Vedolizumab Trough Levels in Children With Anti-Tumor Necrosis Factor Refractory Inflammatory Bowel Disease

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ABSTRACT

Objectives: Inflammatory bowel disease (IBD) can be successfully treated with vedolizumab. Studies in adult IBD patients have shown that differences in response to vedolizumab may be related to variability in vedolizumab trough levels, but in children with pediatric-onset IBD data regarding vedolizumab trough levels are not available. Thus far, the role of trough levels in pediatric-onset IBD treatment remains unclear. We aimed to investigate predictors of vedolizumab trough levels in pediatric-onset IBD patients.

Methods: Data from anti-tumor necrosis factor refractory pediatric-onset IBD patients who received vedolizumab were collected retrospectively. Vedolizumab trough levels were measured in serum samples collected before each infusion. A linear mixed model was conducted to analyze factors that influence trough levels.

Results: Twenty-six pediatric-onset IBD patients (14 ulcerative colitis [UC]), 9 Crohn Disease [CD], 3 IBD-unclassified [IBD-U]) received 258 vedolizumab infusions. Mean vedolizumab trough level at week 6 was 29.9 μg/mL (SD 17.8), and 11.5 μg/mL (SD 4.9) during maintenance therapy. CD patients had significantly lower trough levels than IBD-U patients (β 15.2; 95% confidence interval [CI] −1.1 to 29.2; $P = 0.036$). Higher fecal calprotectin (β −0.009; 95% CI −0.02 to −0.003; $P = 0.007$) and C-reactive protein levels (β −0.4; 95% CI −0.72 to −0.04; $P = 0.027$) were associated with lower trough levels, whereas shortening of time between infusions led to higher trough levels (β −0.77; 95% CI −0.9 to 0.64; $P < 0.001$).

Conclusions: In this group of pediatric-onset IBD patients, trough levels were significantly lower in CD patients compared with UC/IBD-U patients. Higher levels of inflammatory markers were associated with lower vedolizumab trough levels.

Key Words: Crohn disease, pediatric, trough levels, ulcerative colitis

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What Is Known

- Vedolizumab treatment in children with inflammatory bowel disease is safe, but shows variable efficacy.
- In adult patients with inflammatory bowel disease accumulating evidence indicates an exposure-efficacy relationship for vedolizumab.

What Is New

- Trough levels in pediatric patients with inflammatory bowel disease are comparable to those in adult patients with inflammatory bowel disease.
- A pediatric Crohn's disease diagnosis results in significantly lower vedolizumab trough levels when compared with pediatric patients with ulcerative colitis or inflammatory bowel disease unclassified.
- Next to diagnosis, low vedolizumab trough levels in patients with pediatric inflammatory bowel disease are associated with high levels of fecal calprotectin, high levels of C-reactive protein, and more days between infusions.

In pediatric-onset inflammatory bowel disease (PIBD) patients that do not respond to anti-tumor necrosis factor (TNF), vedolizumab (VDZ), a biological agent that is still off-label for pediatric patients, is recommended (1). VDZ is a monoclonal antibody directed against α4β7 integrin, which is expressed on a discrete subset of memory T-helper lymphocytes involved in the intestinal inflammation that characterizes IBD (2). Since 2014, VDZ is registered for adult IBD patients after placebo-controlled trials demonstrated its efficacy in ulcerative colitis (UC) and Crohn disease (CD) patients above 18 years (2–5). Several cohort studies in adults have confirmed VDZ effectiveness and have shown its favorable safety profile (6–8). Data on VDZ use in PIBD patients show that the use of VDZ is safe but that it has variable efficacy (9–12). As the efficacy of VDZ is based on drug exposure, rather than the administrated dose, the variation in response to VDZ may be explained by differences in PIBD phenotype or disease activity affecting VDZ trough levels. VDZ drug monitoring has been described in a limited number of adult IBD patients suggesting that albumin and body weight are factors that influence VDZ trough levels (13). A recent meta-analysis found that 54% of patients with IBD with secondary loss of response to VDZ may benefit from dose optimization (14). The exact positioning of VDZ drug level monitoring and optimal drug levels, however, remain to be defined. Despite these findings in adults, to date, data on VDZ trough levels in children with IBD are lacking. We aimed to report VDZ trough

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levels over time and assess independent clinical factors that influence vedolizumab trough levels in PIBD patients.

