Predictors and Management of Loss of Response to Vedolizumab in Inflammatory Bowel Disease

Eugenia Shmidt, MD[,†], Gursimran Kochhar, MD[‡], Justin Hartke, MD[§], Prianka Chilukuri, MD[§], Joseph Meserve, MD[¶], Khadija Chaudrey, MD[‖], Jenna L. Koliani-Pace, MD[**], Robert Hirten, MD[*], David Faleck, MD[*], Morris Barocas, MD[††], Michelle Luo, MS, PhD[††], Karen Lasch, MD[††], Brigid S. Boland, MD[¶], Siddharth Singh, MD, MS[¶], Niels Vande Casteele, PhD[¶], Sashidhar Varma Sagi, MD[§], Monika Fischer, MD[§], Shannon Chang, MD[‡‡], Matthew Bohm, MD[§], Dana Lukin, MD, PhD[§§], Keith Sultan, MD[¶¶], Arun Swaminath, MD[‖‖], David Hudesman, MD[‡‡], Nitin Gupta, MD[***], Sunanda Kane, MD[‖], Edward V. Loftus Jr, MD[‖], William J. Sandborn, MD[¶], Corey A. Siegel, MD[**], Bruce E. Sands, MD[*], Jean-Frederic Colombel, MD[*], Bo Shen, MD[‡], and Parambir S. Dulai, MD[¶]*

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*Icahn School of Medicine at Mount Sinai, New York, NY, USA; †University of Minnesota, Minneapolis, MN, USA; ‡Cleveland Clinic Foundation, Cleveland, OH, USA; §Indiana University, Indianapolis, IN, USA; ¶University of California, San Diego, La Jolla, CA, USA; ‖Mayo Clinic, Rochester, MN, USA; **Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; ††Takeda Pharmaceuticals USA Inc., Deerfield, IL, USA; ‡‡New York University (NYU), New York, NY, USA; §§Montefiore Medical Center, New York, NY, USA; ¶¶North Shore University Hospital, Manhasset, NY, USA; ‖‖Lenox Hill Hospital, New York, NY, USA; ***University of Mississippi, Jackson, MS, USA

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Author Contributions: Acquisition of data: Eugenia Shmidt , Gursimran Kochhar , Justin Hartke , Prianka Chilukuri , Joseph Meserve , Khadija Chaudrey , Jenna L. Koliani-Pace , Robert Hirten , David Faleck , and Parambir S. Dulai

Statistical analysis: Parambir S. Dulai

Drafting of manuscript: Eugenia Shmidt and Parambir S. Dulai

Critical revision of the manuscript for important intellectual content and final approval: all authors

Study supervision: Parambir S. Dulai

Address correspondence to: Parambir S. Dulai, MD, University of California, San Diego, Division of Gastroenterology, 9500 Gilman Dr, La Jolla, CA 92093. E-mail: pdulai@ucsd.edu

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Background: We quantified loss of response (LOR) to vedolizumab (VDZ) in clinical practice and assessed the effectiveness of VDZ dose intensification for managing LOR.

Methods: Retrospective review (May 2014–December 2016) of a prospectively maintained inflammatory bowel disease (IBD) registry. Kaplan-Meier estimates were used to determine rates of LOR to VDZ . Independent predictors of LOR were identified using univariate and multivariable Cox proportional hazard regression. Success of recapturing response (>50% reduction in symptoms from baseline) and remission (complete resolution of symptoms) after dose intensification was quantified.

Results: Cumulative rates for VDZ LOR were 20% at 6 months and 35% at 12 months, with slightly lower rates in Crohn's disease than in ulcerative colitis (6 months 15% vs 18% and 12 months 30% vs 39%, $P = 0.03$). On multivariable analysis, LOR to a tumor necrosis factor (TNF) antagonist before VDZ use was associated with an increased risk for LOR to VDZ [hazard ratio (HR) 1.93; 95% confidence interval (CI) 1.25–2.97] in all patients. For Crohn's disease patients specifically, higher baseline C-reactive protein concentration was associated with increased risk for LOR to VDZ (HR 1.01 per mg/dL increase, 95% CI 1.01–1.02). Shortening of VDZ infusion interval from 8 to every 4 or 6 weeks recaptured response in 49% and remission in 18% of patients.

