Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease

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Background: Though vedolizumab has received regulatory approval for the treatment of Crohn's disease (CD) and ulcerative colitis (UC) in adults, there is increasing off-label use in children.

Aims: To describe the experience with vedolizumab in pediatric inflammatory bowel disease (IBD) patients at 3 tertiary IBD centers and examine predictors of remission.

Methods: A retrospective review identified pediatric IBD patients (age < 18 yrs) receiving vedolizumab. Data on demographics, disease behavior, location, activity, and previous treatments/surgeries were collected. Disease activity was assessed using the weighted pediatric CD activity index or pediatric UC activity index. Primary outcome was week 14 remission, defined as pediatric UC activity index <10 or weighted pediatric CD activity index <12.5. Descriptive statistics and univariate analyses were performed to examine associations of clinical characteristics with efficacy.

Results: Fifty-two patients, 58% CD and 42% UC, initiated vedolizumab between June 2014 and August 2015. Median age at vedolizumab initiation was 14.9 (range 7–17) years. Ninety percent had failed ≥1 anti-tumor necrosis factor (TNF) agent. Week 14 remission rates for UC and CD were 76% and 42%, respectively ($P < 0.05$). Eighty percent of anti–TNF-naive patients experienced week 14 remission. At week 22, anti–TNF-naive patients had higher remission rates than TNF-exposed patients (100% versus 45%, $P = 0.04$). There were no infusion reactions or serious adverse events/infections.

Conclusions: Our results suggest that vedolizumab is efficacious and safe in pediatric IBD patients, with UC patients experiencing earlier and higher rates of remission than CD patients. Anti–TNF-naive patients experienced higher remission rates than those with anti-TNF exposure. Controlled clinical trial data are needed to confirm these observations.

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Key Words: vedolizumab, pediatrics, inflammatory bowel disease, Crohn's disease, ulcerative colitis

Vedolizumab is an anti-integrin therapy approved in May 2014 for adult patients with Crohn's disease (CD) and ulcerative colitis (UC). It acts on the α4β7 integrin receptor molecule present on the surface of lymphocytes, blocking the ability to bind to its MadCAM-1 counterpart on the intestinal endothelium. This interaction inhibits lymphocyte migration to inflamed gastrointestinal tissue. Its predecessor, natalizumab, binds to the α4 chain nonspecifically, with the α4β1/VCAM-1 interaction interfering with lymphocyte surveillance of the central nervous system, leading to the concern for John Cunningham (JC) virus reactivation and subsequent development of progressive multifocal leukoencephalopathy (PML).[1,2] Vedolizumab, with its gut specificity, does not interfere with immune surveillance in the central nervous system, and thus, there is no apparent association with PML. This was supported by the placebo-controlled GEMINI studies evaluating safety and efficacy of vedolizumab in 2700 patients in nearly 40 countries.[3,4]

The GEMINI 1 study demonstrated vedolizumab's efficacy in adult UC patients with 17% remission at week 6% and 45% at week 52.[3] GEMINI 2 showed a 14.5% week 6 remission rate in CD patients receiving vedolizumab and 39% at week 52.[4] The effect of vedolizumab induction therapy in CD patients previously exposed to anti-tumor necrosis factor (TNF) therapy was found to be delayed to week 10.[5] The rates of serious adverse events, serious infections, and upper respiratory infections were all similar among patients on long-term vedolizumab compared with control patients.

Not unlike their adult counterparts, anti-TNF failure is a common problem in pediatric inflammatory bowel disease

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(IBD). Thus, examination of the anti-integrins in pediatric IBD patients is essential. Natalizumab has been shown to be effective in 2 pediatric CD studies; yet, its use is limited by the PML risk.[6,7] Literature on the safety and efficacy of vedolizumab in the pediatric IBD population is lacking. Given the mechanism of action and presumed superior safety profile of vedolizumab, the efficacy of this anti-integrin therapy in pediatric IBD patients warrants evaluation. We aimed to describe our experience with vedolizumab in 3 tertiary pediatric IBD centers and to examine predictors of remission in pediatric IBD patients receiving vedolizumab.

MATERIALS AND METHODS

Patient Population and Ethical Considerations

We conducted a retrospective review of IBD patients aged less than 18 years who initiated vedolizumab and received at least 6 weeks of therapy between June 2014 and August 2015 at 3 tertiary IBD centers: Cedars-Sinai Medical Center in Los Angeles, CA; Mount Sinai Health System in New York, NY; and Connecticut Children's Medical Center in Hartford, CT. The decision to prescribe vedolizumab was at the discretion of the treating physician. The study was approved by the Institutional Review Board at all 3 institutions.

