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ORIGINAL PAPER

Safety and efficacy of vedolizumab in pediatric inflammatory bowel disease with emphasis on the very-early-onset group

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ABSTRACT

Introduction: Vedolizumab (VDZ) is effective in the induction and maintenance of remission in adults with inflammatory bowel disease (IBD). Pediatric data are still limited. This retrospective cohort study aimed to assess the safety and efficacy of VDZ in pediatric IBD including very-early-onset IBD (VEO-IBD).

Material and methods: A review of pediatric IBD patients receiving VDZ was conducted. Laboratory parameters, nutritional status, and disease activity scores were compared between each follow-up visit and between two groups divided by age of disease onset – VEO-IBD (age of onset < 6-years-old) and non-VEO-IBD (age of onset ≥ 6 years < 17 years).

The primary outcome was clinical response after induction therapy (at 4th dose visit). The secondary outcome was clinical remission after induction (at 4th dose visit) and maintenance phase (at 10th dose visit). Statistical considerations were included.

Results: Seventy-two patients with pediatric IBD were included: 12 with Crohn disease (CD), 60 with ulcerative colitis (UC). The definition of VEO-IBD was met by 21 patients. After the induction phase, a clinical response was observed in 60/72 (83.3%) patients (51/60 with UC and 9/12 with CD) and clinical remission in 44/72 (61.1%) patients (40/60 with UC and 4/12 with CD). Clinical remission after the maintenance phase was achieved by 22/72 (30.6%) patients (16/60 with UC and 6/12 with CD). Improvement in the patients' laboratory parameters and nutritional status was observed. No significant differences were observed in VDZ response between VEO-IBD and non-VEO-IBD.

Conclusions: Vedolizumab was safe and effective in the treatment of pediatric IBD irrespective of age of disease onset.

KEY WORDS:

Crohn disease, ulcerative colitis, vedolizumab, pediatric inflammatory bowel disease, very-early-onset inflammatory bowel disease.

INTRODUCTION

The term inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn disease (CD), which are chronic relapsing and remitting disorders of the gastrointestinal tract. The peak age of IBD onset is adolescence and early adulthood, and up to one-quarter of all cases are diagnosed before the age of 18 [1–3]. The incidence of pediatric IBD (PIBD) appears to be increasing globally with a more significant increase in CD than UC and among adolescent ages rather than among infants and younger children [1, 3].

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Pediatric IBD often has a great propensity for dynamic disease extension and frequently entails lack or loss of response to the regular treatment algorithm and requires novel medical strategies. Children with monogenic IBD are particularly more likely to have an aggressive phenotype of the disease in comparison to children with classical IBD [4, 5].

Vedolizumab (VDZ) is a humanized IgG1 monoclonal antibody to the gut-specific adhesion molecule α4β7 integrin that modulates gut lymphocyte trafficking. Its gut-specific mechanism of action has been confirmed in past research data [6] to support the safety profile of a drug.

Many studies have demonstrated the efficacy, safety and tolerability of VDZ in adults with UC and CD, with better clinical outcomes in UC than in CD and in anti-TNF-naïve than in anti-TNF-exposed patients [7]. The number of studies presenting encouraging data for the safety and efficacy of VDZ in pediatric refractory IBD is still increasing. The results seem to be consistent with those from adult studies [8–12].

Vedolizumab has not yet been approved by the FDA and EMA to treat IBD in pediatric patients, which is why it constitutes a "rescue therapy" only for children with a highly severe course of the disease and lack or loss of response to conventional treatment strategies.

This study aims to evaluate the safety and efficacy of VDZ in the treatment of IBD in children and compare results between PIBD age of onset subgroups.

MATERIAL AND METHODS

This single-center retrospective cohort study reports the experience of VDZ treatment in patients from the Children's Memorial Health Institute. In total, 72 children with severe pediatric-onset IBD (under the age of 17 at diagnosis according to the Paris Modification of the Montreal Classification for IBD [13]) started on VDZ treatment between August 2017 and December 2021 resulting in an observational period of at least 6 weeks and maximum 224 weeks (median therapy duration 52 weeks).

"Rescue therapy" was introduced because of the inadequacy of other treatment options available for children (lack or loss of response, drug intolerance, contraindications).

The dosing regimen of VDZ was either 150 mg or 300 mg intravenously depending on the patient's weight (< 25 kg – dose 150 mg, ≥ 25 kg – dose 300 mg). Induction therapy was administered in weeks 0, 2, and 6, followed by a maintenance phase with infusions every 8 weeks.

Data on demographics and previous treatments (particularly previous exposure to anti-TNF-α agents) were collected from patients' medical charts. At every VDZ infusion visit, laboratory parameters, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin (Hb), hematocrit (Ht) and serum albumin level (ALB), were obtained.

Nutritional status was evaluated using auxological measurements from each visit (weight, height) to estimate the BMI-for-age percentile based on CDC growth charts for children and teens. Underweight was defined as a percentile range less than the 5th percentile. One patient was excluded from BMI data at the 4th dose visit because of a lack of auxological measurements. Disease activity was assessed using the pediatric Crohn disease activity index (PCDAI) for CD or pediatric ulcerative colitis activity index (PUCAI) for UC. Adverse events were documented.