Conclusions: LOR to a TNF antagonist before VDZ use and higher baseline C-reactive protein are important predictors of VDZ LOR. Treatment response can be recaptured in almost half of these patients with VDZ infusion interval shortening.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologics

INTRODUCTION

Variable long-term responses to biologic therapies continue to challenge clinicians caring for patients with inflammatory bowel disease (IBD). Loss of response (LOR) to tumor necrosis factor (TNF) antagonists is reported to occur in up to 40% of patients.[1–3] The most common reasons for the development of LOR to TNF-antagonists are sub-therapeutic drug concentrations and/or immunogenicity (antidrug antibodies). In these patients, dose escalation or interval shortening and/or the addition or adjustment of a concomitant immunosuppressive agent can be considered to recapture response and avoid drug discontinuation.[2,4] These approaches to managing LOR with TNF-antagonists can successfully recapture response in over 50% of patients.[1]

In TNF-antagonist primary nonresponders and those who are unable to regain response to TNF-antagonists, a switch in therapeutic classes can be considered.[5,6] The anti-integrin vedolizumab (VDZ) is now widely available and used for the treatment of Crohn's disease (CD) and ulcerative colitis (UC), in both TNF-antagonist naive and exposed individuals. Patients treated with VDZ may develop immunogenicity or sub-therapeutic drug concentrations secondary to enhanced clearance, which may impact response or durability of response over time.[7,8] The rates of developing LOR to VDZ in clinical practice, and the effectiveness of dose intensification on recapturing response, are yet to be quantified.

In this multicenter cohort study of VDZ-treated IBD patients, we aimed to quantify rates of LOR to VDZ and identify predictors of LOR in clinical practice. We further assessed the effectiveness of VDZ dose intensification for recapturing response and compared this to alternative strategies for managing LOR to VDZ. These data will be of importance to providers as additional biologics become available and decisions regarding VDZ dose intensification, adding or adjusting an immunomodulator or switching to alternative classes of biologics will need to be made.

METHODS

Study Design and Setting

This is a retrospective review of a prospectively maintained registry.[9] In brief this is a multicenter collaborative research group where outcomes are pooled for IBD patients treated with biologics in routine clinical practice. 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.[10]

Variables

Data on variables of interest were collected including: patient characteristics (age at diagnosis, age at VDZ initiation, gender, smoking status, and BMI), disease characteristics (prior hospitalizations, prior surgeries, disease-related complications, or extraintestinal manifestations), 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, premedications), prescribing site and provider, and follow-up assessments (endoscopic, radiographic, or clinical assessments). For patients developing LOR to VDZ, additional variables of interest were collected: date of LOR and strategy to manage LOR (surgery, switch to alternative biologic, addition or adjustment of steroid or immunomodulator, VDZ interval shortening to every 4 or 6 weeks).

Participants

Patients from the consortium were included in the current analysis if they had: (a) a confirmed diagnosis of IBD based on clinical, endoscopic, and/or histologic data; (b) active clinical symptoms attributed to IBD before starting VDZ therapy; (c) achieved a significant response to VDZ (clinical remission and/or >50% reduction in symptoms/severity); and (d) at least 1 follow-up after achieving a significant response to VDZ.

Outcomes

Primary outcome was cumulative rate of LOR to VDZ over 6 and 12 months after achieving a significant response to VDZ. The LOR was defined as recurrence or worsening of IBD-related symptoms that required surgery, a change in treatment, or VDZ interval intensification to every 4 or 6 weeks. Secondary outcomes of interest were to: identify patients more likely to have LOR to VDZ and quantify the proportion of patients who were able to regain response to VDZ. Using the physician global assessment, clinical remission was defined as a complete resolution of all IBD-related symptoms and clinical response was defined as a >50% reduction in IBD-related symptoms/severity.

Statistical Methods

Statistical analyses were performed using Statistical Package for the Social Sciences . Continuous variables were presented as means (and standard deviations,SD), or as medians (and interquartile ranges,IQR) if the distribution was skewed. Categorical or binary variables were presented as proportions or percentages. For the comparison of continuous variables, we used the independent sample *t* test (2 group comparisons) or 1-way ANOVA with Bonferroni correction (3 or more group comparisons), and for the comparison of binary variables, we used Pearson chi-square or Fisher exact test. Primary and secondary outcomes were described quantitatively with Kaplan-Meier survival and time-to-event analyses.

