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Vedolizumab Is Safe and Efficacious for the Treatment of Pediatric-Onset Inflammatory Bowel Disease Patients Who Fail a Primary Biologic Agent

Sujin Choi [ID],[1*] Eun Sil Kim [ID],[2*] Yiyoung Kwon [ID],[3] Mi Jin Kim [ID],[3] Yon Ho Choe [ID],[3] Byung-Ho Choe [ID],[1] and Ben Kang [ID] [1]

[1]Department of Pediatrics, School of Medicine, Kyungpook National University, Daegu, Korea
[2]Department of Pediatrics, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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Address for Correspondence:
Ben Kang, MD
Department of Pediatrics, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 41944, Republic of Korea.
Email: benkang@knu.ac.kr

*Sujin Choi and Eun Sil Kim contributed equally to this work.

ORCID iDs
Sujin Choi [ID]
https://orcid.org/0000-0001-8894-8127
Eun Sil Kim [ID]
https://orcid.org/0000-0003-2012-9867
Yiyoung Kwon [ID]
https://orcid.org/0000-0001-5600-2070
Mi Jin Kim [ID]
https://orcid.org/0000-0002-4505-4083

ABSTRACT

Background: Vedolizumab (VDZ) is currently licensed for use in adults for the treatment of inflammatory bowel disease (IBD). We aimed to investigate the clinical course of pediatric-onset IBD following treatment with VDZ as more than a secondary biologic agent. We also evaluated factors associated with secondary loss of response (LOR) and durability of VDZ treatment.

Methods: Pediatric-onset IBD patients diagnosed at an age younger than 18 years who had received VDZ as more than a secondary biologic agent were included in this retrospective observational study conducted at the Department of Pediatrics of two centers in Korea. Comparative analysis was conducted between groups divided according to the development of secondary LOR during VDZ treatment.

Results: A total of 24 patients comprising 10 patients with Crohn's disease and 14 with ulcerative colitis were included. Of these, 19 were male and 5 were female. The mean age at diagnosis was 14.6 ± 2.5 years. The mean age at initiation of VDZ was 20.5 ± 2.8 years. Nine patients (37.5%) had received two or more biologic agents before starting VDZ. During a median of 0.9 years follow-up from VDZ initiation, 9 patients (37.5%) experienced LOR requiring interval shortening and 4 patients (16.7%) were changed to a different biologic agent. According to multivariate Cox proportional hazard regression analysis, administration of two or more biologic agents before VDZ treatment was the only factor positively associated with LOR (hazard ratio [HR], 5.6; 95% confidence interval [CI], 1.026–30.56; $P = 0.047$), while LOR was the only factor negatively associated with VDZ durability (HR, 0.003; 95% CI, 0.00–0.08; $P = 0.010$). No adverse events were observed during treatment with VDZ.

Conclusion: VDZ is safe and efficacious for the treatment of pediatric-onset IBD patients failing a primary biologic agent. The durability of VDZ may be enhanced by introducing VDZ earlier in the disease course. Further prospective studies in children are required in the future to validate these findings.

Keywords: Vedolizumab; Inflammatory Bowel Disease; Crohn Disease; Ulcerative Colitis; Efficacy; Safety

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Yon Ho Choe
https://orcid.org/0000-0003-1525-7688
Byung-Ho Choe
https://orcid.org/0000-0001-9899-9120
Ben Kang
https://orcid.org/0000-0002-8516-9803

Author Contributions
Conceptualization: Kang B. Data curation: Choi S, Kim ES, Kwon Y. Formal analysis: Choi S, Kim ES, Kim MJ, Kang B. Funding acquisition: Kang B. Investigation: Choi S, Kim ES, Choe YH, Kang B. Methodology: Choe BH, Kang B. Software: Kim ES. Supervision: Kang B. Validation: Choe YH, Choe BH, Kang B. Visualization: Choi S, Kim ES, Kang B. Writing - original draft: Choi S, Kim ES, Kwon Y, Kim MJ. Writing - review & editing: Choe YH, Choe BH, Kang B.