METHODS

Study Design and Patient Management

In this retrospective study, children and adolescents aged up to 18 years receiving VDZ therapy were studied. All patients were included in a single tertiary hospital in the Netherlands between 2015 and 2018. Patients with UC, CD, or IBD unclassified (IBD-U) were eligible if they had received at least 3 intravenous infusions as induction therapy with VDZ, including those who received VDZ combined with other immunosuppressive or immunomodulatory medication. According to local guidelines, patients received VDZ infusions at weeks 0, 2, and 6 (induction), and every 8 weeks thereafter (maintenance). Children >40 kg received 300 mg VDZ and children <40 kg received a weight-based dose of 5 mg/kg. Most patients also received bridging therapy with oral prednisolone (1 mg/kg, maximum of 40 mg) and were tapered with 5 mg per week, based on physician decision and clinical response to VDZ. If disease control during maintenance treatment was insufficient, the interval of VDZ infusions was adjusted to every 6 or 4 weeks. The need for VDZ treatment optimization was assessed by the physician based on clinical data, laboratory results, and/or endoscopic evaluation. Before every infusion, erythrocyte sedimentation rate (ESR), albumin, C-reactive protein (CRP), hemoglobin, hematocrit, thrombocytes, and leucocytes as well as fecal calprotectin levels (Calpro ELISA) were assessed. Clinical disease activity was scored at every infusion by the appropriate clinical disease activity indexes, PUCAI (Pediatric Ulcerative Colitis Activity Index) (15), or PCDAI (Pediatric Crohn disease Activity Index) (16). Endoscopic evaluation was performed when clinically indicated, before and/or after start of VDZ treatment. Mucosal healing was defined as a Mayo endoscopic score of zero in UC and the endoscopic absence of ileal or colonic ulcerations in case of CD. Accordingly, active disease was defined as the absence of mucosal healing.

Vedolizumab Trough Levels

Serum samples were collected before each infusion and stored for retrospective determination of VDZ trough levels. Due to batched analysis, trough levels were not available for clinical decision-making. VDZ trough levels were determined via a quantitative ELISA assay using rabbit anti-VDZ antibodies to capture VDZ and rabbit anti-VDZ F(ab')2 fragments, similar to the previously described method for natalizumab (Sanquin Laboratories, Amsterdam, the Netherlands) (17). The lower limit of quantification (LLOQ) in serum is 100 ng/mL; inter-assay precision and accuracy are 1% to 4% and 87% to 115%, respectively. Anti-VDZ antibodies were also measured as previously described (17). The lower limit of detection was based on mean >3 standard deviations measured in a panel of 30 sera from healthy donors and 45 sera from IBD patients who were treatment-naïve for VDZ.

Outcome Measures and Definitions

Primary outcome was the identification of independent clinical factors that influence VDZ trough levels. Secondary outcomes were therapy response, mucosal healing rates, need for surgical intervention, and the occurrence of serious adverse events. Therapy response was evaluated based on clinical remission and corticosteroid-free remission (CSFR) rates. CSFR was defined as a PUCAI <10 or PCDAI <12.5, without corticosteroid treatment or the need of a surgical intervention.