Cox proportional hazard regression analyses were performed to identify independent predictors of LOR. 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 (HR) with 95% confidence interval (CI) are presented for predictors where a HR <1 indicated a predictor was associated with a reduced probability for VDZ LOR and a HR >1 indicated a predictor was associated with an increased probability for VDZ LOR. A sensitivity analysis was performed excluding patients who responded to VDZ interval escalation after initial primary nonresponse.

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 consortium investigators or statisticians.

RESULTS

Demographics

A total of 788 VDZ-treated IBD patients were identified, of whom 444 patients had a significant response to VDZ therapy. Of the remaining 344 patients with nonresponse or insufficient response (<25% reduction in IBD-related symptoms/severity), VDZ interval shortening was attempted in 51 of whom 15 patients (29%) achieved a significant response to VDZ therapy and were included in the current analysis. Baseline demographics for all 459 patients who achieved a significant response to VDZ are presented in Tables 1, 2. The majority of patients had failed prior TNF-antagonist therapy (n = 346, 75%), and the reason for TNF-antagonist discontinuation before starting VDZ was primary nonresponse in 114 (33%), LOR in 178 (52%), and intolerance in the remaining 54 (15%). Concomitant immunomodulators were used in approximately 40% of patients at the time of VDZ initiation. Rates of prior TNF-antagonist use were lower in UC than CD (67% vs 91%, $P < 0.01$), and UC patients were more often on concomitant steroids at the time of VDZ initiation (58% vs 48%, $P < 0.01$).

LOR Rates and Predictors

Cumulative rates of VDZ LOR at 6 and 12 months were 20% and 35%, respectively. The median time to developing LOR after achieving a significant response to VDZ was 125 days (IQR 65–246), with UC patients having a shorter time to LOR (114 days, IQR 30–263) as compared to CD (182 days, IQR 81–310).

On univariable analyses, patients with UC were more likely to have VDZ LOR as compared to CD (HR 1.54, 95% CI 1.04–2.28), with cumulative rates for LOR at 6 and 12 months being 18% and 39% in UC, and 15% and 30% in CD ($P = 0.03$). Rates for LOR were comparable in TNF-antagonist naive and TNF-antagonist exposed individuals ($P = 0.53$), but patients who had LOR to a TNF-antagonist before VDZ use, were almost twice as likely to have LOR to VDZ (HR 1.94, 95% CI 1.26–2.98), whereas patients who had a primary nonresponse (PNR) to a TNF-antagonist before VDZ use, were almost 50% less likely to have LOR to VDZ (HR 0.60, 95% CI 0.36–0.97) (Table 3, Fig. 1). Among patients who had LOR to a TNF-antagonist before VDZ use, there was no significant difference in LOR to VDZ among those who underwent an attempt at optimizing the TNF-antagonist before VDZ (dose escalation and/or interval shortening to manage) versus those who did not before starting VDZ ($P = 0.20$), or those who were on a concomitant immunomodulator when starting VDZ ($P = 0.71$). On multivariable analyses, the only 2 independent predictors of LOR to VDZ were disease duration (HR 0.97 per year of disease duration, 95% CI 0.95–0.99) and LOR to a TNF-antagonist before VDZ use (HR 1.93, 95% CI 1.25–2.97).

TABLE 1: Baseline Clinical Characteristics Stratified by Loss of Response Status

	No LOR (n = 357)	LOR (n = 102)
Crohn's disease, no. (%)	211 (59)	53 (52)
Ulcerative colitis, no. (%)	146 (41)	49 (48)
Female, no. (%)	187 (52)	48 (47)
Age, median years (IQR)	35 (26–53)	36.5 (28–51)
BMI, median (IQR)	24.8 (22–29)	24.3 (21–29)
Disease duration, median years (IQR)	9.5 (4–17)	9 (4–14)
CRP, median (IQR)	2.6 (0.7–8.2)	5 (1–21)
Albumin, g/dL, median (IQR)	4.1 (3.8–4.3)	4.0 (3.7–4.3)
Prior disease-related hospitalization, no. (%)	238 (66)	63 (62)
Severe disease (clinical or endoscopy), no. (%)	97 (27)	33 (32)
Endoscopically severe disease[a], no. (%)	95 (38)	26 (38)
Prior TNF antagonist use, no. (%)		
Any	283 (79)	86 (84)
0	74 (20)	16 (16)
1	116 (33)	31 (30)
2 or more	167 (47)	55 (54)
PNR of last biologic	93 (33)	21 (24)
LOR of last biologic	129 (46)	49 (57)
Concomitant steroid use	169 (47)	59 (58)
Concomitant IM use	147 (41)	43 (42)

[a]Baseline endoscopy only available in 251 patients who did not have LOR and 69 patients who did have LOR.
LOR, loss of response; IQR, interquartile range; BMI, body mass index; CRP, C-reactive protein; TNF, tumor necrosis factor; PNR, primary nonresponse; IM, immunomodulator.