The primary outcome of the study was clinical response after the induction phase with 3 doses of VDZ defined as a decrease in PCDAI of at least 12.5 points between the baseline (1st dose visit) and the 4th dose visit (after 14 weeks of therapy) for CD and a decrease in PUCAI of at least 20 points between the baseline and the 4th dose visit for UC.

Secondary outcomes included clinical remission after the induction phase (4th dose visit) and the maintenance phase (10th dose visit) defined as PCDAI ≤ 10 points for CD or PUCAI ≤ 10 for UC and improvement in patients' nutritional status and laboratory parameters.

The results among all patients with PIBD were compared between each follow-up visit – 1st, 4th, 10th and 20th dose visit and between two groups divided by age of disease onset – very-early-onset IBD (VEO-IBD) defined as disease diagnosis < 6 years old and non-VEO-IBD defined as disease diagnosis ≥ 6 years old and < 17 years old. The definition of VEO-IBD was met by 21/72 (29.2%) patients. In VEO-IBD patients no monogenic cause was identified; in the non-VEO-IBD group genetic testing was not performed. Depending on the phenotype and the family history of the individual patient, the gene panel included different sets of screened genes enabling identification of monogenic IBD disorders such as atypical *s*evere combined immunodeficiency, immunodeficiency with hyper-IgM, caspase-8 deficiency, autoimmune lymphoproliferative syndrome (type V), chronic granulomatous disease, dyskeratosis congenita – Hoyeraal-Hreidarsson syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, IL-10 deficiency, leukocyte adhesion deficiency 1, Wiskott-Aldrich syndrome and others.

Data were presented as median and interquartile ranges for quantitative variables and numbers of cases with percentages. The distribution of quantitative variables was assessed using the Shapiro-Wilk test. Due to non-normal distribution in most of the cases, non-parametric tests were used. To compare two groups, the Mann-Whitney *U* test was used, while analysis for more than two groups was performed using the Kruskal-Wallis test with a post hoc multiple comparison test. The analysis of time effect on patients' parameters was performed for 7 complete cases using the nonparametric repeated measurements test from nparLD library for RStudio. Qualitative vari-

TABLE 1. General patients' characteristics: frequency (%) minimum, maximum, median (IQR) are presented as appropriate

Parameters	Total, $N = 72$	VEO, $n = 21$	Non-VEO, $n = 51$
Female, *n* (%)	32 (44.4)	8 (38.1)	24 (47.1)
Male, *n* (%)	40 (55.6)	13 (61.9)	27 (52.9)
Ulcerative colitis, *n* (%)	60 (83.3)	16 (76.2)	44 (86.3)
Crohn's disease, *n* (%)	12 (16.7)	5 (23.8)	7 (13.7)
Age of diagnosis (years)	Median 10.2 (4.5–13.6) Min. 0.6 Max. 16.6	Median 2.9 (2.0–4.1) Min. 0.6 Max. 5.8	Median 12.3 (9.4 - 14.1) Min. 6.0 Max. 16.6
Age at first dose visit (years)	Median 14.7 (9.1–16.7) Min. 2.2 Max. 17.9	Median 7.2 (4.8–13.2) Min. 2.2 Max. 16.5	Median 16.1 (13.5–17.0) Min. 8.2 Max. 17.9
Disease duration at first dose visit (years)	Median 3.1 (1.5–5.2) Min. 0.3 Max. 12.6	Median 4 (2.9–8.2) Min. 0.5 Max. 12.6	Median 3 (1.5 - 4.0) Min. 0.3 Max. 11.7
Infliximab exposure, *n* (%)	71 (98.6)	21 (100.0)	50 (98.0)
Infliximab discontinuation reason			
Non-response, *n* (%)	28 (39.4)	11 (52.4)	17 (34.0)
Loss of response, *n* (%)	27 (38.0)	4 (19.0)	23 (46.0)
Allergic reaction, *n* (%)	14 (19.7)	4 (19.0)	10 (20.0)
Other, *n* (%)	2 (2.8)	2 (9.5)	0 (0.0)
Adalimumab exposure, *n* (%)	22 (30.6)	10 (47.6)	12 (23.5)
Adalimumab discontinuation reason			
Non-response, *n* (%)	13 (59.1)	7 (70.0)	6 (50.0)
Loss of response, *n* (%)	6 (27.3)	2 (20.0)	4 (33.3)
Allergic reaction, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other, *n* (%)	3 (13.6)	1 (10.0)	2 (16.7)
Infliximab and Adalimumab exposure, *n* (%)	22 (30.6)	10 (47.6)	12 (23.5)
Anti-TNF-naïve, *n* (%)	1 (1.4)	0 (0.0)	1 (2.0)
Other biological therapies exposure, *n* (%)	11 (15.3)	4 (19.0)	7 (13.7)
Other previous therapies			
Traditional steroids, *n* (%)	67 (93.1)	20 (95.2)	47 (92.2)
Budesonide MMX, *n* (%)	36 (50.0)	12 (57.1)	24 (47.1)
5-ASA, *n* (%)	71 (98.6)	20 (95.2)	51 (100.0)
Azathioprine, *n* (%)	64 (88.9)	19 (90.5)	45 (88.2)
Cyclosporin, *n* (%)	38 (52.8)	12 (57.1)	26 (51)

ables were assessed using the χ^2 test. *P*-values < 0.05 were considered significant. Analysis was performed using the R language in RStudio software.

