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Vedolizumab: An Emerging Treatment Option for Pediatric Inflammatory Bowel Disease

Pooja Shah, PharmD and Danielle McDonald, PharmD

Vedolizumab is a humanized α4β7-integrin antagonist that is currently FDA-approved for adult inflammatory bowel disease. Limited evidence is available to guide use in pediatric patients, though off-label use is described in the form of retrospective reviews and case series. Collectively these publications begin to establish safety and efficacy data in pediatric patients < 18 years of age. Additionally, dosing regimens described in the literature serve to guide weight-based dosing, which is not established at this time. This narrative review aims to summarize the available literature and provide recommendations for vedolizumab use in the pediatric population. A literature search was performed in PubMed (January 2014–December 2020) using the keyword *vedolizumab*. Based on the available evidence, vedolizumab appears to be a safe and moderately effective agent for treatment of refractory pediatric inflammatory bowel disease. Prospective, randomized trials are warranted to optimize dosing regimens and to establish long-term safety.

ABBREVIATIONS CD, Crohn's disease; CRP, C-reactive protein; FDA, US Food and Drug Administration; IBD, inflammatory bowel disease; IBD-U, IBD-undefined; MAdCAM-1, mucosal addressin cell adhesion molecule-1; PML, progressive multifocal leukoencephalopathy; TNF, tumor necrosis factor; UC, ulcerative colitis

KEYWORDS Crohn's disease; inflammatory bowel disease; pediatrics; ulcerative colitis; vedolizumab

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Introduction

Inflammatory bowel disease (IBD) is a chronic condition, with frequent onset in childhood or adolescence.[1] The diagnosis of IBD encompasses 2 major diseases, ulcerative colitis (UC) and Crohn's disease (CD), which present with unique distinguishing features, though treatment strategies for the two commonly overlap. Treatment of IBD includes immune modulation to suppress or reverse the inflammatory pathophysiology of IBD.

The ongoing development of biologic agents provides targeted therapeutic options to manage moderate to severe IBD. Tumor necrosis factor (TNF) is a proinflammatory cytokine implicated in the pathogenesis of IBD. Anti-TNF biologics demonstrate efficacy in UC and CD and have become a mainstay of treatment. As of March 2021, infliximab, adalimumab, certolizumab pegol, and golimumab are all FDA-approved anti-TNF biologics for use in IBD.[2-5] Infliximab and adalimumab are the only FDA-approved agents in pediatric patients with IBD. Infliximab is commonly used as a first-line defense for pediatric patients with moderate to severe IBD, though clinical remission rates have been reported[6] to be as low as 42%. In a study[7] of over 1200 anti-TNF–naïve patients exposed to infliximab or adalimumab, about 25% experienced primary non-response at 14 weeks, and nearly two-thirds experienced non-remission at week 54. Furthermore, patients who are classified as non-responders to one anti-TNF biologic may be less likely to respond to another anti-TNF biologic, which, in some cases, may be a result of anti-drug antibodies.[6,8] Because of the relatively high percentage of non-responders, alternative therapies are vital.

Vedolizumab (Entyvio, Takeda Pharmaceuticals America Inc, Deerfield, IL), a humanized α4β7-integrin antagonist, is FDA-approved for adult IBD and presents an emerging option for pediatric patients. It is thought that mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is selectively expressed on endothelial venules in the gut and in gut-associated lymphoid tissue. The lymphocyte integrin α4β7 is the exclusive integrin receptor for MAdCAM-1, and this interaction is known to contribute to chronic inflammation.[9,10] Vedolizumab specifically inhibits binding of the α4β7 integrin to the MAdCAM-1 receptor, thereby decreasing inflammation. Furthermore, it prevents T-cell migration into the inflamed tissue.[9] It is the only available gut-selective agent to treat IBD.

