

Vedolizumab in pediatric inflammatory bowel disease: a retrospective multi-center experience from the Paediatric IBD Porto group of ESPGHAN

Oren Ledder^{1,2}, Amit Assa^{3,4}, Arie Levine^{4,5}, Johanna C Escher⁶, Lissy de Ridder⁶, Frank Ruemmele⁷, Neil Shah⁸, Ron Shaoul⁹, Victorien M. Wolters¹⁰, Astor Rodrigues¹¹, Holm H Uhlig¹², Carsten Posovsky¹³, Kaija-Leena Kolho¹⁴, Christian Jakobsen¹⁵, Shlomi Cohen^{4,16}, Dror S. Shouval^{4,17}, Mira Friedman¹, Dan Turner^{1,2}

¹Shaare Zedek Medical Center, Jerusalem, Israel; ²The Hebrew University of Jerusalem, Israel; ³Schneider Medical Center, Petach Tikva, Israel; ⁴The Sackler faculty of Medicine, Tel Aviv University, Israel; ⁵Wolfson Medical Center, Holon, Israel; ⁶Erasmus Medical Center, Rotterdam, Netherlands; ⁷Hopital Necker Enfants Malades, Paris, France; ⁸Great Ormond Street Hospital, London, United Kingdom; ⁹Rambam Medical Center, Haifa, Israel; ¹⁰University Medical Center Utrecht, Netherlands; ¹¹Oxford University Children's Hospital, Department of Paediatrics, Oxford, United Kingdom; ¹²Translational Gastroenterology Unit, Oxford University, United Kingdom ¹³University Medical Center, Ulm, Germany; ¹⁴Helsinki University Central Hospital, Helsinki, Finland; ¹⁵Hvidovre University Hospital, Copenhagen, Denmark; ¹⁶"Dana-Dwek" Children's Hospital, Tel Aviv Medical Center, Tel Aviv, Israel; ¹⁷Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel.

Short title:

Vedolizumab in pediatric inflammatory bowel disease

Corresponding author

Dan Turner MD, PhD
Pediatric Gastroenterology and Nutrition Unit
Shaare Zedek Medical Center,
P.O.B 3235
Jerusalem 91031, Israel
Tel +972-2-6666482
Fax +972-2-6555756
Email: turnerd@szmc.org.il

COI:

OL received travel grant from Ferring and Takeda.
AL received research grants, honorariums, travel grants or participated in advisory boards or activities organized by MSD, Janssen, Abbvie and Abbott, Falk, Takeda and Nestle.
JCE received research support from MSD; advisory board honorarium from AbbVie and Janssen.
LdR received consultation fee, research grant or honorarium from Shire, Merck, Janssen, Abbvie and Pfizer.
FR received consultation fee Takeda.
AR advisory board Abbvie.
HHU declares industrial project collaboration with Eli Lilly and UCB Pharma.
CP received travel grants from Abbvie and MSD, participated in advisory boards organized by MSD and Abbvie
KLK received consultation fee from Ferring and Tillotts Pharma and advisory board honorarium from Abbvie and MSD
DT received consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, Abbvie, Takeda, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health, Shire.
AA, RS, NS, VMW, DS, SC, CJ, MF declare no conflict of interest

ABSTRACT

Background: Vedolizumab, an anti-integrin antibody, has proven to be effective in adults with Inflammatory Bowel Disease (IBD), but the data in pediatrics are limited. We describe the short-term effectiveness and safety of vedolizumab in a European multi-center pediatric IBD cohort.

Method: Retrospective review of children (2-18 years) treated with vedolizumab from 19 centers affiliated with the Paediatric IBD Porto group of ESPGHAN. Primary outcome was week 14 corticosteroid-free remission (CFR).

Results: 64 children were included [32 (50%) male, mean age 14.5 ± 2.8 years, with a median follow-up 24 weeks (IQR 14-38; range 6-116)]; 41 (64%) UC/IBDU and 23 (36%) CD. All were previously treated with anti-TNF (28% primary failure, 53% secondary failure).