Vedolizumab is approved in Poland only for adult patients with IBD whereas in PIBD it is used as off-label treatment and requires approval of the National Consultant for Pediatric Gastroenterology.

STATEMENTS AND DECLARATIONS

The data underlying this article will be shared on reasonable request to the corresponding author. The study was conducted in accordance with the Helsinki Declaration. The patients' legal guardians provided written informed consent for the treatment. All authors have contributed significantly to the work and meet all the journal's authorship criteria, and no individual meeting these criteria has been omitted. All authors agreed to submission of the manuscript in its current form.

RESULTS

General patients' characteristics are presented in Table 1. Median therapy duration for all patients was 52 weeks (min. 6, max. 224 weeks, IQR 30–74 weeks) and the median number of doses was 9 (min. 3, max. 30, IQR 6–11).

TABLE 2. Concomitant steroid therapy, concomitant immunomodulators, clinical response rate, clinical remission rate and steroid-free remission rate during vedolizumab therapy among all patients: frequency (%)

Visit	1st	4th	10th	20th
Number of patients remaining in the therapy	72	69	27	7
Concomitant steroid therapy, *n* (%)				
Traditional steroid	27 (37.5)	15 (21.7)	3 (11.1)	0 (0.0)
Budesonide MMX	5 (6.9)	2 (2.9)	3 (11.1)	1 (14.3)
No steroid therapy	40 (55.6)	52 (75.4)	21 (77.8)	6 (85.7)
Concomitant immunomodulators, *n* (%)	33 (45.8)	30 (43.5)	12 (44.4)	1 (14.3)
Clinical response at 4th dose visit, *n* (%)	60 (87.0)	–	–	–
Clinical remission rate, *n* (%)	2 (2.8)	44 (61.1)	22 (30.6)	6 (8.3)
Clinical remission rate among patients remaining in therapy, *n* (%)	2 (2.8)	44 (63.8)	22 (81.5)	6 (85.7)
Steroid-free remission rate, *n* (%)	2 (2.8)	35 (48.6)	19 (26.4)	5 (6.9)
Steroid-free remission rate among patients remaining in therapy, *n* (%)	2 (2.8)	35 (50.7)	19 (70.4)	5 (71.4)

Clinical response at the 4th dose visit was observed in 60/72 (83.3%) patients (51/60 with UC and 9/12 with CD). Clinical remission at the 4th dose visit was achieved by 44/72 (61.1%) patients (40/60 with UC and 4/12 with CD). Clinical remission at the 10th dose visit was achieved by 22/72 (30.6%) patients (16/60 with UC and 6/12 with CD). At the 20th dose visit, clinical remission was achieved by 6/72 (8.3%) patients (4/60 with UC, 2/12 with CD). Criteria of corticosteroid-free remission (clinical remission without any concomitant steroid therapy) at the 4th dose visit, 10th dose visit and 20th dose visit were fulfilled by 35/72 (48.6%) patients (32/60 with UC, 3/12 with CD), 19/72 (26.4%) patients (14/60 with UC, 5/12 with CD), and 5/72 (6.9%) patients (3/60 with UC, 2/12 with CD), respectively.

The percentage of patients receiving concomitant therapy with traditional steroids decreased during VDZ therapy. The percentage of patients receiving concomitant immunomodulatory drugs did not change significantly. Frequency of concomitant therapies, clinical response rate, clinical remission rate and steroid-free remission rate among all patients are presented in Table 2.

A significant decrease was observed in both clinical indexes (PUCAI, PCDAI) from the baseline to each follow-up visit. All laboratory parameters improved significantly from the baseline to each follow-up visit. Figure 1A–G presents the changes in laboratory parameters and disease activity indexes for all patients.

There was no significant improvement in the nutritional status of the patients included in the study – at the baseline, 17/72 (23.6%) patients had BMI < 5th percentile, while at the 4th, 10th and 20th dose visit, there were 9/68 (13.24%) patients, 3/27 (11.11%) patients and 1/6 (14.29%) patients with BMI < 5th percentile, respectively. Figure 2A presents BMI-for-age percentile changes for all patients.

Three patients discontinued therapy after 3 doses of VDZ, 1 patient due to the serious allergic reaction at the third infusion of the drug, while 2 patients were referred for surgical treatment because of non-response. Due to the retrospective character of this trial and the lack of their follow-up visit after 14 weeks of therapy (4th dose visit) they were included only in demographic data and general group characteristics and in the baseline data (1st dose visit).

In two patients, shortening of 8-week intervals to 4-week intervals of the maintenance phase was required starting from the 4th dose infusion and from the 7th dose infusion. Unfortunately, both patients discontinued treatment due to the loss of response after 15 and 10 drug infusions, respectively.