Statistical Analysis

Continuous variables were reported as means and standard deviations (SD) and compared by *t* test if normally distributed. Continuous variables not following a normal distribution were analyzed by the Mann-Whitney *U*-test and presented as median and interquartile range (IQR). Categorical variables were presented as absolute frequencies and percentages and compared by the χ^2-test or Fisher exact test. Kaplan-Meier survival analyses were performed to evaluate duration of VDZ therapy, time to CSFR, and time to surgery. Three linear mixed models were constructed, the first to identify independent predictors at baseline, before the start of VDZ, of VDZ trough levels over time. For both models, covariates were selected based on clinical relevance and findings in studies with adult IBD patients. Fixed effects were days on VDZ, IBD diagnosis (CD or UC/IBD-U), and the following parameters at start of VDZ: age, body surface area (BSA), CRP, ESR, albumin, and fecal calprotectin levels. The second mixed model was constructed to identify independent predictors during the course of VDZ treatment of VDZ trough levels. Fixed effects included the following time variable covariates: days on VDZ, IBD diagnosis (CD or UC/IBD-U), BSA, dose (mg/kg), interval between infusions in days, ESR, CRP, albumin, and fecal calprotectin levels. The third linear mixed model was constructed to calculate mean maintenance trough levels for patients who received VDZ infusions every 4 weeks or every 8 weeks. This interval was included as fixed effect. In all 3 models, random slopes were tested but not included as this did not significantly improve the model. A *P*-value <0.05 was considered statistically significant and no corrections for multiple testing were performed. Calculations were performed using IBM SPSS Statistics 24.0 (IBM Corp, Armonk, NY).

RESULTS

Patient Characteristics

Twenty-six PIBD patients were included at a median age of 12.7 years (IQR 10.1–14.5). Sixty-five percentage (n = 17) of patients were diagnosed with UC/IBD-U (14 UC, 3 IBD-U) and 9 with CD (Table 1). Although UC/IBD-U patients were not significantly younger than CD patients at the start of VDZ therapy, their weight was significantly lower (49 vs 76 kg, $P = 0.001$). All children had been previously exposed to either infliximab (85%), adalimumab (4%) or both (11%). Five out of 17 UC/IBD-U patients had a primary nonresponse to corticosteroids as well as anti-TNF. According to the local treatment protocol, oral prednisone was used as induction and bridging therapy in 18/26 patients (median duration 14 weeks; IQR 6–25). Four patients with a body weight below 40 kg (3 UC/IBD-U patients and 1 CD patient) received the nonstandard weight-based dose of 5 mg/kg, the lowest being 110 mg.

Follow-up and Therapy Response

Median follow-up duration of all PIBD patients in this study was 37 weeks (IQR 20–66). At week 14, 4/16 UC/IBD-U patients and none of the CD patients were in CSFR. After 22 weeks, 2/6 CD patients with available follow-up had reached CSFR (Fig. 1, Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B877*). In 8 UC/IBD-U patients and 2 CD patients, dosing interval was shortened for clinical reasons during maintenance treatment. In total, 34.6% (n = 9) had to undergo surgery because of therapy failure, including 6 UC/IBD-U patients and 3 CD patients. Endoscopic evaluation was performed in 16 patients (13 UC/IBD-U, 3 CD) after a median period of 18 weeks (IQR 14–27) on