Week 14 CFR was 37% in UC, and 14% in CD ($p=0.06$). CFR by last follow-up was 39% in UC and 24% in CD ($p=0.24$). Ten (17%) children required surgery, 6 of whom had colectomy for UC. Concomitant immunomodulatory drugs did not affect remission rate (42% vs 35%; $p=0.35$ at week 22). There were 3 minor drug-related adverse events. Overall 5% achieved endoscopic mucosal healing with 9% achieving stool calprotectin $<100\text{mcg/gm}$.

Conclusion: Vedolizumab was safe and effective in this cohort of pediatric refractory IBD. These data support previous findings of slow induction rate of vedolizumab in CD and a trend to be less effective compared to patients with UC.

Keywords: Vedolizumab; Pediatric; Inflammatory bowel disease

BACKGROUND

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody acting against $\alpha 4\beta 7$ integrin which modulates lymphocyte trafficking specifically to the gut. Results from the GEMINI 1¹ and GEMINI 2² trials demonstrated effectiveness of vedolizumab in induction and maintenance of remission in both ulcerative colitis (UC) and Crohn's disease (CD), respectively, but the clinical benefit seems slightly superior in UC. In GEMINI 1, 106/225 (47%) of patients had a clinical response by week 6 and 107/247 (43% of responders and 18% of all comers to the trial) were in clinical remission by 1 year. In CD 69/220 (31%) showed clinical response by 6 weeks, with 116/308 (38%) of responders in clinical remission by 1 year, representing 12% of all comers to the trial. CD patients who failed anti-TNF treatments were assessed in the induction of remission trial GEMINI 3. In this study 39% exhibited clinical response by week 6, but the clinical remission rate did not surpass the placebo arm until 10 weeks (27% vs. 12%), suggesting that the effects of vedolizumab on clinical remission may not be evident in the initial weeks of treatment, especially in CD.³ Subsequent real life cohort studies in adults support the effectiveness of vedolizumab in inducing and maintaining remission, both in CD and UC.⁴⁻¹⁰

In children with IBD, vedolizumab is available off-label and it is typically reserved for patients who have exhausted other treatment options including anti-TNF. Two case series on vedolizumab from North America have recently been published with inconsistent results, one with 52 children¹¹ and the second with 21 patients¹².

The aim of this multi-center observational study is to report on the short- and long-term outcomes of vedolizumab therapy in pediatric IBD.

METHODS

This retrospective observational study reports the collective experience of vedolizumab in children (2-18 years) from 19 centers affiliated with the Paediatric IBD Porto and Interest groups of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), in Europe and Israel. All children were diagnosed with CD, UC or IBDU by accepted criteria¹³ and were commenced on vedolizumab for any reason, and combined with any other medications. To avoid selection bias, we included all patients receiving at least one infusion, even if treatment had been discontinued for any reason.

Explicit clinical and demographic data, baseline disease characteristics, previous medications and surgeries as well as anthropometric data were recorded 6 months prior to vedolizumab, at vedolizumab onset and 6, 14, 22, and 54 weeks thereafter, when available, as well as at last follow-up. The following data were recorded at each time point: disease activity (captured by the wPCDAI in CD and PUCAI in UC as well as physician global assessment (PGA)), medications, blood tests, and explicit data on adverse events. When available, data on surgery, endoscopic evaluations (captured by the Simple Endoscopic Score in CD (SES-CD) and the UC Endoscopic Index of Severity (UCEIS) in UC/IBDU) and stool calprotectin were recorded. De-identified patient data were recorded on a standardized REDcap web-based case-report forms, managed by the data coordinating center (DCC) at Shaare Zedek Medical Center in Jerusalem. All contributing centers obtained individual ethical approval from their local ethics board.

The primary outcome was treatment success at week 14, defined as steroid and exclusive enteral nutrition (EEN) - free remission (i.e. wPCDAI<12.5 or PUCAI< 10) without the need for new medications or surgical intervention.