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract. Approximately 25% of patients with IBD are diagnosed at younger than 20 years of age.[1] Once IBD is diagnosed in children, the goals of therapy consist of eliminating symptoms, normalizing quality of life, restoring growth, and preventing complications while minimizing the adverse effects of medications.[1,2] In addition, pediatric IBD has a more aggressive disease course than adult-onset disease. Therefore, early introduction of immunomodulators including anti-tumor necrosis factor (TNF) agents is required.[3,4]

Vedolizumab (VDZ) is a humanized monoclonal immunoglobulin (Ig) G1 antibody against α4β7-integrin that inhibits the binding of leukocytes to the endothelium of blood and lymphatic vessels located in the gastrointestinal tract. The gut-selective mechanism of action of VDZ has the advantage of greater safety compared to other biological agents.[5-7] VDZ is currently approved in adults with CD and ulcerative colitis (UC).[8-10] Compared with adults, there is limited experience with VDZ therapy in pediatric IBD. Anti-TNF agents, such as infliximab (IFX) and adalimumab, are the only biological agents approved for usage in pediatric IBD, whereas VDZ is only available for off-label administration.[10,11]

In the present study, we aimed to investigate the clinical course of pediatric-onset IBD following initiation of VDZ as more than a secondary biologic agent. We also aimed to identify factors associated with secondary loss of response (LOR) and durability of VDZ treatment.

METHODS

Patients and study design

This retrospective observational study was conducted at the Department of Pediatrics of two centers in Korea, between 2018 and 2020. Pediatric-onset IBD patients who had been diagnosed under 18 years of age who had received vedolizumab as more than a secondary biologic agent were included. Clinicodemographic data including sex, diagnosis age, age at VDZ start, disease type, number of biologics before VDZ, reason for changing to VDZ, clinical disease status at VDZ start were recorded at baseline. Factors such as age, duration from VDZ start, LOR during VDZ treatment, duration to LOR, concomitant medication, surgery during VDZ treatment, and sustained VDZ treatment were investigated at maximum follow-up. The primary outcome was rate of LOR during VDZ treatment and sustained VDZ treatment at last follow-up. Comparative analysis was conducted between groups divided according to the development of secondary LOR during VDZ treatment. Secondary LOR was defined as a worsening of clinical symptoms and a significant increase in CRP levels at two consecutive visits plus a status that required dose intensification. Dose intensification by interval shortening from 8 weeks to 4 weeks was conducted when secondary LOR occurred.

Statistical analysis

For comparative analysis between groups, the χ^2 test or Fisher's exact test were used for categorical variables and Student's t-test or the Wilcoxon rank-sum test were used for continuous variables. Continuous variables are reported as medians with interquartile range or means with standard deviation. Kaplan-Meier survival analysis was used to determine rates of LOR to VDZ. Univariate and multivariate Cox proportional hazard regression analyses were used to evaluate factors associated with time-to-LOR during VDZ treatment

and VDZ durability at 95% confidence level. Statistical significance was defined as $P < 0.05$. All analyses were conducted on SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital and informed consent was waived due to the retrospective nature of this study (IRB No. 2021-10-005).

RESULTS

Baseline characteristics

Overall, 24 patients were included in this study. Ten patients had been diagnosed with CD and 14 patients with UC. The mean age at diagnosis was 14.6 ± 2.5 years. The mean age at initiation of vedolizumab was 20.5 ± 2.8 years. Three patients received off-label vedolizumab before the age of 18 years. The age of these patients was 15.9, 16.8, and 16.9 years, respectively. Nine patients (37.5%) had received two or more biologic agents before initiation of VDZ. Switching to VDZ occurred due to loss of response in 19 patients and due to adverse events during treatment with previous biologic agents in 5 patients (**Table 1**). Other baseline demographics and clinical characteristics are summarized in **Table 1**.

At maximum follow-up

During a median follow-up duration of 0.9 years after initiation of VDZ, 9 patients (37.5%) experienced loss of response requiring interval shortening. The median duration to LOR was 0.6 years. Eight patients received concomitant immunomodulators and 13 patients received concomitant mesalazine during VDZ treatment. One patient required bowel surgery and one patient underwent perianal surgery during VDZ treatment. At the last follow-up visit, 20 patients (83.3%) remained on VDZ treatment (**Table 2**).

