcomes to optimize the use of VDZ in routine practice.

METHODS

Study design

This is a retrospective review of the VICTORY Consortium registry [5]. In brief, this is a multicenter collaborative research group where outcomes are pooled for inflammatory bowel disease (IBD) patients treated with biologics. Institutional Review Board approval was obtained from each site for ongoing data collection and transfer. Data were collected individually by sites using a standardized data collection form and transferred (after de-identification) to the coordinating site (University of California, San Diego) for data compilation and analysis. The current analysis represents data collected between May 2014 and December 2016. The results of this study are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies [6].

Variables

Data on variables of interest were collected including: patient characteristics (age at diagnosis, age at VDZ initiation, gender, smoking status, body mass index (BMI)), disease characteristics (prior hospitalizations, prior surgeries, disease-related complications or extra-intestinal manifestations, and phenotype classified according to Montreal sub-classifications of E1 through E3), and treatment history (steroids, immunomodulators, and TNFα 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). Disease duration was assessed both as a continuous variable and as a binary variable (<2 years, <5 years) to determine if VDZ use early in the disease course was an important predictor.

Participants

Patients from the VICTORY Consortium were included in the current analysis if they had: (a) a confirmed diagnosis of UC based on clinical, endoscopic, and/or histologic data; (b) active clinical symptoms attributed to UC prior to VDZ therapy; and (c) at least one clinical or endoscopic follow-up after VDZ initiation irrespective of response status after induction. Patients on VDZ with Crohn's disease, indeterminate colitis, or pouchitis were excluded.

Outcomes

Primary effectiveness outcomes were the cumulative rates of clinical remission and endoscopic remission over 6 and 12 months. Secondary effectiveness outcomes included cumulative rates of: clinical response, corticosteroid-free remission, endoscopic improvement, and deep remission (achieving both endoscopic remission and clinical remission). Clinical response to therapy was based on a physician global assessment (PGA), where response was defined as a ≥50% reduction in UC symptoms/severity and clinical remission was defined by complete resolution of all UC-related symptoms. Corticosteroid-free remission rates were reported only in those patients on either prednisone or budesonide-MMX (Multi Matrix System) at the initiation of VDZ and was defined as achieving clinical remission, tapering off steroids, and the absence of a subsequent steroid prescription within 1 month. Endoscopic improvement was defined by an endoscopic Mayo score of ≤1 [7], and endoscopic remission defined as an endoscopic Mayo score of 0. The coordinating site investigator (PSD) used de-identified endoscopy reports to confirm endoscopic Mayo scores and any discrepancies were resolved through consensus between the study sites and the coordinating site. Sensitivity analyses were done for endoscopic outcomes after limiting the analysis to those patients with confirmed endoscopically active disease (Mayo endoscopic sub-score of 1 to 3) within 4 weeks of VDZ initiation.

Safety outcomes of interest included the proportion of patients who developed infusion reactions, serious infections (defined by requiring antibiotics or resulting in discontinuation of VDZ, hospitalization, or death), and serious adverse events (defined by having a serious infection, or a non-infectious complication requiring discontinuation of VDZ, hospitalization, or death); and cumulative rates of colectomy for medically refractory disease.

Statistical analysis

Statistical analyses were performed using SPSS. Continuous variables were presented as means (and standard deviations (SD)) or as medians (and inter-quartile 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 one-way analysis of variance with Bonferroni correction (three or more group comparisons), and for the comparison of baseline binary variables we used Pearson's Chi-square or Fisher's exact test. Primary and secondary effectiveness outcomes were described quantitatively as cumulative rates using Kaplan–Meier survival and time-to-event analyses. Recognizing the risk for attrition bias with observational data, variability in follow-up, and potential impact of right censoring, we performed sensitivity analyses using non-response imputation (NRI) analyses at 12 months to provide a conservative estimate for treatment effectiveness over 1 year. NRI assumes that all patients with follow-up less than 12 months are non-responders irrespective of response status prior to this time point.

Cox proportional hazard regression analyses were performed to identify independent predictors of treatment outcomes. Baseline variables from the univariable analyses with a p value of <0.20 were then fitted and a backward model selection approach was taken where the variable with the highest p value was sequentially selected out until all remaining variables in the model had a p value of <0.05. An assessment of interaction terms was then performed and interactions were retained if they had a p value of <0.05. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented for predictors where a HR of <1 indicated a predictor was associated with a reduced probability for achieving the outcome and a HR of >1 indicated a predictor was associated with an increased probability for achieving the outcome.