Secondary outcomes include remission rate at last follow-up, mucosal healing (defined as SES-CD <3 in CD¹⁴ or UCEIS=0 in UC/IBD-U¹⁵), deep remission (defined as clinical remission with fecal calprotectin <100 mcg/g¹⁶), need for surgical interventions, growth, weight gain and adverse events. Linear growth was assessed by its most sensitive measure, height velocity, during the 6-months prior to starting vedolizumab therapy vs. the paired measure after. Anthropometric measurements are expressed as standard deviation z-scores (SDS) using age and gender matched reference standards ^{17 18}. Height velocity data were standardized using the JMP-derived polynomial calculations based on percentile data ^{17,19}.

Statistical analyses

Data are presented as mean \pm standard deviation, or medians (interquartile range (IQR)), as appropriate for the distribution normality. Intention-to-treat (ITT) analysis was calculated utilizing the modified non-response imputation (NRI), whereby patients in whom vedolizumab was ceased prior to the visit were considered treatment failures in all outcomes. If data were missing due to lack of sufficient follow-up (but the drug was not discontinued) and the 6 week vedolizumab induction period was completed, then the last observation carried forward (LOCF) was utilized. Patients in whom follow-up did not extend beyond vedolizumab induction were included only in the safety analysis and the NRI (if the drug was discontinued) to reflect a conservative yet fair reflection of the drug effect. Data were compared using chi square or Fisher's exact test for categorical variables and Student's t-test or Wilcoxon rank sum test for

continuous variables. Paired data with a non-normal distribution was compared with the Sign test, including pre vs post treatment measures of anthropometric data. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY) with $p < 0.05$ taken as the significance threshold.

RESULTS

Patient characteristics

A total of 64 children were included with a median follow-up of 24 weeks (IQR 14-38) (Table 1). Fifty two (81%) patients were followed for at least 14 weeks, 38 (59%) followed for at least 22 weeks and 10 (16%) followed to at least one year. Of the 12 patients with less than 14 weeks follow-up, 10 ceased vedolizumab and only 2 lacked sufficient follow-up data.

All children were previously exposed to anti-TNF, 57 (89%) of whom failed intensified dosing regimen, and almost half failing a second anti-TNF or third-line therapy (Table 1). At vedolizumab initiation, disease activity was moderate or severe in 40 (63%) of patients, despite 49 (77%) patients taking concomitant corticosteroids or nutritional therapy (Table 1).

Drug administration

Fifty-two (81%) children received the adult dose of 300mg while the others (weighing 19.5-48kg) received 150-250mg or 3.6-10.3mg/kg (median 7.3mg/kg (IQR 5.6-9.8)). The smallest child to receive 300mg weighed 28.5kg, and the largest child to receive a reduced dose weighed 48kg (received 200mg) (suppl figure 1). Of those who commenced lower dose, 4 subsequently had dose increased throughout the treatment

course. One of these children (UC) achieved better response on higher dose but did not achieve remission, two (both UC) were already in remission prior to the dose escalation, and the forth (CD) did not respond to the higher dose.

Vedolizumab was ceased in 14 (22%) of patients throughout follow-up within a median of 14 weeks (IQR 12-22), all but one due to poor response; 10/14 (71%) discontinued within 14 weeks and 13/14 (93%) within 6 months. One patient ceased due to chronic itch as a suspected adverse event of vedolizumab which resolved following drug cessation.

Remission rate (Figure 1)

ITT steroid- and EEN-free remission rates at week 14 were observed in 15/41 (37%) of the UC/IBD-U children and 3/21 (14%) of CD ($p=0.06$; Figure 1). The ITT remission rates at 22 weeks were 14/41 (34%) in UC/IBD-U and 4/21 (19%) for CD ($p=0.22$; Figure 1). Three UC patients who were in remission at week 14 were not in remission at week 22, with two new patients entering remission over that period. In CD, two patients in remission at week 14 lost remission at week 22, but 3 new patients entered remission over that period.

At last follow-up, ITT remission rates were 16/41 (39%) for UC/IBD-U and 5/21 (24%) in CD ($p=0.24$; Figure 1). Clinical activity scores and CRP improved during the treatment course (Table 2).