Comparison between patients with and without LOR

The number of biologic agents received prior to VDZ therapy significantly differed between patients with and without LOR. In the group without LOR, 80% had received only one biologic agent before VDZ. Meanwhile, 33% of patients had received only one biologic

Table 1. Baseline characteristics

Characteristics	Total (N = 24)
Male sex	19 (79.2)
Diagnosis	
CD	10 (41.7)
UC	14 (58.3)
Diagnosis age, yr	14.6 ± 2.5
Age at VDZ start, yr	20.5 ± 2.8
Number of biologics before VDZ	
1	15 (62.5)
2	6 (25.0)
3	3 (12.5)
Reason for changing to VDZ	
LOR	19 (79.2)
Adverse events	5 (20.8)
Clinical remission at VDZ start	2 (8.3)
Sustained VDZ treatment at follow-up	20 (83.3)

Values are expressed as mean ± standard deviation or number (%).
VDZ = vedolizumab, LOR = loss of response.

Table 2. At maximum follow up

Variables	Total (N = 24)
Age at follow-up, yr	21.2 (19.4–23.9)
Duration from VDZ start, yr	0.9 (0.6–1.6)
LOR during VDZ treatment	
Primary LOR	4 (16.7)
Secondary LOR	5 (20.8)
Duration to LOR, yr	0.6 (0.2–1.1)
Concomitant immunomodulator	8 (33.3)
Concomitant mesalazine	13 (54.2)
Surgery during VDZ treatment	
Bowel surgery	1 (4.2)
Perianal surgery	1 (4.2)
Sustained VDZ treatment at follow-up	20 (83.3)

Values are expressed as medians (interquartile range) or number (%).
VDZ = vedolizumab, LOR = loss of response.

Table 3. Comparison between patients with and without LOR

Variables	No LOR (n = 15)	LOR (n = 9)	P
Male sex	12 (80.0)	7 (77.8)	1.000
Diagnosis			0.092
CD	4 (26.7)	6 (66.7)	
UC	11 (73.3)	3 (33.3)	
Diagnosis age, yr	14.6 ± 2.2	14.5 ± 3.1	0.896
Age at VDZ start, yr	20.6 ± 2.4	20.3 ± 3.4	0.775
Number of biologics before VDZ			0.03
1	12 (80.0)	3 (33.3)	
2	3 (20.0)	3 (33.3)	
3	0 (0)	3 (33.3)	
Reason for changing from prior biologic to VDZ			0.615
LOR	11 (80.0)	8 (88.9)	
Adverse events	4 (20.0)	1 (11.1)	

Values are expressed as mean ± standard deviation or number (%).
LOR = loss of response; CD = Crohn's disease, UC = ulcerative colitis, VDZ = vedolizumab.

agent before VDZ in the LOR group. There were no significant differences in other variables between the two groups (**Table 3**).

Factors associated with time-to-LOR during VDZ treatment

Multivariate Cox proportional hazard regression analysis demonstrated a history of two or more biologic agents prior to VDZ treatment was the only factor associated with LOR (hazard ratio [HR], 5.6; 95% confidence interval [CI], 1.026–30.559; $P = 0.047$; **Table 4**).

Factors associated with VDZ durability

A history of two or more biologic agents prior to VDZ treatment was the only factor negatively associated with VDZ durability (HR, 0.169; 95% CI, 0.043–0.656; $P = 0.01$; **Table 5**). No serious adverse events were observed during treatment with VDZ.