In this study, 5 patients were referred for surgical treatment (colectomy) – 2 patients after nonresponse to VDZ induction therapy (surgery after 13 and 14 weeks from the baseline), 3 patients after the loss of response to VDZ after 8, 9 or 11 drug infusions (surgery after 57, 58 or 90 weeks from the baseline, respectively).

Overall, 44 patients discontinued VDZ therapy because of: an allergic reaction (1 patient), loss of response (18 patients), non-response (7 patients), transition to an adult facility (15 patients), other causes – LTx due to PSC/AIH overlap syndrome (1 patient), a diagnosis of right adrenal gland tumor (1 patient), or lack of compliance (1 patient). Their median therapy duration was 53 weeks (min. 6, max. 165 weeks, IQR 30–69 weeks), while their median number of received VDZ doses was 9 (min. 3, max. 22, IQR 6–11).

Vedolizumab therapy is being continued by 28 patients. Their median therapy duration is 52 weeks (min. 10, max. 224 weeks, IQR 32–111 weeks), their median number of received VDZ doses is 9 (min. 4, max. 30, IQR 7–16).

VEO-IBD VS. NON-VEO-IBD

General characteristics for both age groups are presented in Table 1. The percentage of VEO patients in-

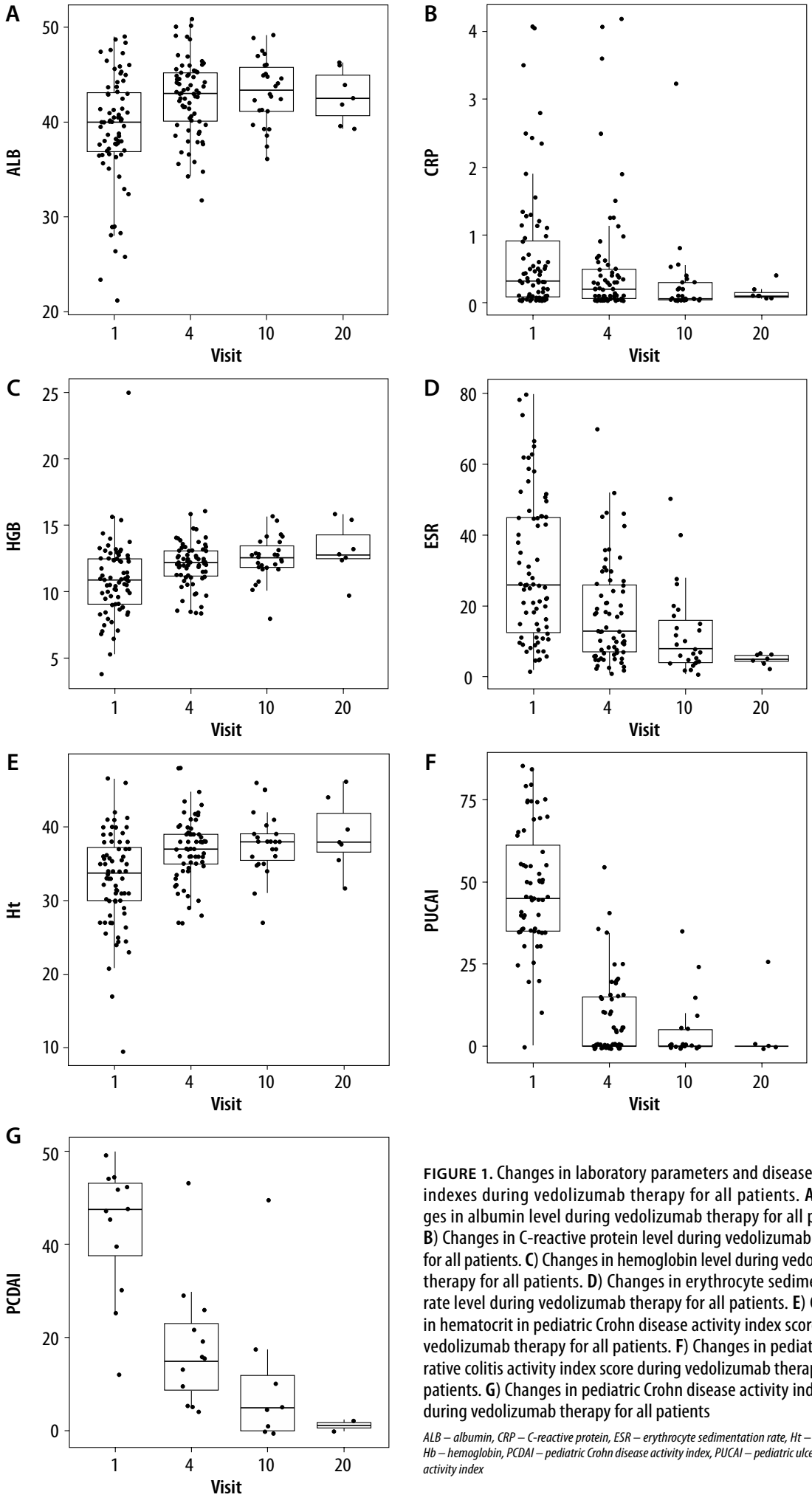

FIGURE 1. Changes in laboratory parameters and disease activity indexes during vedolizumab therapy for all patients. **A**) Changes in albumin level during vedolizumab therapy for all patients. **B**) Changes in C-reactive protein level during vedolizumab therapy for all patients. **C**) Changes in hemoglobin level during vedolizumab therapy for all patients. **D**) Changes