Efficacy of vedolizumab in the adult patient population with IBD was demonstrated in the GEMINI 1 and GEMINI 2 trials, with clinical remission rates of 43% of patients with UC and 38% of patients with CD by end of 1 year of treatment.[11,12] Serious adverse events associated with the use of the vedolizumab include hypersensitivity reactions, risk of infections, and malignancy, which are consistent with all monoclonal antibodies. Since receiving FDA approval in adult patients, several articles have been published describing the use of vedolizumab in pediatric

Table 1. Efficacy Studies With Vedolizumab

Reference (N)	Clinical Response Assessment and Definition	Patients Achieving Clinical Remission	Steroid-Free Remission
Singh[13] (N = 52)	PUCAI <10 or PCDAI <12.5 at 14 wk	Week 14: UC: 76%; CD: 42%	Week 22: UC:71%; CD: 33%
Conrad[14] (N = 52)	Decrease in PUCAI of at least 20 points and decrease in PCDAI of at least 12.5 points from baseline to wks 6, 14, and 22	Week 6: 6/19 (31.6%); UC/IBD-U: 1/4 (25%); CD: 5/15 (33.3%) Week 14: 10/19 (52.6%) Week 22: 11/19 (57.9%); UC/IBD-U: 2/4 (50%); CD: 9/15 (60%)	Definition: Inactive disease (PUCAI/PCDAI <10 points) without steroid therapy. Week 22: achieved inactive disease in 20% of 20 patients
Ledder[15] (N = 64)	Steroid- and exclusive enteral nutrition–free remission	Week 14: 21/62 (29%); UC/IBD-U: 15/41 (37%); CD: 3/21 (14%)	At last follow-up: 39% in UC/IBD-U patients and 24% in CD patients
Schneider[16] (N = 12)	Remission defined as shPCDAI <10 points or PUCAI <10 points	UC cohort: Week 2: 2/5 (40%) Week 6: 1/5 (20%) Week 14: 1/5 (20%) CD cohort*: Week 14: 1/6 (17%)	UC cohort: 4/5 patients treated with concomitant corticosteroids at baseline, and all could be discontinued by week 14 (one patient restarted before week 38) CD cohort: 4/6 patients treated with concomitant corticosteroids at baseline, and all could be tapered but not discontinued
Jossen[17] (N = 68)	Mucosal healing (composite of endoscopic remission and histologic remission)	Week 49: 38% (25/66); UC cohort: 34%; CD cohort: 42%	Steroid use decrease: 66% from baseline Steroid-free clinical remission: UC cohort: 57%; CD cohort: 48%

CD, Crohn's disease; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; shPCDAI, short Pediatric Crohn's Disease Activity Index; UC, ulcerative colitis; wPUCAI, weighted Pediatric Crohn's Disease Activity Index

* One patient discontinued therapy because of systemic allergic reaction.

patients. The purpose of this review is to summarize the available literature and to provide recommendations for use in the pediatric population.

Methods

A literature review was performed in PubMed (January 2014–December 2020) using the keyword *vedolizumab*. The results of this search were limited to the English language, humans, and children (birth to 18 years). An additional search was conducted using the keywords *vedolizumab* and *pediatrics* to identify any relevant articles missing in the original review. The authors reviewed all available studies for safety and efficacy data, including the effect of vedolizumab on biomarkers.

Results

A total of 87 articles were identified. Of those articles, 79 were excluded. Literature included in this review were studies evaluating vedolizumab safety and efficacy in pediatric patients. Exclusion reasons included study population of >21 years of age, alternative medications evaluated, review articles on IBD management, and case reports. The remaining 8 articles were included for analysis in this narrative review. Six studies evaluated efficacy of vedolizumab in pediatric patients. Five of those studies assessed vedolizumab as primary therapy, while one study focused on evaluating the additional effect of tacrolimus in conjunction with vedolizumab. The remaining 2 studies concentrated on the postoperative safety of vedolizumab use in children. Two independent reviewers validated selection of the included articles.