DISCUSSION

Experience with VDZ treatment in pediatric IBD patients is limited compared with adults. In the present study, LOR was less frequent in those whom VDZ was introduced after one biologic than those in whom VDZ was introduced after more than one biologic agent. We found that the use of less biologics and earlier introduction of VDZ may reduce LOR and improve durability in

Table 4. Cox proportional hazard regression analysis of factors associated with time to LOR during VDZ treatment

Variables	Univariate Cox analysis			Multivariate analysis (n = 143)		
	HR	95% CI	P	HR	95% CI	P
Sex (male vs. female)	1.021	0.212–4.922	0.98			
Diagnosis age	0.863	0.647–1.152	0.317	0.299	0.064–1.397	0.125
Diagnosis (UC vs. CD)	0.344	0.086–1.385	0.133			
Age at VDZ start	1.035	0.807–1.327	0.786			
Duration from diagnosis to VDZ start	1.12	0.903–1.391	0.302			
Number of biologics before VDZ ≥ 2	2.583	0.63–10.584	0.187	5.6	1.026–30.559	0.047
Concomitant immunomodulator during VDZ	0.575	0.118–2.812	0.495			
Concomitant mesalazine during VDZ	0.349	0.086–1.415	0.141	0.241	0.048–1.215	0.085

LOR = loss of response, VDZ = vedolizumab, HR = hazard ratio, CI = confidence interval, UC = ulcerative colitis, CD = Crohn's disease.

Table 5. Cox proportional hazard regression analysis of factors associated with VDZ durability

Variables	Univariate Cox analysis			Multivariate analysis (n = 143)		
	HR	95% CI	P	HR	95% CI	P
Sex (male vs. female)	1.782	0.511–6.212	0.365			
Diagnosis age	0.931	0.759–1.141	0.489			
Diagnosis (UC vs. CD)	2.355	0.841–6.597	0.103	2.129	0.723–6.271	0.170
Age at VDZ start	1.035	0.807–1.327	0.786			
Duration from diagnosis to VDZ start	0.096	0.954–1.269	0.188	1.135	0.96–1.341	0.137
Number of biologics before VDZ ≥ 2	0.208	0.057–0.755	0.017	0.169	0.043–0.656	0.010
Concomitant immunomodulator during VDZ	0.434	0.140–1.350	0.150			
Concomitant mesalazine during VDZ	0.972	0.372–2.538	0.953			

VDZ = vedolizumab, HR = hazard ratio, CI = confidence interval, UC = ulcerative colitis, CD = Crohn's disease.

pediatric-onset IBD patients. This is the first study to evaluate factors related to the LOR and durability of VDZ in patients with IBD diagnosed during childhood and adolescence.

According to the European Crohn's and Colitis Organisation (ECCO)/European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline, although VDZ is currently not yet approved for use in children, VDZ may be considered as a second-line biologic therapy after anti-TNF failure in patients with chronically active or steroid-dependent pediatric UC.[11] In addition, VDZ can be considered for off-label use in pediatric CD patients who are unable to maintain clinical remission on anti-TNF agents despite dose optimization and immunomodulator use, or in situations of severe tuberculosis infection.[10,12] In an observational prospective cohort study of children with refractory IBD who had failed anti-TNF therapy prior to initiation of VDZ therapy, clinical response was observed in 31.6% at week 6 and 57.9% by week 22. Steroid-free remission was seen in 5% of subjects at 6 weeks, 15% at 14 weeks, and 20% at 22 weeks.[13] A multicenter retrospective study showed that VDZ was safe and effective in children with IBD. This study included 64 children with IBD who had previously been treated with anti-TNF agents. Remission without corticosteroid was seen in 37% and 39% of UC patients and 14% and 24% of CD patients at week 14 and at final clinic visit (median follow-up period of 24 months), respectively.[14] Another retrospective study of 52 children with IBD included 5 anti-TNF-naïve patients. At week 14, clinical remission was observed in 76% of UC patients and 42% of CD patients. At week 22, anti-TNF-naïve patients had higher remission rates than anti-TNF exposure patients (100% vs. 45%; P = 0.04).[15] These studies of VDZ treatment in pediatric IBD demonstrate VDZ as effective and safe in children. Studies of VDZ in very early-onset IBD (VEO-IBD) are even more limited. In a study of the safety and efficacy of VDZ in VEO-IBD (defined as aged < 6 years), 56.3% patients had clinical response at 14 weeks. Further, there was improvement in nutritional state including body mass index.[16]