Data Collection

Patient charts were reviewed for demographics, diagnosis information, disease behavior, disease location, steroid exposure, surgical history, and biological and immunomodulator history. Vedolizumab treatment information included dose and duration of therapy. We collected data on adverse events, including infusion reactions and serious infections. Key laboratory parameters collected included complete blood count with differential, complete metabolic panel, and C-reactive protein (CRP). Given that CRP levels were obtained at laboratories with different cutoff values, these values were standardized such that 1.0 corresponds to 1 times the upper limit of normal (×ULN). Clinical activity scores, the weighted pediatric CD activity index (wPCDAI)[8] and pediatric UC activity index (PUCAI), were recorded at baseline and at each infusion.

Outcomes

The primary outcome of this study was clinical remission at week 14 defined as PUCAI <10 or wPCDAI <12.5. Secondary outcomes included clinical remission rates at weeks 6, 22, and 30 and CRP responsiveness, and steroid-free remission was examined. Time from last anti-TNF agent, disease location, and concomitant immunomodulator use were examined as predictors of remission. Safety was also described.

Statistical Analyses

Standard descriptive statistics, such as mean, median, range, and standard deviation, were computed for continuous variables. Univariate analyses were performed to examine associations of clinical characteristics with therapeutic efficacy. Categorical variables were summarized by frequency and percentage and were compared across independent groups by the Fisher's exact test. A 2-sided 0.05 significance level was used throughout. Statistical calculations were made using JMP Pro version 12 (SAS Institute, Cary, NC).

RESULTS

Patient Population

A total of 52 patients were included for analysis—58% had CD and 42% UC. The median age at vedolizumab initiation was 14.9 (range 7–17) years, and median disease duration was 3.2 (range 0.2–15.2) years. At the time of vedolizumab initiation, 15 patients (29%) were on a concomitant immunomodulator (6-mercaptopurine/azathioprine/methotrexate). Ninety percent of (47/52) patients had failed at least one anti-TNF agent (infliximab, adalimumab, or certolizumab pegol) and 44% (23/52) had failed at least 2 anti-TNF therapies. In those with previous exposure to anti-TNF, the median time from last anti-TNF dose to vedolizumab initiation was 1.5 (range 0–96) months (Table 1). Eleven patients (21%), all with CD, had IBD operation before vedolizumab initiation with median time from operation to vedolizumab initiation of 10 (range 1–31) months. Type of operation included

TABLE 1. Baseline Demographics of Patients Starting Vedolizumab

	All Patients, N = 52	CD, n = 30	UC, n = 22
Gender, M:F, %	52:48	47:53	59:41
Age at start of vedolizumab (median, yrs)	14.9 (range 7–17)	15.2 (range 7–17)	14.3 (range 7–17)
Duration of disease (median, yrs)	3.2 (range 0.2–15.2)	4.2 (range 0.4–15.2)	2.5 (range 0.2–12)
Switch from natalizumab, %	8	13	0
Number of previous anti-TNF agents (median), %	1.5	2	1
0	10	3	18
1	40	23	64
2	44	63	18
3	3	10	0
Days between last anti-TNF and first vedolizumab, %	Median 45 d	Median 60 d	Median 35 d
Less than 30 d	15	17	9
30–60 d	37	23	45
61–90 d	13	17	0
More than 90 d	33	37	27
Use of concurrent immunomodulator, %	29	33	13
Patients starting vedolizumab postoperatively, %	21	37	0

included colectomy-ileal pouch anal anastomosis (IPAA) or subtotal colectomy (3), colonic resection (1), ileocecectomy (2), other small bowel resection (1), diverting ostomy (2), and perianal abscess drainage (3). Patients with colectomy-IPAA had a preoperative diagnosis of UC, which was switched to CD postoperatively. All patients received vedolizumab intravenously at 0, 2, and 6 weeks and then approximately every 8 weeks. The dose of vedolizumab was 300 mg in 39 patients (75%) and dosed by weight in smaller patients—6 mg/kg in 11 patients and 5 mg/kg in 2 patients. Forty patients (77%) remain on vedolizumab at the time of last follow-up, with median follow-up time of 22 (range 6–70) weeks. At the time of vedolizumab initiation, 29/52 patients (56%) were receiving a corticosteroid—18/52 (35%) were receiving prednisone and 11/52 (21%) were receiving oral budesonide. By week 6, 18/50 (36%) patients were receiving a corticosteroid—12/50 (24%) were on prednisone and 6/50 (12%) on budesonide, and by week 14, 8/42 (19%) were receiving prednisone and no patient was on budesonide.