Efficacy. Five retrospective studies assessing efficacy of vedolizumab treatment in pediatric patients were identified. Table 1 summarizes the pertinent study information, while Table 2 summarizes available dosing information from the studies. In 2016, the first retrospective review[13] evaluated the use of vedolizumab in 52 pediatric patients diagnosed with IBD. Most patients (90%) had previously failed an anti-TNF agent, and 44% had failed 2 anti-TNF agents. The primary endpoint of clinical remission at week 14 was defined using validated tools and was achieved in 76% of patients with UC and 42% of patients with CD. At baseline, 50% of patients were on corticosteroids, and this percentage decreased to 35% by week 6 and to 19% by week 14. The reported doses of vedolizumab administered were 300 mg in 39 patients, 6 mg/kg in 11 patients, and 5 mg/kg in 2 patients. Three patients were transitioned to a more frequent dosing interval—from every 8 weeks to

Table 2. Dosing Strategies in Vedolizumab Studies

Reference (N)	Dose of Vedolizumab (% Receiving)	Frequency
Singh[13] (N = 52)	300 mg (75) 6 mg/kg (21) 5 mg/kg (4)	Induction: 0, 2, 6 wk Maintenance: every 8 wk (3 pts transitioned to every 4 wk)
Conrad[14] (N = 19)	300 mg (100)	Induction: 0, 2, 6 wk Maintenance: Every 8 wk
Ledder[15] (N = 64)	19.5 kg to 48 kg: 150–250 mg (3.6–10.3 mg/kg/dose) 300 mg (81.2)	Induction: 0, 2, 6 wk Maintenance: Every 8 wk
Schneider[16] (N = 12)	6 mg/kg/dose (max: 300 mg)	Induction: 0, 2, 6 wk Maintenance: every 4–8 wk, depending on disease course
Jossen[17] (N = 68)	19–29 kg: 6–10 mg/kg/dose >30 kg (91): 300 mg	Maintenance: every 8 wk (13 pts changed to every 4 wk, 1 pt every 5 wk, 3 pts every 6 wk)
Hamel[18] (N = 12)	10 mg/kg/dose (max: 300 mg)	Not specified
Zimmerman[22] (N = 13)	300 mg or 5 mg/kg	Induction: 0, 2, 6 wk Maintenance: every 8 wk

Max, maximum; pt, patient; pts, patients

every 4 weeks during maintenance therapy. Interestingly, 4 patients were transitioned from natalizumab to vedolizumab because of concerns for progressive multifocal leukoencephalopathy (PML). By week 14, 3 of the 4 patients achieved remission on vedolizumab.

In 2016, Conrad et al[14] demonstrated efficacy of vedolizumab in a retrospective evaluation of 21 children diagnosed with UC or CD, all of whom were refractory to anti-TNF therapy. Two patients were not included in the final analysis because of an immediate need for surgical intervention, requiring discontinuation of vedolizumab. The primary outcomes were clinical response, defined using validated tools, and steroid-free remission at weeks 6, 14, and 22. By week 22, clinical response was observed in 2 of 4 patients with UC/IBD-undefined (IBD-U) and 9 of 15 patients with CD. Steroid-free remission, defined as inactive disease without steroid therapy, was achieved in 20% of patients by week 22. All patients were greater than 13 years of age and 40 kg, so a standard vedolizumab dose of 300 mg was administered at 0, 2, and 6 weeks, followed by a maintenance regimen of every 8 weeks. Nine patients were continued on concomitant immunomodulator therapy while on vedolizumab.