When looking at CD and UC separately, baseline C reactive protein (CRP) was also identified to be an independent predictor of LOR to VDZ for CD on multivariable analyses (HR 1.01 per mg/dL, 95% CI 1.01–1.02), in addition to disease duration (HR 0.95 per year of disease duration, 95% CI 0.92–0.99), and LOR to a TNF-antagonist before VDZ use (HR 2.55, 95% CI 1.31–4.96) (Table 3). For UC specifically, there were no independent predictors identified for LOR to VDZ. Results were unchanged after excluding the 15 patients who underwent VDZ interval escalation for initial primary non-response.

Management of LOR

For patients who developed LOR to VDZ, management strategies included: VDZ interval shortening to every 4 or 6 weeks (n = 47), adding a prednisone course (n = 15), adding or adjusting a concomitant immunomodulator (n = 5), antibiotic course (n = 2), switching to an alternative biologic (n = 10 TNF-antagonist, n = 5 ustekinumab, n = 1 tofacitinib), surgery (n = 10), or complete discontinuation (n = 2). The 2 patients who discontinued without any additional therapy had developed LOR to VDZ during pregnancy. Follow-up assessments were available in 54 of these patients within a median (IQR) follow-up of 6[4–9] months, and 23 (43%) recaptured a significant response to VDZ (UC 9/28, 32%; CD 14/26, 54%), with 9 (17%) achieving clinical remission (UC 3/28, 11%; CD 5/26, 19%).

Among the 15 patients who achieved a clinical response after VDZ interval shortening for the management of initial nonresponse, none had LOR during follow-up. Among patients who underwent VDZ interval shortening for the management of LOR to VDZ, a significant response was recaptured in 49% (n = 16/33), and remission in 18% (n = 6/33). This is numerically higher, but not statistically significant, as compared to using immunosuppressives (prednisone and/or immunomodulators) to recapture a significant response (35%, n = 7/20; $P = 0.87$) or remission (10%, n = 2/20; $P = 0.65$).

DISCUSSION

LOR to biologics remains a significant problem in clinical practice. Data are lacking on rates of LOR to VDZ, and expectations with various strategies traditionally used to manage LOR with biologics. We report outcomes for over 450 patients and made several key observations: (1) Cumulative rates for LOR with VDZ were 20% and 35% at 6 and 12 months; (2) rates were higher among UC patients (as compared to CD); (3) among patients with prior exposure to a TNF-antagonist these rates were higher among patients who had a LOR to a TNF-antagonist before VDZ use (as compared to those who had intolerance or PNR to a TNF-antagonist), (4) VDZ interval shortening for LOR recaptured a significant overall response in 49% and remission in 18% of patients; and (5) VDZ interval

TABLE 2: Baseline Clinical Characteristics in Crohn's Disease Versus Ulcerative Colitis Patients

	CD (n = 264)	UC (n = 195)
Female, no. (%)	138 (52)	98 (50)
Age, median years (IQR)	35 (26–51)	36 (27–53)
BMI, median (IQR)	24.6 (22–29)	24.8 (22–29)
Disease duration, median years (IQR)	11 (6–20)	7 (3–12)
CRP, median (IQR)	2.6 (0.7–8.2)	1.9 (0.5–6.2)
Albumin, g/dL, median (IQR)	4.0 (3.7–4.3)	4.1 (3.8–4.4)
Prior disease-related hospitalization, no. (%)	200 (76)	101 (52)
Severe disease (clinical or endoscopy), no. (%)	72 (27)	58 (30)
Endoscopically severe disease[a], no. (%)	57 (34)	64 (42)
Prior TNF antagonist use, no. (%)		
Any	238 (91)	131 (67)
0	26 (10)	64 (33)
1	61 (23)	86 (44)
2 or more	177 (67)	45 (23)
PNR of last biologic	74 (31)	40 (31)
LOR of last biologic	111 (47)	67 (51)
Concomitant steroid use	115 (48)	113 (58)
Concomitant IM use	114 (43)	76 (39)

[a]Baseline endoscopy only available in 169 CD and 151 UC patients.
BMI, body mass index; CD, Crohn's disease; CRP, C-reactive protein; IM, immunomodulator; IQR, interquartile range; LOR, loss of response; PNR, primary nonresponse; TNF, tumor necrosis factor; UC, ulcerative colitis.

shortening for initial nonresponse or insufficient response to VDZ resulted in a significant response to VDZ being achieved in 29% of patients.