Corticosteroid and nutritional therapy were used as directed by treating physician with variable dosing courses as per clinical need. Forty one patients (67%) were on corticosteroid therapy at commencement, 12 of whom received high dose induction therapy (above 0.8mg/kg). There was no impact of initial high dose steroid use on

week 14 remission rates in both CD or in UC/IBD-U ($p=1.0$ and $p=0.89$ respectively). Throughout follow-up there were fewer patients on additional therapy, with a drop in median dose of steroids, over time (Table 2).

At vedolizumab commencement, 21/64 (67%) patients were on concomitant thiopurines or methotrexate therapy. This dropped to 20/40 (50%) at 22 weeks and 7/14 (50%) at 1 year. Remission rates did not differ in those with combination therapy at 14 weeks vs. those on monotherapy (11/30 (37%) vs 7/21 (33%); $p=0.52$) and not at 22 weeks (8/19 (42%) vs 7/20 (35%); $p=0.35$).

Secondary outcomes

Univariate analysis showed no association between remission rates and gender, age at diagnosis, disease duration, CRP, presence of perianal disease and reason for previous anti-TNF failure both in UC/IBD-U and in CD (all $p>0.28$; data not shown). There was no association between remission rates and disease location in CD or disease extent in UC. All CD patients who achieved remission by last follow-up had ileocolonic disease, however remission rate of ileocolonic distribution was not significantly different than the smaller cohort with isolated colonic disease (5/19 (26%) vs 0/4 (0%), respectively; $p=0.26$).

There was no demonstrated catch-up growth in the CD patients. The reduced height velocity seen overall prior to vedolizumab did not improve over the 6 months thereafter (median z-score -1.55 (IQR $-4.9 - 2.8$) vs -1.88 ($-2.9 - 1.2$); $p=0.96$). To more accurately evaluate height velocity changes requires bone age or Tanner score to assess pubertal stage, data which were largely missing. Sub-analysis of height velocity was performed in those patients with Tanner stage recorded between 1-3, in whom linear growth is assumed to be ongoing. Amongst this cohort there remained no

significant improvement in height velocity (median z-score -4.98 (-6.4 - -3.3) vs -3.55 (-6.12 - -1.88); $p=0.36$). Catch up growth was noted amongst the 5 CD patients who achieved remission by end of follow-up, (post-treatment height velocity z-score 5.96 (IQR -1.9- 5.96)), higher than pre-treatment height velocity z-score (-0.67 (IQR-1.9 - 0.67)); however with the limited number of patients who met this criteria this did not reach statistical significance ($p=0.18$). None of these patients had Tanner stage recorded as 1-3.

Weight gain was not seen over the 6 months following treatment commencement, both among UC/IBD-U patients (median weight z-score at baseline -0.57 (-1.1- 0.38) vs -0.46 (-1.0-0.78) after 6 months; $p=0.07$) and CD patients (-1.22 (-1.8- -0.1) vs -0.89 (-2.2-0.04); $p=0.92$).

Fifty six children (88%) had a standard induction course with 8 weekly maintenance infusions, 8 (12%) commenced 4 weekly infusions from the outset. Of the formers, 7 (13%) increased dosing to 4 or 6 weekly infusions due to poor response. Of these, four patients had CD, one of whom subsequently achieved remission, and 3 had UC of whom one subsequently achieved remission, another partially responded and the third had no response. There was no difference in success rate between those who commenced on 8 week dosing intervals and those commenced on 4 week dosing intervals from the outset (20/45 (44%) vs 1/7 (14%) respectively; $p=0.14$).

Nineteen children had both baseline and follow-up colonoscopic assessment.

Amongst these children both UCEIS in UC and SES-CD in CD dropped significantly (Figure 2). Two of 13 UC/IBD-U patients (15%, 5% of all UC/IBD-U patients) and 1/6 CD patients (17%, 4% overall CD) achieved mucosal healing.