In 2017, Ledder et al[15] published another retrospective observational study describing use of vedolizumab in 64 children aged 2 to 18 years diagnosed with IBD. All patients had previously failed one or more anti-TNF agents. The primary outcome of clinical remission, defined as steroid- and exclusive enteral nutrition–free remission without the need for new medication or surgery, was achieved in a total of 18 (29%) patients by week 14, and 21 patients had sustained remission at 1 year. Clinical remission was observed in 15 of 41 patients with UC/IBD-U and 3 of 21 patients with CD. Corticosteroid-free remission was achieved in 39% of UC/IBD-U patients and 24% of CD patients at last follow-up. Fifty-two patients received the standard dose of 300 mg. Patients weighing 19.5 to 48 kg received 150 to 250 mg (3.6–10.3 mg/kg). Of the patients who received lower doses initially, 4 had doses increased throughout their therapy. Fifty-six (88%) children received a standard induction course with every-8-week maintenance infusions, while 8 (12%) children received every-4-week infusions. Treatment efficacy was improved in 3 of the 7 patients with shortened infusion intervals. Of note, 14 patients (22%) discontinued vedolizumab at a median of 14 weeks, primarily because of poor response. Weight gain or improvement in height velocity were not noted with treatment. Mucosal healing was observed in 3 of the 19 patients who had baseline and follow-up colonoscopy assessment.

In 2018, Schneider et al[16] published a retrospective case series of 12 pediatric patients with IBD who received vedolizumab. Patients were initiated on therapy after failure of or intolerance to TNF-antagonists. The primary outcome of the study was clinical response by week 14. This was achieved in 5 patients (45%), and only 2 patients had sustained remission at 52 to 96 weeks. At week 14, complete remission was achieved in 4 of 5 patients in the UC cohort and in 1 of 6 patients diagnosed with CD. Primary non-response, defined at week 22, or loss of response, in weeks 34 or 37, occurred in 3 patients, which prompted discontinuation of treatment.

The remaining 3 patients had a partial response. All patients were dosed at 6 mg/kg to a maximum dose of 300 mg at standard intervals.

Most recently, Jossen et al[17] conducted a retrospective review of 68 pediatric patients on vedolizumab aged <21 years for the treatment of IBD with endoscopic evaluation. This study evaluated mucosal healing rates, defined as the composite of endoscopic and histologic remission. Unlike previous studies, approximately half of the patients were anti-TNF naïve. Thirty-eight percent of patients met the primary outcome of mucosal healing, with significantly higher rates of endoscopic remission achieved in anti-TNF–naïve patients compared with those with prior anti-TNF exposure. Mucosal healing rates were not significantly different in patients with UC (34%) compared with patients with CD (42%). While most patients received the adult dose of 300 mg, 6 patients (<30 kg) received doses between 6 and 10 mg/kg. In patients with clinical non-response or persistent elevations in serum inflammatory markers, the frequency was decreased from every 8 weeks to every 4, 5, or 6 weeks.

Hamel et al[18] studied the addition of a calcineurin inhibitor with vedolizumab to provide a steroid-sparing effect. The median time to starting vedolizumab therapy after failure of anti-TNF treatment was 8 weeks. This study retrospectively evaluated 12 pediatric patients with IBD, all of whom failed initial treatment with anti-TNF agents. They were concomitantly managed with tacrolimus, with an initial target goal trough of 10 to 15 ng/dL and then 8 to 10 ng/dL based on improved clinical symptoms. Clinical remission was achieved in 9 patients, none of whom required IBD-related surgery. At a 24-week follow-up, 8 patients did not require surgery, and after an 80-week follow-up period, 6 of the 12 patients were off tacrolimus therapy. All patients received vedolizumab at a 10 mg/kg/dose up to a maximum dose of 300 mg. This study demonstrated the benefit of potentially combining tacrolimus therapy with vedolizumab to provide a steroid-sparing effect.

Biomarkers, including albumin, C-reactive protein (CRP), stool calprotectin, and hematocrit, are often trended in patients with IBD to detect disease activity. In the patients evaluated by Singh et al,[13] CRP was relatively normal at baseline in a large majority of UC patients, while a decrease in CRP was observed in patients with CD by week 14. Conversely, a significant increase was noted in median CRP concentrations in the study reported by Conrad et al.[14] The patients evaluated in Ledder et al[15] had a decrease in CRP concentrations from baseline; however, this was not sustained in patients with CD by week 52. Improvements in serum albumin and hematocrit were observed from baseline to week 22 in patients described by Conrad et al.[14] Improvements in serum hematocrit were documented with vedolizumab therapy in 5 of 13 patients. When evaluated, stool calprotectin dropped significantly in patients with UC and CD after vedolizumab treatment.[15] Baseline biomarker and biomarker changes with stool calprotectin were not associated with mucosal healing.[17]