Study sponsor

Takeda Pharmaceuticals provided funding for statistical support to analyze the data. Takeda Pharmaceuticals and associated employees did not have access to any of the data, and all data analyses were performed at the University of California, San Diego, by VICTORY Consortium investigators or statisticians.

RESULTS

Demographics

A total of 321 UC patients from the VICTORY Consortium dataset were included in the current analysis. The median duration of clinical follow-up was 10 months (IQR 5.5–14). A total of 49% were female, and 71% had prior exposure to TNFα antagonists (Table 1). The majority of patients had moderate-to-severe disease, with 34% of patients having severe disease at baseline. Pancolitis at the time of treatment initiation was present in 56% of patients. Patients initiating VDZ for proctitis had moderate–severe endoscopic disease activity despite systemic steroids and a majority of them were failing TNFα antagonist therapy ($n=11/16$). Concomitant immunosuppressive agents were used in most patients, including concurrent steroid use (prednisone or budesonide-MMX) in 60% of patients and immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) in 38% of patients.

Treatment outcomes

Cumulative rates. At 6 and 12 months, the overall cumulative rates of clinical response were 54% and 75%, respectively (Table 2, Fig. 1). The overall cumulative rates of clinical remission at 6 and 12 months were 36% and 51%, respectively. Overall cumulative rates of corticosteroid-free clinical remission at 6 and 12 months were 21% and 37%, respectively. Overall cumulative rates of endoscopic improvement (Mayo endoscopic sub-score of 0 or 1) and endoscopic remission (Mayo endoscopic sub-score of 0) at 6 months were 29% and 18%, respectively, with corresponding rates at 12 months of 62% and 41%. Among patients with confirmed endoscopically active disease at baseline, cumulative rates of endoscopic improvement were 28% and 61% at 6 and 12 months, respectively. Corresponding rates among these patients with confirmed baseline endoscopically active disease for endoscopic remission were 15% and 43%, respectively. Overall cumulative rates of deep remission (achieving both clinical remission and endoscopic remission) were 14% at 6 months and 30% at 12 months.

The overall median time to achieving clinical response, clinical remission, corticosteroid-free remission, and endoscopic remission were 96 days (IQR 53–178), 167 days (IQR 81–320), 215 days (IQR 111–386) and 195 days (IQR 112–309), respectively. Among patients who were naive to TNFα antagonist therapy, the median time to achieve these outcomes was shorter for clinical response (77 days, IQR 45–123), clinical remission (77 days, IQR 45–135), and corticosteroid-free remission (147 days, IQR 86–270), but not endoscopic remission (196 days, IQR 137–293).

Non-response imputation. A total of 224 patients had >6 months of follow-up and 124 had >12 months of follow-up. The most common reasons for lack of follow-up beyond these time points were: achieving complete clinical remission prior to these time points and not being seen in clinic thereafter ($n=70$), achieving a significant response but no follow-up to assess for complete clinical remission ($n=36$), lack of significant response to date resulting in VDZ discontinuation ($n=56$), need for colectomy ($n=29$), or an adverse event resulting in discontinuation of therapy ($n=6$). Of the 70 patients who had achieved complete clinical remission and were not seen in follow-up thereafter, all 28 who were on steroids at baseline had achieved corticosteroid-free deep remission at last follow-up.

Using a NRI analysis the proportion achieving a clinical response at 12 months was 27% ($n=86/321$). Clinical remission was achieved in 20% ($n=64/321$), and corticosteroid-free remission in 15% ($n=30/195$). Endoscopic improvement and endoscopic remission were achieved in 30% ($n=51/203$) and 17% ($n=35/203$), respectively. Deep remission was achieved in 14% ($n=28/203$) (Table 3).