TABLE 1. Baseline characteristics

Characteristics		All IBD patients (n = 26)	CD (n = 9)	UC/IBD-U (n = 17)	*P* value
Gender, n (% male)		13 (50)	6 (67)	7 (41)	0.216
Ethnicity, n (% Caucasian)		9 (35)	3 (33)	6 (35)	0.920
Age at diagnosis, years (IQR)		12.7 (10.1–14.5)	14.0 (10.9–14.3)	12.2 (9.7–14.6)	0.634
Findings at start of vedolizumab therapy					
Age, years (IQR)		15.0 (12.4–16.9)	15.5 (13.0–17.1)	13.8 (12.1–16.6)	0.458
Disease duration, years (IQR)		1.7 (1.1–2.4)	2.2 (0.9–3.3)	1.5 (1.1–2.2)	0.396
Weight, kg (IQR)		51.3 (41.7–66.9)	76.0 (69.9–77.7)	49.0 (34.8–59.2)	**0.001**
Body surface area, m^2 (IQR)		2.3 (1.6–3.0)	2.71 (1.8–3.8)	2.2 (1.4–2.7)	0.136
PCDAI		–	27.5 (15.7–37.5)	–	
PUCAI		–	–	35.0 (20.0–52.5)	
Location CD, n (%)	L1	–	1 (11)	–	
	L2	–	5 (55)	–	
	L3	–	3 (33)	–	
	L4a/b	–	4 (44)	–	
Behavior CD, n (%)	B1	–	8 (89)	–	
	B2	–	1 (11)	–	
	B3	–	–	–	
Perianal disease, n (%)		2 (8)	2 (22)	–	
Growth delay*, n (%)		6 (23)	2 (22)	4 (24)	
Location UC/IBD-U, n (%)	E1	–	–	–	
	E2	–	–	6 (35)	
	E3	–	–	-	
	E4	–	–	11 (65)	
Severity UC/IBD-U, n (%)	S0	–	–	12	
	S1	–	–	5	
Endoscopy performed (n)		15	5	10	
	Mayo score 1			1	
	Mayo score 2			3	
	Mayo score 3			6	
	Active disease†		4		
ESR, mm/hr (IQR) (N = 19)		20 (11–28)	27 (14–37)	18 (9–21)	0.272
CRP, mg/L (IQR) (N = 24)		2.5 (0.3–16.3)	14.0 (0.3–26.5)	2.1 (0.3–11.0)	0.726
FCP, μg/g (IQR) (N = 10)		721 (553–825)	579 (NA)	721 (562–827)	0.711
Indication to start vedolizumab, n (%)	IFX failure	22 (85)	6 (67)	16 (94)	0.053
	Adalimumab failure	1 (4)		1 (6)	
	Failure IFX and Adalimumab	3 (11)	3 (33)		
Reason failure anti-TNF therapy, n (%)	Low level, ADA	3 (11)	2 (22)	1 (6)	0.809
	Adequate level, loss of response	19 (73)	5 (56)	14 (82)	
	Low level, no ADA	2 (8)	1 (11)	1 (6)	
	Side effects	2 (8)	1 (11)	1 (6)	

P-values in bold denote significance. *P*-values are calculated using a Pearson's χ^2 test for categorical variables, Mann-Whitney *U*-test for continuous variables and a Kruskal-Wallis Test for ordinal variables. ADA = anti-drug antibodies; CD = Crohn disease; IBD = inflammatory bowel disease; IBD-U = IBD-unclassified; IFX = infliximab; IQR = interquartile range; NA = not available; PCDAI = pediatric Crohn Disease activity index; PUCAI = pediatric ulcerative colitis disease activity index; UC = ulcerative colitis.

*Defined as a height *z*-score at diagnosis or subsequently significantly less than expected *z*-score; or current height *z*-score significantly less than height *z*-score at diagnosis (reduction in height *z*-score since diagnosis is >0.75).

†Defined as the presence of ileal/or colonic ulcerations.

VDZ therapy. Twenty-five percentage was in clinical remission at the moment of endoscopy. Mucosal healing was seen in 4/13 (31%) UC/IBD-U patients and none of the CD patients.

Complete information on the first year of follow-up after start of VDZ was available in 19 out of 26 patients (Fig. 2). At week 22, 88% of UC/IBD-U patients (n = 14) and 75% (n = 6) of CD patients were still using VDZ. After 1 year, 9 of 19 (47%) PIBD patients remained on VDZ treatment (8 UC/IBD-U, 1 CD) (Fig. 2). In 1 CD patient, VDZ was stopped because of severe exercise intolerance and fatigue accompanied by tachycardia, which was possibly related to VDZ treatment.