Twenty five patients (5 CD, 20 UC/IBD-U) had stool calprotectin measured at baseline with follow-up measures. There was a significant drop in the calprotectin levels following treatment with a median decrease of 518 mcg/gm (IQR 202-2327) in UC/IBD-U and 499 mcg/gm (39-1620) in CD, with no difference in magnitude of the drop between UC/IBDU and CD ($p=0.62$) (Figure 3). Deep remission, defined as fecal calprotectin < 100 mcg/gm, was achieved by six children (24% of those in whom calprotectin was measured, 9% overall). All of these children had UC/IBD-U (6/41 (15%) of UC/IBD-U vs 0/23 (0%) of CD patients; $p=0.03$). Eleven children (44% of those with serial calprotectin, and 17% overall) had calprotectin <300 mcg/gm (2/23 (9%) of CD patients and 9/41 (22%) with UC; $p=0.09$).

Ten (17%) patients underwent surgical resection at a median of 4 months (IQR 3.3-5.8), four of whom had CD (17% of the entire CD cohort) and 6 had UC/IBD-U (15% of entire UC/IBD-U cohort).

Safety

No serious drug-related adverse events were reported. Three mild potential drug related adverse events were recorded: one (13 year old female) developed otitis externa and periorbital edema after the first and second infusion which subsequently resolved and she remained on treatment; the second (17 year old female) developed an intractable itch after the first infusion and vedolizumab was subsequently ceased; and the third (17 year old female) developed mild shortness of breath during the fourth infusion, which improved with antihistamine and a slower infusion rate. Vedolizumab was continued in this patient, only ceasing later due to poor drug effectiveness.

DISCUSSION

In this largest real-life cohort of vedolizumab use in pediatric IBD to date, we show that vedolizumab is safe and effective in pediatric IBD. EEN and steroid-free remission rates at last follow-up of 39% and 24% in UC/IBD-U and CD respectively. Furthermore, in this previously refractory cohort, amongst those who underwent evaluation, 15% and 17% had demonstrated mucosal healing and 30% and 0% achieved calprotectin <100mcg/gm, respectively. Consistent with the finding in GEMINI 3³ there was a slower response rate in CD than that seen in UC. The slower rate of response in CD as demonstrated in our study is a finding of potential clinical significance when selecting appropriate patients for vedolizumab therapy.

Considering the refractory nature of our cohort, these data show promise for this newer class of biological therapy in pediatric UC and to a lesser extent also in CD.

Our remission rate in CD is comparable to the pediatric cohort of Conrad et al who reports week 14 remission rate of 15%,¹² but significantly lower in both UC and CD remission rates than reported by Singh et al (week 14 remission of 76% and 42% respectively).¹¹ When comparing to adult data, one year clinical remission rates in the GEMINI 1 and 2 were 18% and 12% respectively, lower than that seen in our study. A more accurate comparison would be with the GEMINI 3 study of TNF refractory CD patients in whom 27% achieved clinical remission by week 10. Adult real world cohorts report week 14 CFR rates between 19-31% for CD and 19-36% for UC⁴⁻¹⁰, comparable to our data.

Consistent with our findings was the lack of serious adverse events associated with vedolizumab in both of these series. Nonetheless, Conrad et al reported 29 adverse events in children including upper respiratory tract infections, nausea, fatigue,

headaches, nasopharyngitis, skin infections and sinusitis¹². While GEMINI 1 revealed no difference in adverse events between vedolizumab and placebo¹, GEMINI 2 demonstrated a higher incidence of nasopharyngitis with vedolizumab than with placebo (12.3% vs 8%)². The adult US VICTORY consortium of 212 patients reported enteric infections (5 per 100 patient year follow-up (PYF)), sinopulmonary infections (4.4 per 100 PYF) and arthralgia (3.1 per 100 PYF), among other less common adverse events⁹. Other real-life cohorts report infections from 0-25%, nasopharyngitis 0-23%, arthralgia 2-20% and one report of anaphylaxis and rash⁴⁻⁸. Pruritis as an adverse event of vedolizumab has not been previously reported.