Vedolizumab Effectiveness

Week 14 Clinical Remission

At baseline, the median wPCDAI for the 30 CD patients was 32.5 (interquartile range [IQR], 17.5–45), 2 patients in remission with a wPCDAI score <12.5. By week 6, the median wPCDAI was 15 (IQR, 5.6–27.5), with 9/26 (35%) patients in remission. At week 14, median wPCDAI was 20 (IQR, 0–35), with 10/24 (42%) patients being in remission. At baseline, the median PUCAI for the 22 UC patients was 30 (IQR, 10–55), with 4/22 (18%) patients in remission. By week 6, the median PUCAI was 2.5 (IQR, 0–15), with 14/22 (63%) patients in remission, and week 14 median PUCAI was 0 (IQR, 0–10), with 13/17 (76%) patients being in remission (Table 2). Patients with UC were more likely to be in remission at week 14 than patients with CD (76% versus 42%, $P < 0.05$) (Fig. 1).

Of patients who had information available for a disease activity index to be calculated at both weeks 6 and 14, 17 of 19 (89%) IBD patients in clinical remission at week 6 had a sustained remission at week 14. Four of 20 (20%) additional patients not in remission at week 6 entered remission at week 14. Week 6 remission was associated with week 14 remission ($P < 0.001$).

Corticosteroid-Free Remission

Although there was a trend, there was no significant difference between UC and CD patients being in a corticosteroid-free remission at week 6 ($P = 0.09$) or at week 14 ($P = 0.10$). Week 6 corticosteroid-free remission was associated with week 14 corticosteroid-free remission ($P < 0.0001$). Between weeks 6 and 14, 2 patients had been switched from budesonide to prednisone and 1 patient was started on prednisone who was previously steroid free. In the 32 IBD patients followed for at least 22 weeks, UC patients were more likely to be in a corticosteroid-free remission than those with CD (UC 71% versus CD 33%, $P = 0.03$).

Disease Phenotype and Clinical Characteristics

Patients with colonic-only disease (UC or isolated Crohn's colitis, with no small bowel involvement) were more likely to be in remission at week 6 (colonic 62% versus noncolonic 26%, $P = 0.01$) and at week 14 (colonic 70% versus noncolonic 39%, $P < 0.05$). Extent of colon involvement and CD behavior per the Montreal Classification was not associated with clinical remission. There was no association between concomitant immunomodulator therapy, neither thiopurines nor methotrexate, and vedolizumab efficacy at any time point.

Biomarkers on Vedolizumab Treatment

In UC patients, the median CRP at baseline was 0.46 (IQR, 0.23–2.44) ×ULN with 77% (5/22) having a normal baseline CRP. The median CRP for UC patients remained below the ULN at weeks 6 and 14. In CD patients, the median CRP at week 0 was 1.72 (IQR, 0.84–2.68) ×ULN, with 27% (22/30) having a normal baseline CRP. CRP decreased to 1.3 (0.5–4.79) ×ULN at week 6 and 1.14 (0.5–5.06) ×ULN at week 14 (Table 2). Both median albumin level and hematocrit were normal at baseline and did not change over time.

TABLE 2. Clinical Scores Over Time on Vedolizumab

	Week 0	Week 2	Week 6	Week 14	Week 22	Week 30
CD	n = 30	n = 30	n = 26	n = 24	n = 18	n = 11
wPCDAI (median) (IQR)	32.5 (17.5–45)	18.75 (9.3–32.5)	15 (5.6–27.5)	20 (0–35)	16.25 (3.75–28.1)	7.5 (0–22.5)
CRP (median, ×ULN) (IQR)	1.72 (0.84–2.68)	1.64 (0.52–4.22)	1.3 (0.5–4.79)	1.14 (0.50–5.06)	1.43 (0.28–3.99)	0.46 (0.2–1.85)
UC	n = 22	n = 22	n = 22	n = 17	n = 14	n = 8
PUCAI (median) (IQR)	30 (10–55)	15 (0–30)	2.5 (0–15)	0 (0–10)	0 (0–16.25)	0 (0–20)
CRP (median, ×ULN) (IQR)	0.46 (0.23–2.44)	0.22 (0.08–0.68)	0.56 (0.25–1.2)	0.21 (0.09–0.83)	0.63 (0.07–1.1)	1.04 (0.16–1.78)

Previous Biological Exposure

Anti-TNF Therapy

A total of 47 of the 52 patients (90%) had been exposed to anti-TNF therapy before their first vedolizumab infusion. Patients whose last exposure to anti-TNF therapy was more than 1 month before vedolizumab initiation were more likely to be in remission at week 2 than those exposed to anti-TNF within 1 month (46% versus 12%, $P = 0.02$). This exposure effect was not seen at any other efficacy time points.