Our observed rates for LOR to VDZ at 12 months in CD (30%) were comparable to rates reported with infliximab (33%) and adalimumab (30%), but lower than those reported with certolizumab (41%).[3] For UC, our observed rates for LOR with VDZ at 12 months (39%) were also comparable, but on the lower end of those observed with TNF-antagonists (40%–60%).[2,11–13] Higher VDZ concentrations are associated with higher response and remission rates,[8] and VDZ undergoes an elimination process similar to that seen with other monoclonal antibodies.[14] Therefore, it is not surprising that observed rates for LOR to VDZ in our cohort were comparable to those seen with TNF-antagonists. Moreover, the importance of adequate exposure to VDZ was confirmed as interval shortening recaptured response in a substantial proportion of patients. Although therapeutic drug monitoring was not performed routinely for patients in the consortium, these observations may support a role for therapeutic drug monitoring to optimize treatment outcomes and to manage or prevent LOR to VDZ. A prior population pharmacokinetic analysis of VDZ in patients with CD and UC showed a comparable clearance of VDZ for both diseases (0.155 L/day vs 0.159 L/day, respectively).[15] However, an association between Mayo endoscopic subscore and clearance of VDZ was observed, indicating that sicker patients with UC may need higher doses of VDZ to achieve therapeutic VDZ serum concentrations. It should be noted that the optimal therapeutic concentration for VDZ has yet to be determined.

Prior work from our group has shown that exposure to TNF-antagonists reduces VDZ treatment effectiveness, but the reason for TNF-antagonist failure (LOR vs PNR) had no impact on VDZ outcomes.[9] In the current study, among patients with prior exposure to TNF-antagonists, we observed a 2-fold increased risk for LOR to VDZ among patients with LOR to a TNF-antagonist before use of VDZ. Furthermore, among patients with prior exposure to TNF-antagonists, we observed that patients with PNR to a TNF-antagonist were less likely to have LOR to VDZ. The mechanisms through which monoclonal antibodies are cleared from the circulation are similar across biologics. It can be speculated that patients who develop an immunogenic reaction to 1 biologic may be at risk to develop antidrug antibodies to a subsequent biologic.[16,17] Furthermore, clearance of VDZ was associated with body weight and albumin concentration, as is also observed for infliximab and certolizumab pegol.[18–20] Thus, certain patients may be inherently more likely to develop LOR to a biologic because of immune-mediated or nonimmune-mediated accelerated clearance, which might explain the increased risk for LOR to VDZ among patients who had LOR to a TNF-antagonist, but evidence on VDZ serum drug and antidrug antibody concentrations from real-life clinical practice is lacking.

TABLE 3: Univariable and Multivariable Predictors of Vedolizumab Loss of Response

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)
All IBD patients		
IBD type (UC vs CD)	1.54 (1.04–2.28)	
Disease duration	0.97 (0.95–0.99)	0.97 (0.95–0.99)
Prior hospitalization	0.84 (0.66–1.06)	
Baseline CRP	1.01 (0.99–1.02)	
LOR with last biologic	1.94 (1.26–2.98)	1.93 (1.25–2.97)
PNR with last biologic	0.60 (0.36–0.97)	
Concomitant steroids	1.49 (1.01–2.21)	
Crohn's disease		
BMI	0.96 (0.91–1.02)	
Disease duration	0.98 (0.95–1.00)	0.95 (0.92–0.99)
Baseline CRP	1.01 (1.01–1.02)	1.01 (1.01–1.02)
Baseline albumin	0.69 (0.41–1.15)	
LOR with last biologic	1.92 (1.09–3.41)	2.55 (1.31–4.96)
PNR with last biologic	0.57 (0.30–1.10)	
Ulcerative colitis		
TNF-antagonist failure	1.64 (0.90–2.99)	
LOR with last biologic	1.93 (0.99–3.77)	
Concomitant steroids	1.64 (0.89–3.02)	

Variables selected based on univariable analyses ($P < 0.20$) and backward model selection approach used to derive final multivariable model ($P < 0.05$).
BMI, Body mass index; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IBD, inflammatory bowel disease; LOR, loss of response; PNR, primary nonresponse; UC, ulcerative colitis.