Predictors of treatment outcomes

On univariable analyses, prior exposure to a TNFα antagonist was associated with a reduced probability of achieving clinical response (HR 0.71), clinical remission (HR 0.52), endoscopic improvement (HR 0.63), and endoscopic remission (HR 0.51)

Table 1 Demographics of study patients

	Overall ($n=321$)	TNFα antagonist naive ($n=93$)	1 TNFα antagonist ($n=140$)	≥2 TNFα antagonists ($n=88$)
Demographics				
Gender, female	158 (49)	56 (60)	57 (41)	45 (51)
Median age, years (IQR)	38 (27–55)	39 (25–59)	38 (28–52)	36 (26–57)
Median disease duration, years (IQR)	6 (2–12)	6 (2–12)	5 (2–10)	7 (3–14)
Ever smoker	83 (26)	27 (29)	36 (26)	20 (23)
Hospitalized last 12 months	85 (26)	20 (22)	38 (27)	56 (64)
BMI, median (IQR)	24.1 (21.6–29.1)	23.9 (21.9–28.1)	24 (21.3–29.2)	25.2 (21.6–30.1)
CRP, median (IQR)	1.9 (0.5–6.7)	1.0 (0.3–4.2)	2.2 (0.7–8.4)	2.9 (0.7–9.3)
Albumin, median (IQR)	4.0 (3.7–4.3)	4.1 (3.8–4.4)	4.0 (3.7–4.3)	4.0 (3.7–4.3)
Extent, *n*/*N* (%)				
E1	16/319 (5)	5/91 (6)	8/140 (6)	3/88 (3)
E2	125/319 (39)	41/91 (45)	49/140 (35)	35/88 (40)
E3	178/319 (56)	45/91 (49)	83/140 (59)	50/88 (57)
Clinical severity, *n*/*N* (%)				
Mild	32/321 (10)	14/94 (15)	11/140 (8)	7/87 (8)
Moderate	180/321 (56)	61/94 (65)	76/140 (54)	43/87 (49)
Severe	109/321 (34)	19/94 (20)	53/140 (38)	37/87 (43)
Endoscopic severity, *n*/*N* (%)				
Mayo 1	25/248 (10)	6/70 (8)	11/109 (10)	8/69 (12)
Mayo 2	117/248 (47)	44/70 (63)	47/109 (43)	26/69 (38)
Mayo 3	106/248 (43)	20/70 (29)	51/109 (47)	35/69 (50)
Therapies, *n* (%)				
TNFα antagonist exposure	228 (71)	–	–	–
TNFα antagonist failure	195 (61)	–	121 (86)	74 (84)
Concomitant steroids	195 (60)	50 (54)	84 (60)	61 (68)
Concomitant IM	122 (38)	24 (26)	57 (41)	35 (40)

Variables are listed as *n* (%) unless otherwise indicated
BMI body mass index, *CRP* C-reactive protein, *IM* immunomodulator

Table 2 Overall cumulative rates of treatment outcomes stratified by TNFα antagonist exposure

	Overall		TNFα antagonist naive		1 TNFα antagonist		≥2 TNFα antagonists	
	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo
Response	54%	75%	63%	74%	52%	78%	45%	70%
Remission	36%	51%	51%	61%	31%	48%	28%	44%
CSF-REM	21%	37%	25%	44%	17%	32%	18%	33%
EI	29%	62%	36%	65%	28%	60%	23%	43%
ER	18%	41%	24%	51%	16%	45%	14%	28%
Deep remission	14%	30%	20%	40%	13%	35%	9%	19%
Colectomy	6%	13%	0%	2%	6%	19%	11%	18%

Deep remission defined as achieving both clinical remission and endoscopic remission
CSF-REM corticosteroid-free remission, *EI* endoscopic improvement, *ER* endoscopic remission