LOR to biologic therapy is a relatively common issue in clinical practice. LOR may occur due to factors such as antibody formation, changes in drug clearance, and non-TNF-induced inflammatory mechanisms.[17] Accordingly, it is important to be able to predict and manage LOR to biologics. In our study, the median duration to LOR was 0.6 years and 9 patients (37.5%) experienced LOR requiring interval shortening. There are limited previous studies regarding predictors of LOR to VDZ in adults. A retrospective study including a total of 788 IBD patients treated with VDZ reported rates of LOR to VDZ of 20% at 6 months and 35% at 12 months. In that study, LOR to anti-TNF agents prior to VDZ administration was associated with an increased risk of LOR to VDZ and higher baseline serum C-reactive protein level was reported as an important predictor of LOR.[18]

In our study, the number of biologics received prior to initiation of VDZ was found to be associated with LOR. Predicting response and LOR to biologics is clinically challenging. Previous studies reporting predictive factors of response to biologic therapy in patients with IBD remain controversial,[19-21] and there is currently no clear consensus regarding patient-related and disease-related factors. For VDZ, no single prognostic indicator has yet been reported, although a scoring system to predict outcomes of VDZ treatment has been recently developed and validated.[22-29]

Although the reason for changing to VDZ was not identified as a statistically significant factor in our study, a study by Singh et al.[30] found that response to second-line biologics differed depending on the reason for discontinuing primary therapy in patients with IBD. In this study, patients with primary non-response to anti-TNF agents were less likely to respond to secondary non-TNF biologics compared to patients who discontinued treatment for secondary LOR or intolerance. In another study comprising 41 patients in clinical remission, switching from anti-TNF agents to VDZ for reasons other than LOR was analyzed. Most patients switched treatment due to adverse events (56.1%) or infection (14.6%). After change, follow-up endoscopy was performed in 30 patients, with 25 patients (83.3%) confirmed to be in endoscopic remission.[31] In the GENIMI 1 study, rates of response to VDZ and placebo at week 6 were 53.1% and 26.3%, respectively, in patients with naïve to anti-TNF and 39.0% and 20.6%, respectively, in patients with anti-TNF failure. At week 52, rates of remission with VDZ and placebo were 46.9% and 19.0%, respectively, in patients naïve to anti-TNF, and 36.1% and 5.3%, respectively, in patients with anti-TNF failure.[32] The GEMINI 2 and 3 trials evaluated 516 anti-TNF naïve patients and 960 anti-TNF failure patients and reported 48.9% of anti-TNF naïve and 27.7% of anti-TNF failure patients were in remission with VDZ at week 52.[33] These results may be due to differing pharmacokinetics and pharmacodynamics of anti-TNF agents in individual patients.

Pediatric IBD has a complex and aggressive disease course.[1] Therefore, timely and appropriate treatment is essential to prevent deterioration that may require surgical intervention. In the treatment of pediatric IBD, it is most important to maintain growth and minimize drug side effects in addition to controlling symptoms. In this study, no serious adverse events were observed during VDZ treatment, corroborating previous studies of VDZ in pediatric IBD.[13-15] Only one patient underwent bowel surgery and 20 patients (83.8%) had sustained VDZ treatment at the final follow-up visit.

This study has several limitations. First, this study had a retrospective design and was limited by a small sample size. Thus, caution is required when interpreting the results of this study. Although, we had concluded that the durability of VDZ may be enhanced by introducing

VDZ earlier in the disease course, the reason that VDZ was not efficacious in those with a previous treatment history of various biologics may be merely due to the fact that the disease severity of these patients was severe to not respond to any biologics. Larger prospective studies in pediatric IBD are warranted. Second, a further limitation is that selection bias may have occurred. Third, data on the application of VDZ in young children were insufficient. Only three patients used off-label VDZ before the age of 18 years. Evaluation of the safety and efficacy of VDZ at younger ages would require licensing approval and further research. Furthermore, data regarding growth could not be evaluated in the present study since patients were mainly young adults. The effect of VDZ on patient growth, an important pediatric consideration, should be evaluated through long-term follow-up in pediatric patients with IBD.

The findings of the present study demonstrate VDZ as safe and efficacious for the treatment of pediatric-onset IBD in patients failing a primary biologic agent. The durability of VDZ may be enhanced by introducing VDZ earlier in the disease course. Future prospective studies in children are required to validate the findings of the present study.

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