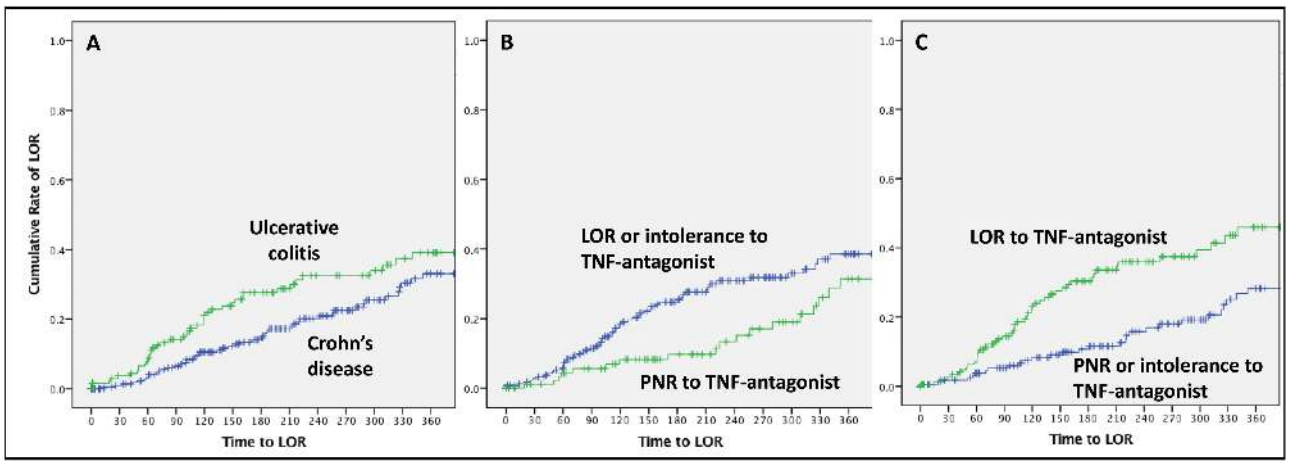

FIGURE 1. Cumulative rate of loss of response for clinical predictors. Loss of response during vedolizumab maintenance therapy classified by A, inflammatory bowel disease type ($P = 0.028$); B, primary nonresponse to TNF antagonist used before vedolizumab (vs loss of response or intolerance to TNF antagonist, $P = 0.037$); C, loss of response to TNF antagonist used before vedolizumab (vs primary nonresponse or intolerance to TNF antagonist, $P = 0.002$).

Although our study has several strengths and the observations made help to expand our understanding of VDZ effectiveness and durability, it has several limitations that should be noted. First, the retrospective nature of data review and characterization of LOR across academic centers carries inherent risks for biases in data and observations. Second, decreased detection of LOR has been reported with other retrospective studies as compared to prospective studies,[3] which may impact our estimates for LOR to VDZ. It is important to note that we used time-to-event analyses to estimate cumulative rates for

LOR, which censors for loss to follow-up and incomplete data. Thus, our reported rates for LOR are on the conservative side and may help to overcome these limitations. We have reported on short-term management strategies to recapture response, but the long-term durability of these interventions for maintaining response will need to be determined and a more objective assessment of drug concentrations, antidrug antibodies, and changes with different management strategies will need to be made. We have identified several predictors for LOR but are unable to fully explain or understand why disease duration might be an important factor and further work will be needed to understand outcomes when using VDZ early or late in the disease course. Finally, the lack of therapeutic drug monitoring during the study period limits our ability to assess or evaluate the impact of VDZ concentrations and antidrug antibodies on LOR and recapture of response.

In conclusion, rates of LOR to VDZ were lower in CD patients as compared to UC. Among patients who were PNR to VDZ or those who were experiencing a LOR to VDZ, interval shortening of infusions successfully achieved clinical response in 29% and 49% of patients, respectively. Prior LOR to a TNF-antagonist significantly impacted the risk for VDZ LOR and this should be taken into consideration when attempting to optimize VDZ durability, possibly through therapeutic drug monitoring. Further studies are needed to identify the optimal VDZ concentration to maintain treatment durability, and the impact of proactive therapeutic drug monitoring for VDZ in IBD.

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