Within the pediatric population, responses to IBD treatment differ between older children and those with early-onset or very early-onset IBD²⁰. In our cohort dosing was based on adult recommended dose with non-standardized, weight-based modifications in younger children. Since children weighing less than 30kg are best dosed by body surface area (BSA),²¹ until formal dosing is available it is reasonable to dose children in the equivalent of 300mg/1.73m² (ie. 175mg/BSA), and over 40kg as adults.

Our cohort did not show superiority of combination therapy over monotherapy with vedolizumab, however this analysis is limited by the small sample size and limited follow-up. This comparative analysis was not specifically presented in the two previous pediatric case series. Shelton et al did not find any benefit of combination therapy over sole vedolizumab in their adult cohort, but noted that the sample size may have been too small to detect a difference⁴.

Considering the small sample size and the lack of comparison group, we found that shortening infusion interval from 8 to 4 weeks led to improved effect in 3/7 (43%).

This is supported by recent pharmacokinetic data demonstrating significant correlation between higher vedolizumab drug levels and clinical response in IBD patients.²²⁻²⁴

In our cohort we did not demonstrate any disease features associated with better response, including age at diagnosis, disease location or extent, or disease duration, however this needs to be reassessed in larger studies.

Our study is limited by its retrospective nature and hence a lack of standardized treatment regimens and concomitant therapies as well as endoscopic evaluation in only some. Despite being the largest cohort to date, the cohort is still limited in size. Response rates are difficult to relate solely to vedolizumab effect, since variable use of induction corticosteroids and nutritional therapy obviously contribute to clinical response. Since vedolizumab in pediatric IBD is limited to off-label use, our cohort was represented entirely by patients failing conventional therapies. Previous anti-TNF failure may be associated with lower remission rates than anti-TNF naïve patients, however results from studies assessing these differences are conflicting.^{4,8,9,25-27}

Our study presents encouraging data that vedolizumab is safe and effective in pediatric UC and to a lesser extent, also in CD. Although it might seem that combination therapy is not required, a larger focused study is required to address this question with certainty. Clinicians should be aware of possible adverse events related to the upper respiratory and nasopharyngeal regions with vedolizumab. We show preliminary data suggesting that shortening infusion interval to q 4 weeks may improve effectiveness in some patients. The currently enrolling prospective multicenter VEDOKIDS cohort study will further define the role of vedolizumab in

pediatric IBD and will provide trough drug monitoring data to predict the success and required dosing in children.

Acknowledgements

Authors have made substantial contributions to the following: the concept and design of the study: OL, DT; acquisition of data: OL, AA, AL, JE, LdR, FR, NS, RS, VW, AR, HU, CP, KKK, CJ, SC, DS, DT; analysis and interpretation of data: OL, MF, DT; drafting the article: OL, DT; critical review and approval of draft: all authors.

LEGENDS TO FIGURES

Figure 1: Steroids- and EEN-free intention to treat remission rate in week 14 (Figure 1a), week 22 (Figure 1b), and last follow-up (Figure 1c)

Footnote: Intention-to-treat analysis

Figure 2: Change in endoscopic scores; UCEIS in UC (Figure 2a), and SES-CD in Crohn's disease (Figure 2b)

Footnote: Repeat colonoscopy at median 14 weeks (IQR 14-22)

Figure 3: Change in stool calprotectin; all patients (Figure 3a), UC/IBD-U (Figure 3b), Crohn's disease (Figure 3c)

Footnote: Repeat measure at median 54 weeks (IQR 22-54)