Of the 5 (4 UC and 1 CD) patients started on vedolizumab with no previous anti-TNF exposure, 4/5 (80%) achieved clinical remission by week 6 and all 4 patients who had reached week 14 were in clinical remission at week 14. Four of the 5 were on a steroid at the time of vedolizumab initiation—1 on prednisone and 4 on budesonide with none in remission (median: PUCAI, 42.5; PCDAI, 30), and all were in a steroid-free clinical remission by week 14, but not by week 6. At week 22, anti–TNF-naive patients had higher remission rates than TNF-exposed patients (100% n = 4 versus 45% n = 28, $P = 0.04$). At the time of last follow-up of anti–TNF-naive patients (range 6–38 wk), all remain receiving vedolizumab and in clinical remission.

Natalizumab

Four patients had been previously treated with natalizumab for a median of 8 (range 1–18) months. All 4 patients transitioned to vedolizumab at a median of 1 month (range 1–3 mo) of discontinuing natalizumab, and 2/4 were JC virus antibody positive at the time of transition. All 4 patients were transitioned because of concerns of PML. None of these patients were on corticosteroids at the time of vedolizumab initiation, and none were in clinical remission. By week 2, 50% (2/4) were in clinical remission, and by week 14, 75% (3/4) were in remission and remained steroid free.

Vedolizumab Durability

Three patients were escalated from every 8 to 4 weeks of vedolizumab at week 14 or 22. Two remain on drug every 4 weeks. A total of 9 patients had discontinued therapy as of last follow-up. Three CD patients discontinued vedolizumab between weeks 22 and 30 due to lack of efficacy. Four UC and 2 CD patients (11.5%) underwent an IBD-related operation within the first 30 weeks of treatment with vedolizumab. Four of these patients underwent colectomy and 2 ileocecectomy. Two patients who underwent operation remained on vedolizumab postoperatively, and both continued on vedolizumab and were in clinical remission at the time of last follow-up.

Safety

As of last follow-up, there have not been any infusion reactions or serious adverse events, including tuberculosis and meningitis. There have been no cases of PML observed.

DISCUSSION

Our data demonstrate that pediatric patients with UC and CD can experience clinical benefit after induction and maintenance therapy on vedolizumab. We observed higher rates of remission than those reported in the GEMINI studies. However, due to the relatively small number of patients in our study, caution and further experience are needed. There were no safety concerns with vedolizumab in our pediatric patients, including infusion reactions and serious infections. A recent meta-analysis of safety data from 6 adult vedolizumab trials similarly showed no increased risk of any infection or serious infection in vedolizumab-exposed patients.[9]

There is evidence that anti-TNF agents downregulate MadCAM-1 expression.[10] This downregulation may partially explain the reason that CD patients with previous anti-TNF exposure in the GEMINI studies required a longer duration of vedolizumab treatment to achieve remission.[5] We similarly found that patients who discontinued an anti-TNF agent for at least 1 month before vedolizumab initiation were more likely to be in remission at week 2 than patients who discontinued anti-TNF agent within 1 month.

In our study, 80% of all anti–TNF-naive patients were induced into remission by week 6 and all achieved clinical remission by week 14, with remission sustained at the time of last follow-up. Although not all of them were steroid free at week 6, at week 14, all were steroid free. Recently, the AGA Care Pathway for UC has published recommendations that vedolizumab be offered as an alternative to anti-TNF or immunomodulator therapy in UC patients.[11] Given the observed efficacy and relatively quick time to induction of remission in pediatric UC patients naive to anti-TNF therapy, vedolizumab might be a reasonable consideration in biological naive patients requiring escalation of therapy.

Standard dosing in adult vedolizumab patients is 300 mg per infusion, and no specific guidelines exist for pediatric dosing. Pediatric patients, many of them smaller in size and weight, may require an individualized dose. Although 75% of our patients received the standard dosing, most others received 6 mg/kg up to a maximum of 300 mg. This 5 to 6 mg/kg dose was derived by using an average adult weight of 50 to 60 kg and extrapolating a weight-based dosing from the standard adult dose of 300 mg.