Safety. Conrad et al[14] described 12 serious adverse effects that led to hospitalizations. Three patients developed extraintestinal manifestations of IBD during therapy. Other common (occurring in 4 patients) adverse effects reported in this study included upper respiratory tract infections, nausea, fatigue, and vomiting. Ledder et al[15] did not note any significant adverse effects. Observed adverse effects included otitis externa and periorbital edema that resolved with continued treatment, intractable itching requiring cessation of therapy, and mild shortness of breath, which resolved with treatment and allowed continued vedolizumab therapy. Schneider et al[16] reported only one severe adverse event, in which a patient experienced a systemic allergic reaction at the time of the second vedolizumab infusion.

Because of the mechanism of vedolizumab, by which leukocyte migration to the intestines is blocked, there exists concern for postoperative complications in patients who receive vedolizumab preoperatively. Data in adult and pediatric studies regarding postoperative complications are conflicting because of the existence of many confounding factors.[19] To date, 2 pediatric studies were designed to evaluate the safety of vedolizumab use preoperatively. Lightner et al[20] conducted a retrospective chart review assessing the risk of postoperative complications in 13 pediatric patients who received vedolizumab and 36 who received anti-TNF agents within 12 weeks of an abdominal operation. None of the vedolizumab-treated patients experienced a postoperative infectious complication within 30 days of the operation. Zimmerman et al[21] conducted a similar study comparing 13 vedolizumab-exposed post-surgical patients to 16 vedolizumab-naïve patients. The differences in complications between the groups were not found to be statistically significant. The study authors did note an increased rate of mucocutaneous separation in the vedolizumab-exposed group, which was not statistically significant. While these retrospective reviews suggest that postoperative infectious complications in vedolizumab-treated patients may not be a risk in the pediatric population, the sample sizes of both studies were small, so future studies are warranted to corroborate these findings.

Discussion

Clinical Implications. Five retrospective studies[13-17] provide efficacy data for use of vedolizumab in pediatric patients diagnosed with IBD. Clinical remission rates varied from 20% to 76% among the pediatric studies depending on patient characteristics, treatment history, and IBD subtype. Although the rates were variable, they correlated with the induction rates of clinical remission in

the GEMINI studies. In GEMINI 1 and 2, induction therapy achieved clinical response at week 6 in 47% and 14% of patients, respectively. Maintenance response at week 52 in GEMINI 1 and 2 occurred in 42% and 39% of patients receiving vedolizumab every 8 weeks and in 45% and 37% of patients receiving vedolizumab every 4 weeks, respectively.[11,12] Similar to the GEMINI studies, most patients enrolled in the pediatric studies were refractory to or intolerant of one or more anti-TNF agent. Jossen et al[17] demonstrated efficacy in an objective endpoint of mucosal healing, including histologic remission and endoscopic evaluations. These objective outcomes are reflective of the new FDA guidance for ideal primary efficacy assessment of new IBD treatments.[22] Clinical benefits observed with vedolizumab include a significant decrease in concomitant steroids and exclusive enteral nutrition-free remission.[15] Furthermore, although not consistent among all studies evaluated, there are some improvements in biomarkers in pediatric patients on vedolizumab.

Efficacy rates with vedolizumab in pediatric patients were lower and time to remission delayed in patients with CD compared with patients with UC. This is comparable to adult patients, in whom it is noted that those with CD and previous TNF-antagonist exposure have required a longer duration of treatment with vedolizumab to achieve treatment response.[11,12,23] Because of the limited number of prospective pediatric studies, it is difficult to identify significant differences in efficacy between IBD subtypes.