in erythrocyte sedimentation rate level during vedolizumab therapy for all patients. **E**) Changes in hematocrit in pediatric Crohn disease activity index score during vedolizumab therapy for all patients. **F**) Changes in pediatric ulcerative colitis activity index score during vedolizumab therapy for all patients. **G**) Changes in pediatric Crohn disease activity index score during vedolizumab therapy for all patients

ALB – albumin, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, Ht – hematocrit, Hb – hemoglobin, PCDAI – pediatric Crohn disease activity index, PUCAI – pediatric ulcerative colitis activity index

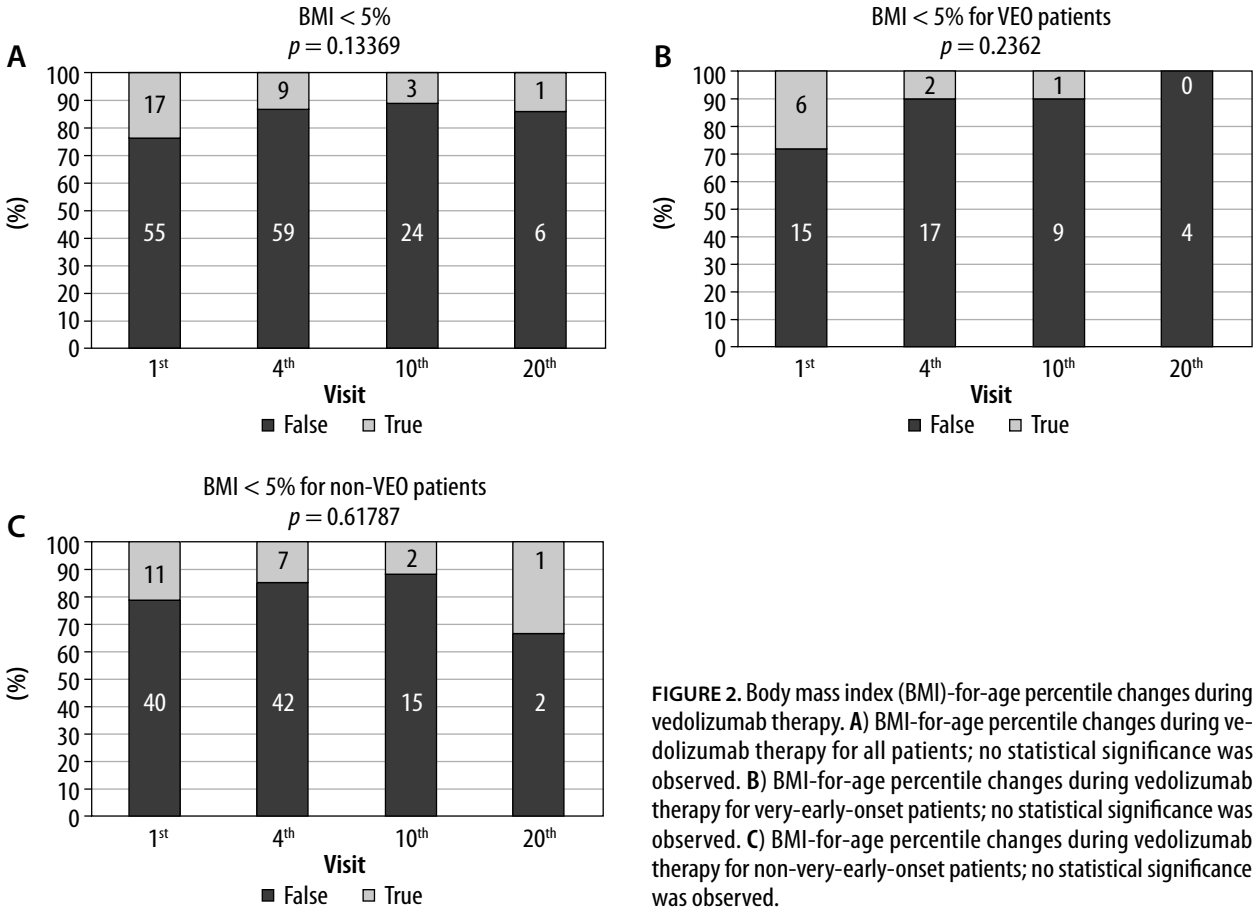

FIGURE 2. Body mass index (BMI)-for-age percentile changes during vedolizumab therapy. **A**) BMI-for-age percentile changes during vedolizumab therapy for all patients; no statistical significance was observed. **B**) BMI-for-age percentile changes during vedolizumab therapy for very-early-onset patients; no statistical significance was observed. **C**) BMI-for-age percentile changes during vedolizumab therapy for non-very-early-onset patients; no statistical significance was observed.

creased during VDZ therapy, although it was not statistically significant. Their median therapy duration is 60 weeks (min. 7, max. 224 weeks, IQR 21–120 weeks), while their median number of received VDZ doses is 9 (min. 3, max. 30, IQR 5–17). The median therapy duration for non-VEO patients is 51 weeks (min. 6, max. 166 weeks, IQR 30–63 weeks), while the median number of received VDZ doses is 9 (min. 3, max. 23, IQR 6–10).