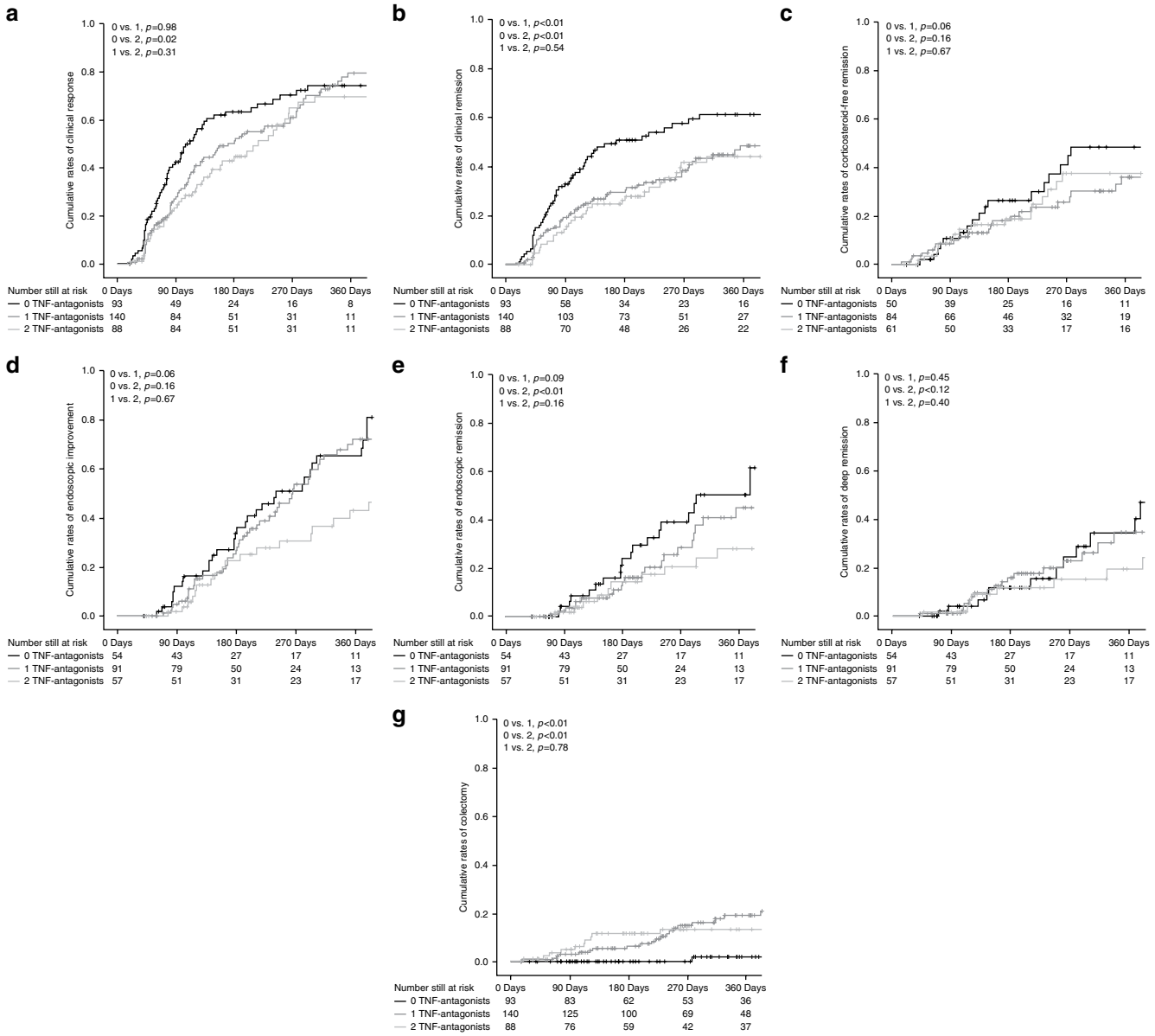

Fig. 1 Kaplan–Meier curves for treatment effectiveness stratified by number of prior TNF antagonists. **a** Cumulative rates of clinical response (>50% reduction in physician global assessment); **b** cumulative rates of clinical remission (complete resolution of all UC-related symptoms); **c** cumulative rates of corticosteroid-free remission (reported in those on prednisone or budesonide at baseline; achieving clinical remission, tapering off steroids, and absence of repeat steroid prescription within 1 month); **d** cumulative rates of endoscopic improvement (Mayo endoscopic sub-score of 0 or 1); **e** cumulative rates of endoscopic remission (Mayo endoscopic sub-score of 0); **f** cumulative rates of deep remission (clinical remission and endoscopic remission); **g** cumulative rates of colectomy. All comparisons performed using log-rank statistics

(Table 4). On multivariable analyses, prior exposure to a TNFα antagonist remained statistically significant and was associated with a reduced probability of achieving clinical remission (HR 0.53), endoscopic improvement (HR 0.63), and endoscopic remission (HR 0.51). Cumulative rates of clinical outcomes were higher in TNFα antagonist-naive patients, and there was an incremental reduction in effectiveness with the number of TNFα antagonists previously used (Tables 2 and 3). For all outcomes examined (clinical response and remission, corticosteroid-free remission, endoscopic improvement, endoscopic remission, and deep remission), among patients with prior TNFα antagonist exposure, there was no significant difference between patients who were prior treatment failures vs. those who were exposed but not failures, and those with primary non-response to TNFα antagonists compared to those who had previously experienced loss of response.