Trough levels

In 22 PIBD patients, VDZ trough levels were measured during induction as well as maintenance treatment, resulting in 134 trough level measurements. During induction, mean trough levels were 32.1 μg/mL (SD 8.5) at week 2 and 29.9 μg/mL (SD

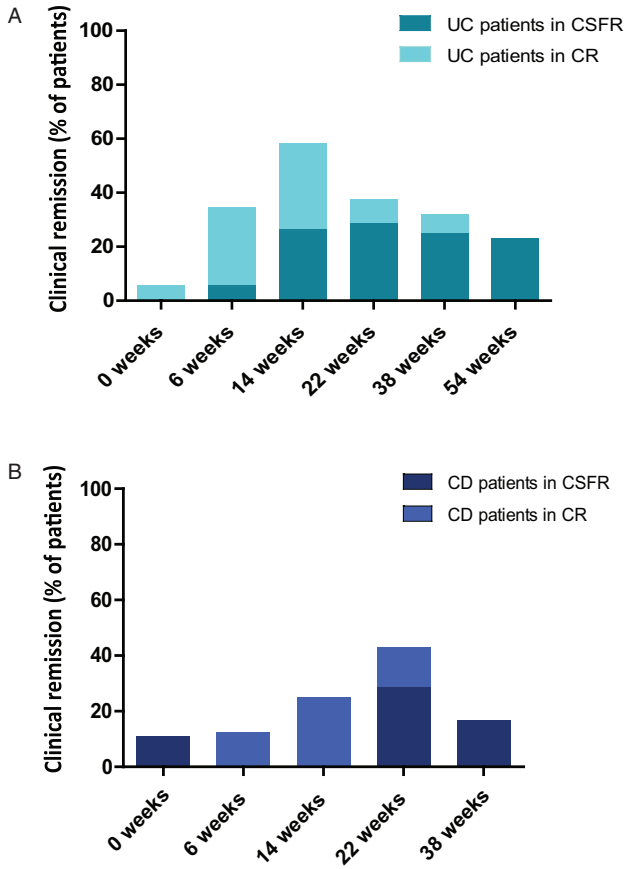

FIGURE 1. Clinical remission rates per time point during vedolizumab therapy. (A) Percentage of patients with UC/IBD-U in corticosteroid-free remission (CSFR) and clinical remission (CR) at different time points after start of vedolizumab therapy. (B) Percentage of Crohn disease patients in CR and CSFR at different time points after start of vedolizumab. Percentages are based on all patients who were still receiving vedolizumab therapy or discontinued vedolizumab therapy at an earlier time point. Patients who were lost to follow-up were excluded from this group. CD = Crohn disease; CR = clinical remission defined as a PUCAI<10 or a PCDAI<12.5; CSFR = corticosteroid-free remission defined as clinical remission and no use of corticosteroids at that time point; IBD-U = IBD-unclassified; UC = ulcerative colitis.

17.8) at week 6. The lowest trough levels were measured at start of maintenance treatment (week 14). Mean trough levels during both induction and maintenance therapy were numerically higher in UC/IBD-U patients than in CD patients (Fig. 3A). Mean trough levels were, after correction for repeated measurements, 13.5 μg/mL in UC/IBD-U patients (SD 5.6) and 9.6 μg/mL in CD patients (SD 10.8) in patients receiving VDZ every 8 weeks. If VDZ was given every 4 weeks, mean trough levels were 28.6 μg/mL in UC/IBD-U patients (SD 5.6) and 13.0 μg/mL in CD patients (SD 5.6) (Fig. 3B). Antibodies to VDZ were measured in all samples, but none were positive for antibodies to VDZ.

Factors that Influence Vedolizumab Trough Levels

A multivariate analysis that assessed the association of characteristics before the start of VDZ with VDZ trough levels over time showed that higher BSA was associated with lower VDZ trough levels (β −12.8; 95% CI −10.7 to 4.9, $P = 0.002$). With regards to laboratory measurements, a lower serum albumin before the start of VDZ was associated with lower VDZ trough levels (β 1.52, 95% CI 0.42 to 2.62, $P = 0.008$), whereas CRP, ESR, and fecal calprotectin before start of VDZ showed no significant association with trough levels over time. Findings from a second multivariate analysis to assess factors during VDZ therapy associated with VDZ trough levels showed that CD patients had significantly lower trough levels than UC/IBD-U patients (β 15.2; 95% CI −1.1 to 29.2; $P = 0.036$, Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B877*). Also, higher fecal calprotectin levels (β −0.009; 95% CI −0.02 to −0.003; $P = 0.007$), higher CRP (β −0.4; 95% CI −0.72 to −0.04; $P = 0.027$) and more days between infusions were associated with lower trough levels (β −0.77; 95% CI −0.9 to 0.64; $P < 0.001$).