Significant differences between these two age groups were observed in median Ht value but only in the 10th dose visit – the median was lower in the VEO group than in the non-VEO group (36.05% vs. 38.00%). No significant differences were observed between the VEO group and the non-VEO group in the rest of the laboratory parameters, the percentage of patients with their BMI < 5th percentile and both disease activity indexes. Figures 2B,C and 3A–G present the BMI-for-age percentile, laboratory parameters and PUCAI/PCDAI changes in VEO and non-VEO patients.

The clinical response rate at the 4th dose visit did not differ significantly between those groups. Significant differences were only observed in the clinical remission rate at the 1st dose visit (higher in the VEO group) and steroid-free remission rate at the 10th dose visit (higher in the non-VEO group). Concomitant steroid therapy, clinical response rate, clinical remission rate and steroid-free remission rate for VEO and non-VEO patients are presented in Table 3.

SAFETY

One patient discontinued therapy due to a severe general systemic allergic reaction with Quincke's edema, urticaria, and tachycardia at the third infusion of VDZ. No other serious adverse events were reported. During the whole observation of the study, 1 patient reported boils, 1 patient reported skin abscesses, 1 patient reported herpes labialis, 1 patient reported headache, 6 patients reported arthralgia, and 1 patient reported low-grade fevers. There were 23 mild infections of the upper respiratory tract, 2 cases of pneumonia and 1 SARS-CoV-2 infection.

DISCUSSION

This retrospective study demonstrates the outcomes of VDZ treatment in PIBD.

In our previous study we performed a retrospective review of 16 children with VEO-IBD receiving VDZ, confirming the safety and efficacy of this drug despite the more severe course in this age of onset group [14]. Currently under our supervision there are far more patients receiving VDZ with relatively long therapy duration. It has enabled us to report the outcome for a relatively large, single-center group of children with PIBD and compare this outcome between two groups divided according to age of disease onset.