On univariable and multivariable analyses, proctitis (versus more extensive disease) was a statistically significant predictor of achieving clinical response (HR 1.99), clinical remission (HR 2.43), endoscopic improvement (HR 2.10), and endoscopic remis-

Table 3 Proportion achieving treatment outcomes at 12 months stratified by TNF-α antagonist exposure using non-response imputation analysis

	Overall	TNFα antagonist naive	1 TNFα antagonist	≥2 TNFα antagonists
Response	27%(*n*=86/321)	30%(*n*=28/93)	26%(*n*=36/140)	25%(*n*=22/88)
Remission	20%(*n*=64/321)	27%(*n*=25/93)	17%(*n*=24/140)	17%(*n*=15/88)
CSF-REM	15%(*n*=30/195)	20%(*n*=10/50)	11%(*n*=9/84)	18%(*n*=11/61)
EI	30%(*n*=61/203)	37%(*n*=20/54)	27%(*n*=25/92)	28%(*n*=16/57)
ER	17%(*n*=35/203)	22%(*n*=12/54)	16%(*n*=15/92)	14%(*n*=8/57)
Deep remission	14%(*n*=28/203)	22%(*n*=12/54)	12%(*n*=11/92)	9%(*n*=5/57)
Colectomy	9%(*n*=30/321)	1%(*n*=1/93)	14%(*n*=19/140)	11%(*n*=10/88)

Deep remission defined as achieving both clinical remission and endoscopic remission
CSF-REM corticosteroid-free remission, *EI* endoscopic improvement, *ER* endoscopic remission

sion (HR 3.87). On univariable analyses, higher baseline albumin was associated with an increased probability of achieving clinical response (HR 1.44), endoscopic remission (HR 2.00), and deep remission (HR 2.11). This did not remain significant on multivariable analyses (Table 4).

Safety

Overall, VDZ was well tolerated in this population. There were a total of 15 infusion reactions during the 2483 infusions, equating to an incidence of 6 per 1000 infusions. None of these required discontinuation of VDZ, and they all occurred after the first or second infusion with the majority being characterized by rash. Serious adverse events and serious infections were reported in 6% and 4%, respectively. Serious infections were as follows: *Clostridium difficile* ($n=5$, 1 required hospitalization), *Entamoeba histolytica* ($n=1$), cytomegalovirus colitis ($n=1$), cholangitis ($n=1$), sinusitis ($n=2$, 1 resulted in discontinuation of drug), pneumonia ($n=1$), transverse myelitis ($n=1$), and diverticulitis ($n=1$). All patients experiencing serious infections had prior exposure to TNFα antagonists. The single patient with transverse myelitis had prior exposure to infliximab and symptoms resolved over time, with no residual symptoms remaining. An additional 5 patients had self-resolving upper respiratory tract symptoms that did not require antibiotics or discontinuation of therapy, and 6 patients had diffuse myalgias and flu-like symptoms of which 4 required discontinuation of therapy. A seizure occurred in 1 patient after the second dose of VDZ, requiring discontinuation of therapy. Further work-up revealed a mural thrombus in the heart on echocardiography.

The cumulative rate of colectomy at 6 and 12 months was 6% and 13%, respectively. Cumulative rates were statistically significantly lower in TNFα antagonist-naive patients (0% at 6 months, 2% at 12 months), as compared to TNFα antagonist-exposed patients (8% at 6 months, 17% at 12 months, $p<0.001$), and there was an incremental increase in cumulative rate of colectomy based on the number of TNFα antagonist agents previously used (Tables 2 and 3).

DISCUSSION

RCTs have demonstrated VDZ efficacy in UC with no signs of safety concern [3, 8], and with several small real-world studies confirming treatment benefit in clinical practice [9–11]. Although these cohorts help to confirm clinical trial findings, the small size (<100 patients) makes it difficult to confidently estimate treatment effectiveness, particularly among sub-populations of interest. Through the VICTORY consortium, we report on a large cohort of UC patients treated with VDZ in a real-world clinical setting.