No difference in remission rates at any time points was noted in patients receiving 300 mg compared with weight-based dosing. Three CD patients on the standard 300 mg dosage were dose escalated to every 4-week infusions. Similar to anti-TNF drug clearance, it is likely that patients have variable vedolizumab clearance, leading to decreased drug trough concentrations and subsequent clinical symptoms. A recent study showed improvement in mean disease activity scores with an increase in vedolizumab frequency to every 4 weeks from every 8 weeks dosing, without any increase in adverse events.[12] Early identification of patients who may need more intensive dosing is important to prevent loss of response. Further investigation into factors

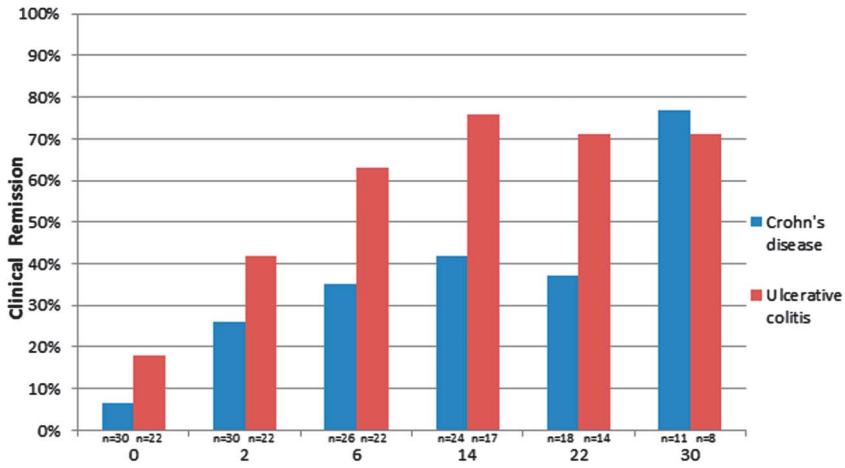

FIGURE 1. Remission rates in CD and UC patients on vedolizumab therapy.

affecting vedolizumab clearance and subsequent ideal dosing in pediatric patients is required.

When examining CRP as a marker of disease activity, we found that the median CRP had decreased at week 14 of vedolizumab treatment in subjects with CD. UC patients starting vedolizumab had no elevation of median CRP levels but high PUCAI scores at baseline, consistent with others' observations that many UC patients do not mount an elevated CRP despite having evidence of active inflammation.[13]

Given the overlapping α4β7/MadCAM-1 interaction of vedolizumab and natalizumab, we anticipated a similar remission rate of pediatric CD patients. The published remission rates at week 10 in pediatric CD patients on natalizumab are between 29% and 50%,[6,7] encompassing the 44% remission rate we saw in pediatric CD patients at week 14 on vedolizumab therapy. However, our study was not powered for direct comparisons, and the sample sizes are small. Four of our patients were transitioned to vedolizumab from natalizumab directly, due to PML safety concerns. Half of these patients achieved clinical remission within 2 weeks of vedolizumab treatment, and 75% were in remission within 14 weeks. Given the improved safety profile of vedolizumab over natalizumab, it should be the preferred anti-integrin agent in IBD patients. However, there may be a subset of patients who respond better to one agent more so than the other but that is yet to be determined.

Potential limitations to this study include its small sample size and retrospective design. However, our results seem similar to the real-world postmarketing experience in adult patients with IBD.[14] It is possible that nonserious adverse events, such as nasopharyngitis, would have been missed, but all serious events, such as hospitalizations and infections, would not have been missed. Another limitation is that patients were started on vedolizumab at the discretion of the treating physician, without a set standard inclusion or exclusion criteria. Furthermore, lack of standardized dosing for pediatric patients led to variation of dosing in this study, which introduces this as a potentially confounding factor. An additional limitation is the heterogeneous population we examined, including postoperative patients, patients with differing baseline clinical status, disease type, and previous medication exposures. This population reflects the variety of IBD patients seen and treated in clinical practice. Prospective clinical trials with the use of a more homogenous population are warranted.

We report that pediatric IBD patients experienced remission in the induction and maintenance phases of vedolizumab therapy. Pediatric UC patients responded earlier and had higher remission rates than their CD counterparts. Anti–TNF-naive UC pediatric patients had experienced remission at higher rates than those with previous anti-TNF exposure. Despite the small sample size, these data support the efficacy and safety of vedolizumab in pediatric IBD patients and the need for a rigorous dose finding clinical efficacy trial.

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