Supp figure 1: Weight range by dose

REFERENCES

1. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699-710.
2. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369:711-21.
3. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014;147:618-27 e3.
4. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of Vedolizumab as Induction Therapy in Refractory IBD Patients: A Multicenter Cohort. *Inflamm Bowel Dis* 2015;21:2879-85.
5. Vivio EE, Kanuri N, Gilbertsen JJ, et al. Vedolizumab Effectiveness and Safety Over the First Year of Use in an IBD Clinical Practice. *J Crohns Colitis* 2016;10:402-9.
6. Amiot A, Grimaud JC, Peyrin-Biroulet L, et al. Effectiveness and Safety of Vedolizumab Induction Therapy for Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2016;14:1593-601 e2.
7. Baumgart DC, Bokemeyer B, Drabik A, Stallmach A, Schreiber S, Vedolizumab Germany C. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice--a nationwide consecutive German cohort study. *Aliment Pharmacol Ther* 2016;43:1090-102.
8. Stallmach A, Langbein C, Atreya R, et al. Vedolizumab provides clinical benefit over 1 year in patients with active inflammatory bowel disease - a prospective multicenter observational study. *Aliment Pharmacol Ther* 2016;44:1199-212.
9. Dulai PS, Singh S, Jiang X, et al. The Real-World Effectiveness and Safety of Vedolizumab for Moderate-Severe Crohn's Disease: Results From the US VICTORY Consortium. *Am J Gastroenterol* 2016;111:1147-55.
10. Kopylov U, Ron Y, Avni-Biron I, et al. Efficacy and Safety of Vedolizumab for Induction of Remission in Inflammatory Bowel Disease-the Israeli Real-World Experience. *Inflamm Bowel Dis* 2017.
11. Singh N, Rabizadeh S, Jossen J, et al. Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2016;22:2121-6.
12. Conrad MA, Stein RE, Maxwell EC, et al. Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2016;22:2425-31.
13. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;58:795-806.
14. Mazzuoli S, Guglielmi FW, Antonelli E, Salemm M, Bassotti G, Villanacci V. Definition and evaluation of mucosal healing in clinical practice. *Dig Liver Dis* 2013;45:969-77.
15. Vuitton L, Peyrin-Biroulet L, Colombel JF, et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. *Aliment Pharmacol Ther* 2017.
16. Nakar I, Focht G, Church P, et al. The association of mucosal healing (MH), transmural healing (TH) and calprotectin in paediatric Crohn's disease: a report from the ImageKids study. *Journal of Pediatric Gastroenterology and Nutrition* 2017.
17. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn disease. *Inflamm Bowel Dis* 2007;13:424-30.
18. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med* 1992;11:1305-19.

19. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr* 1985;107:317-29.
20. Kelsen JR, Grossman AB, Pauly-Hubbard H, Gupta K, Baldassano RN, Mamula P. Infliximab therapy in pediatric patients 7 years of age and younger. *J Pediatr Gastroenterol Nutr* 2014;59:758-62.
21. Feber J, Al-Matrafi J, Farhadi E, Vaillancourt R, Wolfish N. Prednisone dosing per body weight or body surface area in children with nephrotic syndrome: is it equivalent? *Pediatr Nephrol* 2009;24:1027-31.
22. Yarur A, Bruss A, Jain A, et al. Higher vedolizumab levels are associated with deep remission in patients with Crohn's disease and ulcerative colitis on maintenance therapy with vedolizumab. Abstract - European Crohn's and Colitis Organisation 2017 Annual Meeting 2017:DOP020.
23. Schulze H, Esters P, Hartmann F, et al. A prospective cohort study to assess the relevance of Vedolizumab drug level monitoring in IBD patients Abstract - European Crohn's and Colitis Organisation 2017 Annual Meeting 2017;P521.
24. Williet N, Paul S, Del tedesco E, Phelip JM, Roblin X. Serum vedolizumab assay at week 6 predicts sustained clinical remission and lack of recourse to optimisation in inflammatory bowel disease Abstract - European Crohn's and Colitis Organisation 2016 Annual Meeting 2016;P632.
25. Vermeire S, Loftus EV, Jr., Colombel JF, et al. Long-term Efficacy of Vedolizumab for Crohn's Disease. *J Crohns Colitis* 2016.
26. Loftus EV, Jr., Colombel JF, Feagan BG, et al. Long-term Efficacy of Vedolizumab for Ulcerative Colitis. *J Crohns Colitis* 2016.
27. Feagan BG, Rubin DT, Danese S, et al. Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. *Clin Gastroenterol Hepatol* 2017;15:229-39 e5.