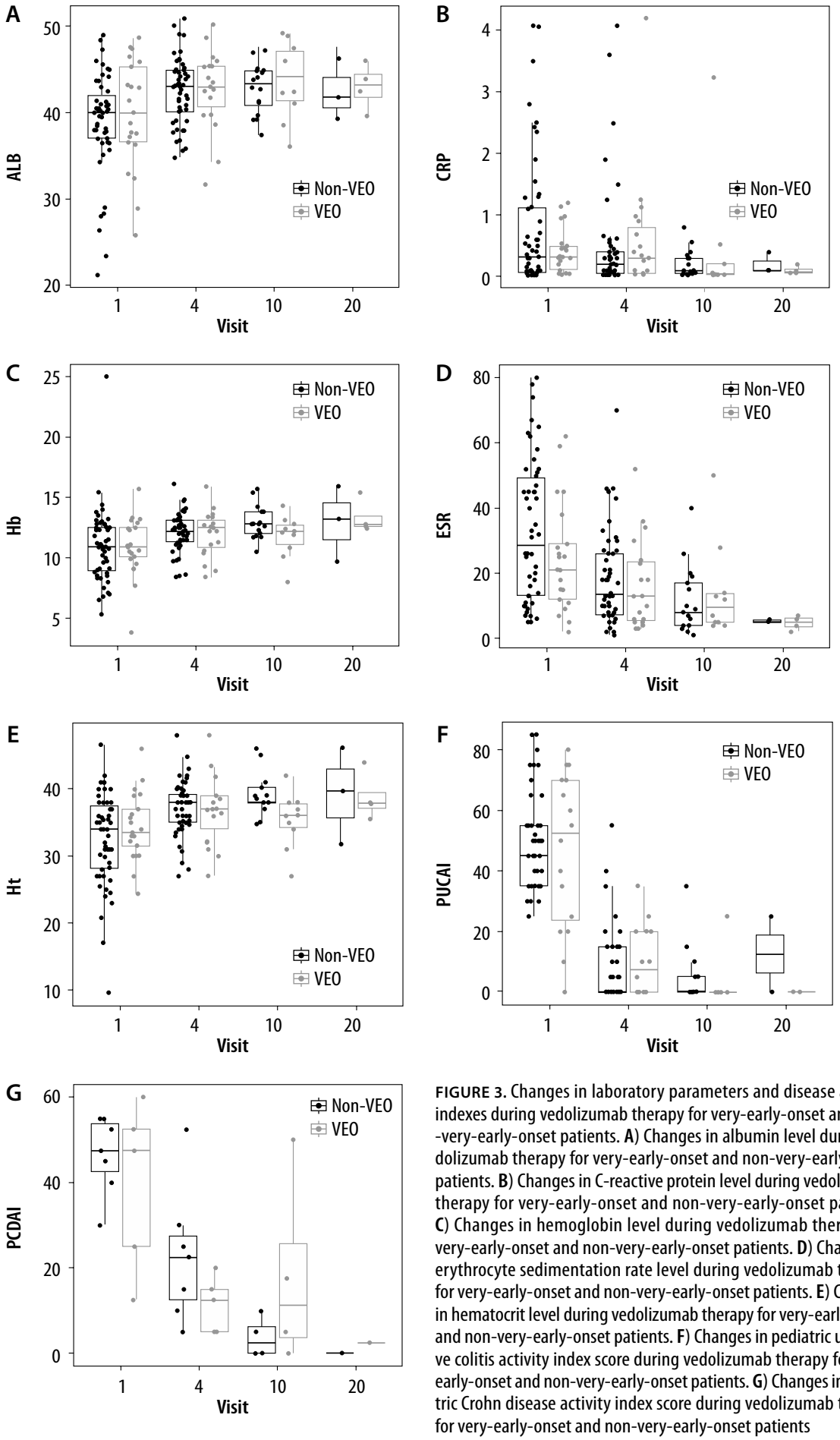

FIGURE 3. Changes in laboratory parameters and disease activity indexes during vedolizumab therapy for very-early-onset and non-very-early-onset patients. **A**) Changes in albumin level during vedolizumab therapy for very-early-onset and non-very-early-onset patients. **B**) Changes in C-reactive protein level during vedolizumab therapy for very-early-onset and non-very-early-onset patients. **C**) Changes in hemoglobin level during vedolizumab therapy for very-early-onset and non-very-early-onset patients. **D**) Changes in erythrocyte sedimentation rate level during vedolizumab therapy for very-early-onset and non-very-early-onset patients. **E**) Changes in hematocrit level during vedolizumab therapy for very-early-onset and non-very-early-onset patients. **F**) Changes in pediatric ulcerative colitis activity index score during vedolizumab therapy for very-early-onset and non-very-early-onset patients. **G**) Changes in pediatric Crohn disease activity index score during vedolizumab therapy for very-early-onset and non-very-early-onset patients

ALB – albumin, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, Ht – hematocrit, Hb – hemoglobin, PCDAI – pediatric Crohn disease activity index, PUCAI – pediatric ulcerative colitis activity index

TABLE 3. Concomitant steroid therapy, clinical response rate, clinical remission rate and steroid-free remission rate among very-early-onset (VEO) and non-VEO patients remaining in the vedolizumab therapy at each follow-up visit: frequency [%] and p-value are presented. *P*-values < 0.05 were considered significant

Parameters	Visit	Non-VEO	VEO	*p*-value
Number of patients remaining in therapy	1st	51	21	0.39331
Traditional steroid, *n* (%)		17 (33.3)	10 (47.6)	–
Budesonide MMX, *n* (%)		4 (7.8)	1 (4.8)	–
No steroid, *n* (%)		30 (58.8)	10 (47.6)	–
Clinical response, *n* (%)		N/A	N/A	N/A
Clinical remission, *n* (%)		0 (0.0)	2 (9.5)	0.02541
Steroid-free remission, *n* (%)		0 (0.0)	2 (9.5)	0.14810
Number of patients remaining in therapy	4th	50	19	0.39331
Traditional steroid, *n* (%)		8 (16.0)	7 (36.8)	–
Budesonide MMX, *n* (%)		1 (2.0)	1 (5.3)	–
No steroid, *n* (%)		41 (82.0)	11 (57.9)	–
Clinical response, *n* (%)		45 (90.0)	15 (78.9)	0.37460
Clinical remission, *n* (%)		33 (66.0)	11 (57.9)	0.53152
Steroid-free remission, *n* (%)		28 (56.0)	7 (36.84)	0.24920
Number of patients remaining in therapy	10th	17	10	0.39331
Traditional steroid, *n* (%)		0 (0.0)	3 (30.0)	–
Budesonide MMX, *n* (%)		2 (11.8)	1 (10.0)	–
No steroid, *n* (%)		15 (88.2)	6 (60.0)	–
Clinical response, *n* (%)		N/A	N/A	N/A
Clinical remission, *n* (%)		15 (88.2)	7 (70.0)	0.24659
Steroid-free remission, *n* (%)		15 (88.2)	4 (40.0)	0.02680
Number of patients remaining in therapy	20th	3	4	0.39331
Traditional steroid, *n* (%)		0 (0.0)	0 (0.0)	–
Budesonide MMX, *n* (%)		0 (0.0)	1 (25.0)	–
No steroid, *n* (%)		3 (100.0)	3 (75.0)	–
Clinical response, *n* (%)		N/A	N/A	N/A
Clinical remission, *n* (%)		2 (66.7)	4 (100.0)	0.16558
Steroid-free remission, *n* (%)		2 (66.7)	3 (75.0)	0.46520

VEO – very-early-onset, N/A – not applicable
Frequency (%) and p-value are presented. P-values < 0.05 were considered significant.