In a refractory population of UC patients of whom 71% had prior TNFα antagonist exposure, cumulative 12-month outcomes of clinical response (75%), clinical remission (51%), corticosteroid-free remission (37%), endoscopic improvement (62%), and endoscopic remission (41%) were encouraging and are comparable to the results described in GEMINI 1 [3]. Furthermore, overall results reported in the VICTORY consortium are similar to those reported in the real-world experiences from France [9] and Sweden [11], except for a somewhat higher clinical response rate in our UC population (75%–VICTORY vs. 50.4%–France, 59%–Sweden) and a higher corticosteroid-free remission rate in the Swedish population (57%–Sweden vs. 37%–VICTORY, 40.5%–France). The discrepancy in clinical response rates could be explained by our use of a PGA rating to establish clinical response rather than strict criteria based on the partial Mayo score. Furthermore, up to 98% of patients were previously exposed to TNFα antagonists in France and Sweden compared to 71% in VICTORY, suggesting that our patients may have been more responsive to VDZ based on their natural history. With respect to the higher corticosteroid-free remission rates reported in Sweden, their shorter disease duration (4 years–Sweden vs. 6 years–VICTORY, 8.4 years–France) and greater use of concomitant immunosuppression (46%–Sweden vs. 38%–VICTORY, 20.7%–France) could have resulted in an abbreviated steroid taper. In contrast to these real-world studies, diminished rates of clinical response (38%), clinical remission (25%), and corticosteroid-free remission (22%) at week 54 were observed in the German real-world study, which can be explained by the fact that this study used a NRI analysis and it included patients who

Table 4 Univariable and multivariable predictors

	Univariable analyses			Multivariable analyses		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Clinical response						
Age	0.99	0.99–1.00	0.19			
Albumin	1.44	1.03–2.02	0.03			
TNFα antagonist exposure	0.71	0.53–0.96	0.03			
Proctitis only	2.05	1.16–3.62	0.01	1.99	1.13–3.52	0.02
Clinically severe	0.73	0.53–0.99	0.04	0.72	0.52–0.98	0.04
Clinical remission						
Age	0.99	0.98–1.00	0.09			
Female	1.23	0.90–1.76	0.18			
Albumin	1.37	0.94–2.01	0.11			
TNFα antagonist exposure	0.52	0.37–0.74	<0.01	0.53	0.38–0.75	<0.01
Steroids	0.79	0.56–1.10	0.16			
Proctitis only	2.38	1.38–4.42	<0.01	2.43	1.31–4.53	<0.01
Clinically severe	0.66	0.46–0.97	0.03			
Corticosteroid-free remission						
Age	0.99	0.97–1.00	0.13			
Female	1.44	0.89–2.42	0.17			
Disease <2 years	0.58	0.30–1.12	0.10			
TNFα antagonist exposure	0.59	0.34–1.02	0.06			
Clinically severe	0.53	0.30–0.95	0.03	0.53	0.30–0.95	0.03
Endoscopic improvement						
Age	0.98	0.95–1.01	0.19			
Albumin	1.42	0.87–2.32	0.16			
TNFα antagonist exposed	0.63	0.42–0.95	0.03	0.63	0.42–0.95	0.03
Steroids	0.64	0.44–0.94	0.02			
Proctitis only	2.00	1.01–3.99	0.05	2.10	1.05–4.20	0.04
Clinically severe	0.76	0.51–1.13	0.17			
Endoscopic remission						
Albumin	2.00	1.02–3.92	0.05			
TNFα antagonist exposure	0.51	0.30–0.88	0.01	0.51	0.29–0.88	0.02
Steroids	0.59	0.34–0.99	0.05			
Imunomodulator	0.67	0.40–1.13	0.13			
Proctitis only	3.58	1.67–7.65	<0.01	3.87	1.80–8.33	<0.01
Clinically severe	0.69	0.40–1.20	0.19			
Deep remission						
Female	1.46	0.83–2.59	0.19			
Albumin	2.11	1.12–3.98	0.02	2.11	1.12–3.98	0.02

were unable to complete VDZ induction therapy in this analysis [10]. When using a NRI analysis in our cohort, we observed clinical remission and corticosteroid-free remission in 20% and 15% of patients, respectively. It is worth noting however that a majority of patients who had inadequate follow-up and were therefore deemed non-responders using this approach had actually already achieved

a significant response or remission prior to the 12-month time point. Doing well at their last visit, the provider may have simply felt there was no clinically indicated reason to bring them back routinely thereafter for an assessment of activity or they may have returned to the original referring provider given the tertiary nature of the centers involved in this study. However, in the absence of having the full 12-month follow-up, it is also possible that some of these patients lost response by 12 months. This highlights the importance of presenting both cumulative rates to account for variable follow-up in clinical practice related to practice patterns and NRI analyses to provide more conservative estimates given the lack of controlled design with observational data and potential for right censoring of data.