Adverse effect rates among all studies were generally low. An infusion-related reaction was noted in one patient and described as a systemic allergic reaction. It is important to continue to monitor for adverse effects in larger, prospective studies to understand the medication's safety profile in children. Increased risk of postoperative infectious complications was observed in adult patients and may be elucidated as a concern in pediatric patients with more widespread use. Progressive multifocal leukoencephalopathy is a concern with the use of monoclonal antibodies. No cases of PML were observed in the pediatric studies described in this review.[9] Singh et al[13] described the successful switch from natalizumab to vedolizumab in patients with concern for PML. Vedolizumab may be an option for patients experiencing PML on other monoclonal antibody therapy.

Currently, anti-TNF agents remain a first-line defense for pediatric patients diagnosed with IBD requiring biologic therapy. In patients refractory to TNF-antagonists, limited treatment options remain.[24] In lieu of new therapies, surgery is often the only remaining option, and a total colectomy may be required. The available literature describes vedolizumab as a safe and effective alternative for these patients to induce and maintain remission.

Dosing Strategies. The available evidence describes varied weight-based dosing strategies in pediatric patients, as outlined in Table 2. The most commonly reported weight-based doses averaged between 5 and 7 mg/kg/dose, maximizing at the adult FDA-approved dose of 300 mg. Pending safety and efficacy outcomes from pediatric prospective studies, it is reasonable to use a dose of 6 mg/kg for patients < 45 kg and 300 mg for patients ≥ 45 kg. A recent study[25] evaluated therapeutic drug monitoring to assess the trough serum concentrations of vedolizumab in pediatric-onset IBD patients. Trough concentrations were inversely correlated with inflammatory marker concentrations. Additionally, trough concentrations were reported to be significantly higher in patients with UC compared with patients with CD. Therapeutic drug monitoring may be useful in dictating frequency of administration to target clinical remission among IBD subtypes. Evidence in adults implies there may be improved efficacy with higher exposure. Further research is necessary to maximize efficacy of vedolizumab treatment using this approach.

Future Studies. Currently, 3 clinical trials are being conducted in pediatric patients to evaluate vedolizumab use in pediatric IBD. The first trial is a multi-center prospective cohort study enrolling patients < 18 years treated with vedolizumab for any indication.[26] Patients in this study will be followed for up to 3 years to evaluate serum samples, stool samples, and clinical outcomes. The regimen used will be 177 mg/m^2 (maximum = 300 mg) at week 0, 2, and 6 and then every 8 weeks. The second prospective, randomized trial will evaluate pediatric patients aged 2 to 17 years with moderately to severely active UC or CD to determine the pharmacokinetics, efficacy, and safety of vedolizumab.[27] Patients in the high-dose group will receive 300 mg for patients weighing ≥30 kg and 200 mg for weights 10 kg to <30 kg. Patients in the low-dose group will receive 150 mg if patient weight is ≥30 kg and 100 mg if weight is 10 kg to <30 kg. Patients will be switched to the high-dose group if there is lack of response by 14 weeks. Doses are to be administered on day 1 and weeks 2, 6, and 14. Preliminary data results have been posted on the clinicaltrials.gov website. The third trial will evaluate long-term safety outcomes in pediatric patients with UC or CD, using the same dosing groups as the previously described trial.[28] Patients will receive vedolizumab every 8 weeks for up to 5 years. Results from all 3 studies are pending but will provide valuable information to guide use of vedolizumab in pediatric patients.

Conclusion

Overall, vedolizumab appears to be a moderately effective and safe option for pediatric patients with IBD refractory to standard-of-care therapy. While the medication adds a promising option to the armamentarium of therapies for pediatric IBD patients, larger, prospective studies are warranted to more clearly define the drug's place in therapy as well as optimal dosing and long-term safety.

Article Information

Affiliations. Department of Pharmacy Practice (PS), Rutgers University, The State University of New Jersey, Piscataway, NJ; Department of Pharmacy (DM), Cooper University Health Care, Camden, NJ; Department of Pharmacy (PS), Hackensack University Medical Center, Hackensack, NJ.

Correspondence. Pooja Shah, PharmD; pooja.shah@pharmacy.rutgers.edu

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