Trough Levels as Predictor of Response

Mean trough levels at 14 weeks after start of VDZ were similar in patients who continued VDZ therapy at the end of follow-up (as a proxy for maintenance of remission) and patients who discontinued VDZ treatment (10.5 μg/mL, SD 7.5 vs 16.3 μg/mL, SD 7.8, respectively; $P = 0.166$, Supplemental Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/B877*). Shortening the dose interval led to increased trough levels in all patients, including those that eventually discontinued VDZ treatment (β −0.61, 95% CI −0.77 to −0.45; $P < 0.001$) or were not in CSFR at week 52 (β −0.47, 95% CI −0.62 to −0.41; $P < 0.001$).

DISCUSSION

In adult patients with IBD, accumulating evidence for the role of therapeutic drug monitoring in VDZ treatment is emerging. But other than for anti-TNF, findings are not straightforward and the available data is limited. Most of the currently available studies are based on data from the clinical GEMINI trials (3–5,18), and only on few real-world cohorts (19–22). Our study, describing a real-world cohort of anti-TNF refractory PIBD patients, is the first to report VDZ trough levels in children with IBD.

The mean VDZ trough level in adult UC patients as measured by the GEMINI 1 study during induction therapy (27.9 μg/mL at week 6, n = 654, SD 15.5) was numerically lower than the mean trough level we found in our pediatric cohort of UC/IBD-U patients (31.8 μg/mL, n = 12, SD 14.6) (3). Numerical differences were similar during maintenance therapy, showing levels in 77 adults that were lower (11.2 μg/mL, SD 7.2) than those of the children in our study (13.5 μg/mL, SD 5.6). This may be explained by the lower median body weight of UC/IBD-U patients in our cohort compared with the adult GEMINI study population, considering children received the standard dosing if they were >40 kg. Trough levels of CD patients in our cohort during induction were comparable with those found by Sandborn et al (4) (26.8 μg/mL, SD 17.5, n = 827, week 6). We, however, observed lower trough levels during maintenance therapy (13.0 ± 9.1 vs 9.6 ± 10.8 μg/mL), which could be a result of ongoing inflammation in these patients during maintenance treatment (20,21,23). Multivariate analysis in our cohort, taking inflammatory markers, such as CRP and calprotectin into account, showed VDZ trough levels in pediatric CD patients are significantly lower than those in pediatric UC/IBD-U patients. This might be because of the transmural inflammation in CD (vs more superficial in UC), and subsequent increased disease-mediated clearance of VDZ in the affected tissue. The VDZ mechanism of action in different IBD subtypes is, however, not fully understood.