A reduced response to biologic therapy in UC patients who had previous TNFα antagonist exposure has been commonly reported in phase 3 RCTs and real-world cohorts [12–14]. When considering response to VDZ after TNF antagonist exposure, the German real-world experience similarly observed that VDZ was more effective in inducing clinical remission at week 54 in TNFα antagonist-naive patients vs. TNFα antagonist-exposed patients (6/11 vs. 9/49, $p=0.02$) [10]. In a post-hoc analysis of GEMINI 1, UC patients naive to TNFα antagonists had numerically greater treatment differences at week 6 in relation to placebo compared to UC patients who previously failed TNFα antagonists [15]. When comparing the week 52 results of the GEMINI 1 study to the 12-month VICTORY consortium data with regard to TNFα antagonist-naive patients, outcomes were generally consistent with only minor numeric differences across sub-populations. Thus, our findings are consistent with prior literature and expand on them by the observation that VDZ efficacy in UC appears to correlate inversely with previous TNFα antagonist exposure, with a reduction of effect of greater magnitude noted in those patients who have failed ≥2 agents. Of note, we did not observe an association between treatment outcomes and the clinical mechanism of TNFα antagonist failure (primary non-responder versus loss of response, and failure versus intolerance). This might suggest that the reduction in effectiveness with multiple TNFα antagonists is a function of disease duration with increasing TNFα antagonist exposure over time. However, disease duration was similar across patients when stratified by the number of TNFα antagonists used and was not significant ($p>0.20$) in univariable analyses when assessed both as a continuous variable and as a binary variable. It could be hypothesized that incremental exposure to a TNFα antagonist alters the immunological landscape to reduce the effectiveness of VDZ. This is of particular importance when considering the optimal position of VDZ in UC treatment algorithms and the fact that a number of insurance companies still require therapeutic failure of 1 or 2 TNF antagonists prior to VDZ approval [16].

In the age of personalized medicine, predictors of response to biologic agents are frequently sought and can include clinical, serologic, and genotypic parameters [17]. To date, limited data on clinical predictors of response to VDZ have been published. In our cohort, in addition to previous TNFα antagonist exposure being associated with a decreased likelihood of achieving desirable clinical and endoscopic outcomes, disease severity, disease extent, and baseline albumin were identified to be independent predictors of treatment response. Clinical response (HR 0.72) and corticosteroid-free remission (HR 0.53) were lower in patients with baseline severe disease activity. Despite the early resolution of clinical symptoms observed in some patients with UC treated with VDZ, this finding along with the median time to clinical remission of nearly 6 months indicates that others can have a slower onset of action compared to TNFα antagonists [18], and that a subset of patients with severe disease may not respond in the short term, leading to treatment failure. Patients with ulcerative proctitis were excluded from the GEMINI 1 trial and the impact of disease extent on outcomes has not yet been assessed. We observed that patients with ulcerative proctitis were more likely to achieve clinical response (HR 1.99), clinical remission (HR 2.43), endoscopic improvement (HR 2.10), and endoscopic remission (HR 3.87) compared to patients with more extensive disease phenotypes. The explanation for this phenomenon is unclear but it is an observation that deserves further attention as predictors of proximal disease extension in ulcerative colitis remain elusive [19], and perhaps volume and site of trafficking of intestinal lymphocytes plays a role in patients with more extensive disease. Lastly, higher albumin concentrations were associated with a greater chance of deep remission (HR 2.11) similar to the clinical benefit already documented in UC patients on infliximab [20]. Pharmacokinetic data have illustrated that linear clearance of VDZ for a patient with a serum albumin of 3.2 g/dL is 30% higher compared to a patient with a serum albumin of 4.0 g/dL [21].

The safety of vedolizumab observed in our study was similar to what was reported in the GEMINI trials [8]. Serious infections were observed in 4% of UC patients in our cohort, and 4.9% of patients in the GEMINI studies [8]. The rate of serious adverse events was 6%, and some of these events may not have been directly related to vedolizumab, including the patients who experienced seizure and transverse myelitis. No malignancies or cases of progressive multifocal leukoencephalopathy were observed in our cohort. Infusion-related reactions were uncommon, similar to what was previously reported from the GEMINI trials [8]. Although we observed that all patients developing serious infections had prior exposure to TNFα antagonists, we could not accurately capture interval between the last dose of TNFα antagonists and first dose of VDZ. Recent literature would suggest that simultaneous exposure to TNFα antagonists and VDZ is safe [22], and our observation may therefore be related to other factors such as disease severity or concomitant medications.