Each follow-up visit was combined with a subsequent VDZ infusion and was named with reference to it to unify and simplify the terminology in the presented research study – 1st dose visit, 4th dose visit, 10th dose visit, 20th dose visit.

Outcome data after the induction therapy of 3 VDZ doses were collected after 14 weeks of therapy (at the 4th dose visit) based on the reports that the full effect of VDZ is achieved after 6 to 14 weeks of treatment [11].

A significant decrease was observed in the clinical scores – PCDAI for CD and PUCAI for UC – between the 1st dose visit and each follow-up visit. This resulted in a high clinical response rate as well as clinical remission and steroid-free remission rate in both IBD groups – CD and CU. Concomitant traditional steroids were common at the baseline as the VDZ administration decision was made usually during exacerbation of PIBD. It could have an impact on the relatively high clinical response rate and clinical remission rate after 3 doses of VDZ, while the percentage of patients in remission during their maintenance treatment phase radically dropped and reflects more the data known in the adult studies [15, 16]. However according to a retrospective multi-center experience from the Paediatric IBD Porto Group of ESPGHAN [9], there was no impact of initial high dose steroid use on Week 14 remission rates in either CD or UC/IBD-U.

Previously published data indicate a superior clinical benefit in UC than CD and that the full effect of VDZ is slightly delayed in the CD group in comparison to the UC group. Data of a better VDZ outcome in UC than CD and the retrospective character of this study naturally resulted in an uneven split between the two diagnoses in our co-

hort (patients with UC were more likely to be treated with VDZ due to a greater benefit from the therapy than patients with CD). That is why the relatively small number of CD patients in our cohort made proper comparison of outcomes between CD and UC groups impossible.

According to previous data from adult studies, VDZ is more effective in anti-TNF-naïve patients than in anti-TNF-exposed patients and could be a first-line treatment with a safety and efficacy profile comparable with, or even superior to, TNF-α antagonists [7]. There are only a few pediatric studies confirming these observations [10]. Controlled clinical trials are definitely needed. Currently, in the pediatric field, VDZ is reserved primarily for children with a very severe disease course and a lack or loss of response, drug intolerance or contraindications to conventional treatment strategies including anti-TNF agents. Thus, in pediatric studies, the majority of, or all the patients had exposure to infliximab and/or adalimumab. In our study cohort, only one patient was anti-TNF-naïve. He was treated with strong immunosuppressants due to the liver transplant in the course of PSC/AIH overlap syndrome. That is why he was prescribed "rescue therapy" with VDZ to treat IBD with benefits from the drug safety profile resulting from its selective local effect limited to the gastrointestinal tract.

No significant improvement was observed in BMI percentile, which is consistent with another large pediatric cohort study, where no significant weight gain and no improvement in height velocity were observed during VDZ therapy [9].

There were significant improvements in the laboratory parameters CRP, ESR, ALB, Hb, and Ht. Analysis of the time effect on laboratory parameters was additionally performed for 7 complete cases. Statistical significance was observed in all listed parameters except Ht level, like in previous pediatric studies [8, 11].

A meta-analysis of 33 studies (6 randomized controlled trials and 27 cohort studies) indicated that combining VDZ or ustekinumab with an immunomodulator is no more effective than monotherapy in induction or maintenance of remission [17]. The percentage of patients receiving concomitant immunomodulatory drugs in the present research study was relatively stable despite the increase of clinical remission rate and steroid-free remission rate among patients remaining in the therapy during each follow-up visit.

Due to the retrospective character of this study and incomplete data, it was not possible to include fecal calprotectin (FCP) levels in the analysis. Therefore, no clear conclusions can be drawn on the effect of VDZ on this parameter.

One patient had a severe systemic allergic reaction which was followed by discontinuation of the treatment. No other serious adverse events were reported in comparable pediatric studies.

Comparing the VEO and the non-VEO group, no significant differences were observed in most cases. This confirms that VDZ therapy is safe and effective for PIBD patients irrespective of age of disease onset. It can also reflect the recent data describing no difference between IBD presentation across the pediatric age categories, except for children with monogenic IBD [4, 5].

The increasing percentage of VEO patients during VDZ therapy and noticeably greater median therapy duration deserve attention, although the present observations are statistically insignificant. It suggests that their response to VDZ could be even more long-lasting than among non-VEO patients. It requires more research on larger groups.

The limitation of the present study is its retrospective character, which made it impossible to draw proper conclusions about additional parameters (FCP level, endoscopy) and the uneven split between the two diagnoses in our cohort (UC vs. CD). A longer follow-up period and larger size of the group of patients would also be beneficial.

CONCLUSIONS

Vedolizumab was found to be safe and effective in the treatment of the most challenging group of patients with severe pediatric-onset IBD who have failed conventional therapies, irrespective of age of disease onset. A prospective multi-center long-term research study is still definitely needed to define the role of VDZ in the PIBD treatment strategy.

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DISCLOSURE

The authors declare no conflict of interest.

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