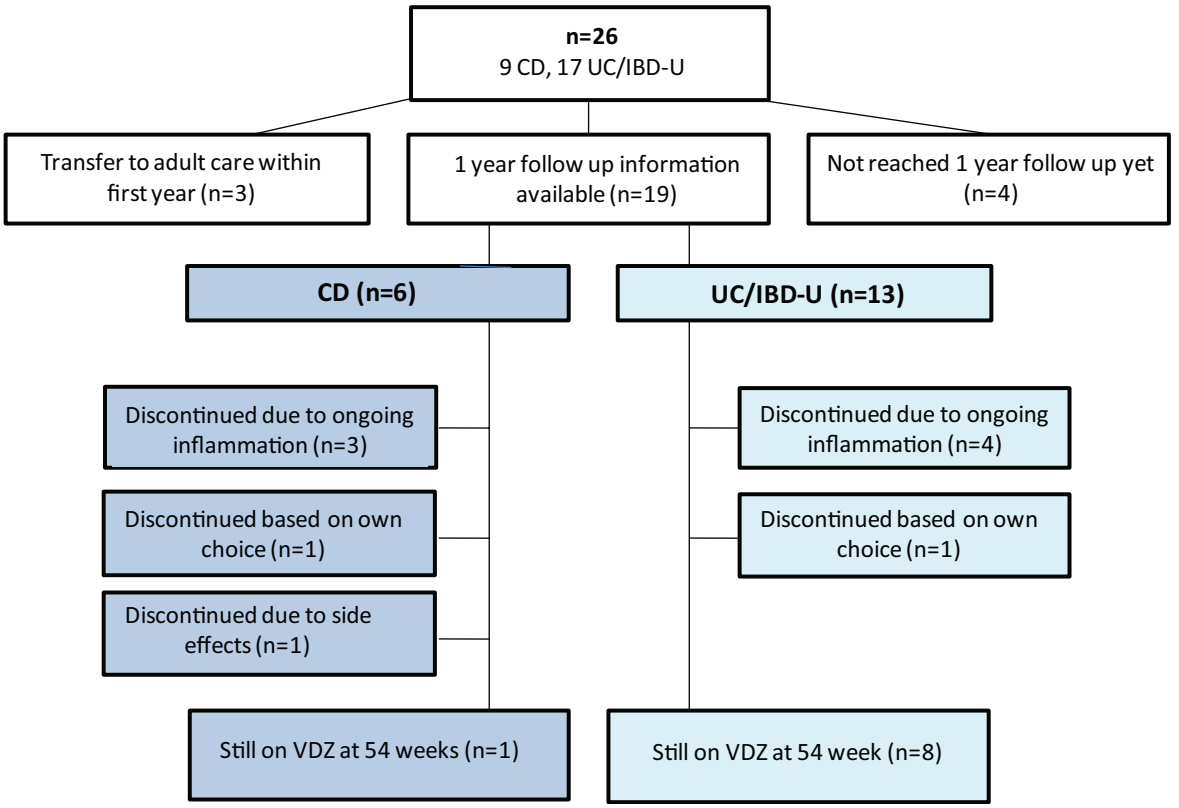

FIGURE 2. Flow chart of included patients. CD = Crohn disease; IBD-U = IBD-unclassified; UC = ulcerative colitis; VDZ = vedolizumab.

Studies based on GEMINI trial data did not show a significant difference in trough levels between UC/IBD-U and CD patients (18). In a population model, characterizing the pharmacokinetic properties of VDZ, they found a similar linear clearance for UC and CD patients (13,17).

In our cohort, only a small number of UC patients and none of the CD patients were in CSFR 14 weeks after the start of VDZ therapy. Despite the relatively long duration of corticosteroid use, it seems that CD patients are less likely to respond to VDZ and need a longer duration on VDZ therapy in order to improve clinically. These findings are in line with findings in another PIBD cohort. They showed that after a median follow-up of 24 weeks, UC patients were more likely to be in remission (39%) than CD patients (24%) (9). The remission rates reported in adult studies are higher than the rates observed in the children in our cohort (17,24), which may be explained by inclusion of anti-TNF refractory PIBD patients only, whereas this was not the case in the adult studies. This is supported by studies showing significantly better outcomes in anti-TNF-naïve IBD patients (25–27). Although an accelerated clearance because of immunogenicity is a frequently reported