Our study expands on the current literature for VDZ use in UC, and it has several strengths when compared to prior published work. First, this is the largest cohort study published to date ($n=321$) and it includes over 10 academic medical centers across the United States. Thus, it has a wide representation of patient populations and practice variations among tertiary referral centers that specialize in IBD care. Second, we add to the growing body of evidence supporting VDZ for achieving endoscopic remission in UC and expand on it by reporting rates of endoscopic improvement, remission, and deep remission, and by original observations regarding the incremental reduction in effectiveness with multiple TNFα antagonist and disease extent. There is a growing emphasis

being placed on achieving complete endoscopic remission given the association between complete healing and reduction in long-term disease-related risks [23], and our work helps providers better predict and communicate expectations for VDZ. Finally, we expand on safety data, which is reassuring and mirrors the GEMINI data.

Our study does have important limitations. The retrospective nature of data review and lack of well-validated clinical indices for measuring treatment response may impact response estimates. The variability in follow-up intervals or assessments may have also impacted response estimates. By using Kaplan–Meier statistics, which account for drop-out and loss to follow-up, we attempt to account for this but acknowledge that heavy censoring at later time points or lack of independence between censoring and events could have influenced our estimates. The NRI analyses provide a more conservative estimate and a minimum response rate to be expected in clinical practice at 12 months when using VDZ. Furthermore, although our multi-center study is wide-ranging with respect to sites and patient populations, it may still suffer from referral biases inherent to academic center-based outcomes reporting. Variations in academic practice patterns compared to those in non-academic or international populations, particularly with regard to the use of concomitant immunomodulators and/or steroids, may further limit the generalizability of our results. Finally, although the rates of serious infection and serious adverse events were comparable to other cohorts and the GEMINI trial, the relatively small size of the study with regard to safety and short follow-up period limit the robustness of our safety assessment.

In summary, in this large real-world study exploring the efficacy and safety of VDZ in UC patients, we made several key observations: (1) a substantial proportion of patients can achieve clinical and endoscopic outcomes of importance to patients and providers, (2) treatment effectiveness is significantly impacted by prior exposure to TNFα antagonists with an incremental loss of effectiveness after each successive TNFα antagonist used; (3) baseline albumin, disease extent, and disease severity were important predictors of treatment outcomes; and (4) VDZ is well tolerated with serious infections and serious adverse events being reported in 4–6% of patients. These data will help to better guide the use of VDZ, and further refine the optimal position of this biologic in current treatment algorithms.

CONFLICT OF INTEREST

Guarantor of the article: Parambir S. Dulai.

Specific author contributions: Acquisition of data (NN, FP, JM, GK, KC, JH, PC, JLKP, AW, LK, ES, RH, MP, DW, MB, DL, KS, AS, DH, NG, PSD). Statistical analysis (PSD). Drafting of manuscript (NN, FP, PSD). Critical revision of the manuscript for important intellectual content and final approval (all authors). Study supervision (PSD).

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Vedolizumab (VDZ) is an effective treatment option for moderately to severely active ulcerative colitis (UC).
- ✓ Data on safety and effectiveness of VDZ in a practical/real-world setting are limited by cohort size.

WHAT IS NEW HERE

- ✓ In this multi-center US-based consortium, cumulative rates for clinical remission, corticosteroid-free remission, endoscopic remission, and deep remission (clinical and endoscopic remission) were 51%, 37%, 41%, and 30%, respectively, after 12 months of treatment. Corresponding rates for minimal expected effectiveness using non-response imputation were 20%, 15%, 17%, and 14%, respectively.
- ✓ The overall median time to achieving clinical response, clinical remission, corticosteroid-free remission, and endoscopic remission were 96 days (IQR 53–178), 167 days (IQR 81–320), 215 days (IQR 111–386), and 195 days (IQR 112–309), respectively.
- ✓ Treatment effectiveness was significantly impacted by prior exposure to TNFα antagonists with an incremental loss of effectiveness after each successive TNFα antagonist used. Patients naive to TNFα antagonists also had shorter median times to achieving clinical response, clinical remission, and corticosteroid-free remission.
- ✓ Baseline albumin, disease extent, and disease severity were important predictors of treatment outcomes.
- ✓ VDZ was well tolerated with serious infections and serious adverse events being reported in 4–6% of patients.

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