Table 1: Baseline patient characteristics (frequency (%), mean±SD or median (IQR) are presented as appropriate)

	Total (n=64)	CD (n=23)	UC (n=33) / IBD-U (n=8)
Male	32 (50%)	13 (57%)	19 (46%)
Age at diagnosis (years)	10.7±3.6	9.5±3.5	11.4 ±3.5
Disease duration (months)	37 (22-60)	61 (34-92)	33 (20-43)
Follow-up (weeks)	24 (14-38; range 6-116)	22 (14-38; range 6-56)	24 (14-36; range 6-116)
Location/Extent		L2 4 (17%)	E1 1 (2%)
		L3 11 (48%)	E2 4 (10%)
		L3/L4a 6 (26%)	E3 6 (15%)
		L3/L4b 2 (9%)	E4 30 (73%)
		Perianal 4 (17%)	
Behavior		Inflammatory 17 (74%)	Severe 37 (90%)
		Stricturing 5 (22%)	
		Penetrating 1 (4%)	
		Growth delay 15 (65%)	
Extra-intestinal manifestations	16 (25%)	8 (35%)	8 (20%)
Clinical assessment			
Baseline PGA			
Severe	22 (37%)	7 (33%)	15 (39%)
Moderate	24 (41%)	7 (33%)	17 (45%)
Mild	11 (19)	6 (29%)	5 (13%)
Remission	2 (3%)	1 (5%)	1 (3%)
Baseline wPCDAI/PUCAI		37.5 (24-61)	45 (30-65)
Baseline endoscopy (SES-CD/UCEIS)		19.5 (10.5-23.3)	20 (15-25)
Previous therapies:			
Anti-TNF	64 (100%)	23 (100%)	41 (100%)
Primary failure	18 (28%)	6 (26%)	12 (29%)
Secondary failure	34 (53%)	10 (44%)	24 (59%)
Adverse event	9 (14%)	5 (22%)	4 (10%)
Second anti-TNF	36 (56%)	18 (78%)	18 (44%)
Third-line therapy			
Tacrolimus	4 (6%)		4 (10%)
Thalidomide	1 (2%)	1 (4%)	
Prior surgery	5 (8%)	4 (17%)	1 (2%)

Table 2: Indicators of disease activity over time (frequency (%) or medians (IQR) are reported as appropriate)

	Week 0	Week 6	Week 14	Week 22	Week 52
CD	n=22	n=22	n=16	n=14	n=4
wPCDAI	38 (24-61)	31 (14-46)	19 (9-29)	18 (8-26)	18 (9-39)
Clinical remission	2 (9%)	5 (23%)	4 (25%)	5 (36%)	1 (25%)
CRP (mg/dL)	1.6 (0.37-4.9)	0.72 (0.2-3.36)	0.8 (0.46-2.94)	0.85 (0.34-2.19)	1.9 (0.58-5.48)
Number normal	6 (27%)	8 (36%)	6 (38%)	5 (36%)	1 (25%)
Steroid use	14 (64%)	9 (41%)	2 (13%)	1 (7%)	0
Dose (mg)	25 (15-40)	20 (7.5-33)	17.5 (10-17.5)	5	
Enteral Nutrition	7 (32%)	7 (32%)	3 (19%)	2 (14%)	1 (25%)
UC / IBD-U	n=39	n=38	n=34	n=26	n=10
PUCAI	45 (30-65)	25 (9-40)	10 (0-28)	10 (0-15)	2.5 (0-22.5)
Clinical remission	2 (5%)	9 (24%)	16 (47%)	12 (46%)	6 (60%)
CRP (mg/dL)	0.41 (0.1-1.4)	0.23 (0.07-0.67)	0.14 (0.05-0.71)	0.15 (0.04-0.51)	0.09 (0.04-0.28)
Number normal	24 (62%)	28 (74%)	19 (56%)	19 (73%)	9 (90%)
Steroid use	27 (69%)	19 (50%)	9 (26%)	4 (15%)	0
Dose (mg)	25 (20-40)	20 (10-40)	12.5 (10-20)	15 (6-24)	