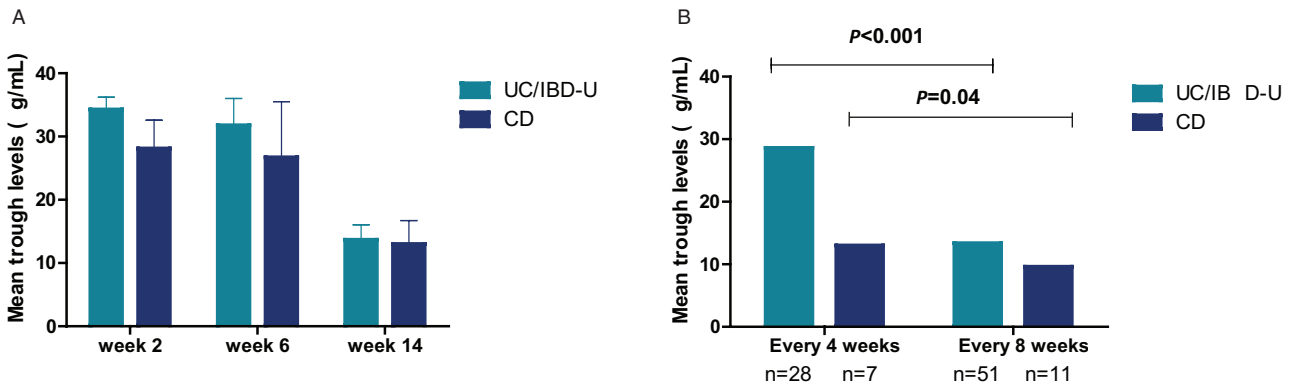

FIGURE 3. Mean vedolizumab trough levels. (A) Mean vedolizumab trough levels ± standard deviation (SD) per time point during induction therapy. (B) Mean vedolizumab trough levels during maintenance therapy (weeks 14–176). Depicted for patients with normal dosing interval (every 8 weeks) and intensified dosing interval (every 4 weeks). The difference in trough levels following the different dosing intervals was evaluated for each diagnosis. *P* values were considered significant if <0.05.

explanation for loss of response to anti-TNF, our data do not suggest that nonresponse or loss of response to VDZ can be explained by the formation of antibodies to VDZ (28). This is consistent with studies in adults that indicate immunogenicity to occur in <5% of cases (17,29).

Accumulating evidence of an exposure-efficacy relationship is emerging in adult IBD patients (18–21). Ungaro et al (23) included 258 IBD patients, and found significantly higher VDZ concentrations if patients were in clinical, biochemical, and endoscopic remission. Lower trough levels could very well be a reflection of disease activity and increased clearance (13). This is in line with findings in our cohort showing that higher CRP and fecal calprotectin levels are associated with lower trough levels. On the contrary, in another cohort of 73 IBD patients, VDZ trough levels were not associated with clinical, biological, or endoscopic outcomes (30). A systematic review and meta-analysis by Singh et al (31) showed that in UC patients, VDZ trough levels are significantly higher in patients that are in clinical and endoscopic remission; however, for CD patients, no significant differences were found. Due to the heterogeneity in the available adult studies and their findings, optimal therapeutic ranges for VDZ have not yet been determined (32).

Our findings indicate that there is an important role for therapeutic drug monitoring of VDZ in this pediatric population that has very limited treatment options left. Following a multivariate approach to repeated measures in our cohort, we found IBD diagnosis to be a significant predictor of trough levels. The finding of CD diagnosis as an independent predictor of lower trough levels in our cohort indicates that pediatric CD patients may profit from therapeutic drug monitoring and higher dosing of VDZ. Our statistical analysis did not result in a significant difference in trough levels between patients who were in CSFR and those who were not, which is likely to be because of the number of patients included in this study.

There are limitations to this study, of which some can be addressed in future research. The most important limitation being the retrospective design of the study and the small number of included PIBD patients. A larger cohort is needed to assess the exposure-efficacy relationship, but because of the off-label use of VDZ in this pediatric population studies in a large group of PIBD patients are extremely challenging. Importantly, as we collected a large number of through levels during follow-up, the small cohort did not limit our analysis of factors that influence VDZ trough levels. A second limitation is the long duration of corticosteroid treatment as induction and bridging therapy, which may affect the interpretation of the effectiveness of VDZ therapy.

To our best knowledge, we are the first to present data on VDZ trough levels in children with IBD. We hereby show that VDZ trough levels are comparable to those in adults and provide insight in which clinical factors influence VDZ trough levels in children with IBD. A pharmacokinetic/pharmacodynamic model in PIBD patients, including patients using lower doses of VDZ, would improve our knowledge on clearance of VDZ, as well as the relation between drug levels and response in these children. Larger prospective cohorts are needed to validate our findings and optimize dosing and treatment guidelines regarding VDZ therapy in PIBD patients.

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