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Postoperative outcomes in vedolizumab-treated pediatric patients undergoing abdominal operations for inflammatory bowel disease☆,☆☆

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ABSTRACT

Introduction: Recent studies have found vedolizumab to be an independent predictor of increased rates of postoperative complications and surgical site infections (SSIs) in adults with inflammatory bowel disease (IBD), but studies in the pediatric surgical population are lacking. We sought to determine the 30-day postoperative infectious complication rate among pediatric IBD patients who received vedolizumab within 12 weeks of a major abdominal operation.

Methods: A retrospective chart review was performed on pediatric IBD patients who underwent an abdominal operation between 5/20/2014 and 6/1/2017. The study cohort was comprised of pediatric patients (≤18 years) who received vedolizumab within 12 weeks prior to their abdominal operation. The control cohort was all patients operated on for IBD during the same time on anti-TNF therapy within 12 weeks of their abdominal operation.

Results: Thirteen pediatric patients (5 female) received vedolizumab within 12 weeks of an abdominal operation and 36 patients received anti TNF therapy (20 female). There were no differences in the vedolizumab and anti-TNF therapy with regard to sex, median age of diagnosis or operation, IBD type, body mass index (BMI), smoking status, diabetes mellitus (DM), preoperative serum laboratory values, steroid or immunomodulatory use. The number of biologics previously exposed to was significantly higher in the vedolizumab treated patients ($p < 0.0001$). There were no significant differences in operative characteristics including laparoscopic versus open surgery, construction of an anastomosis, or diversion of an anastomosis. There were also no significant differences found in 30-day postoperative complications including nonsurgical site infections (SSIs), all SSIs, small bowel obstruction (SBO)/ileus, hospital readmission, or return to the operating room (ROR). There were four RORs in total: one in the vedolizumab group was for a missed enterotomy and stoma revision; three in the anti-TNF cohort were for ileostomy revisions.

Conclusions: None of the thirteen pediatric patients who received vedolizumab within 12 weeks of an abdominal operation experienced a 30-day postoperative SSI or non SSI infectious complication, suggesting that vedolizumab is safe in the perioperative period for pediatric patients with IBD. Owing to the small sample size, future study, perhaps multi-institutional, will be important to confirm these findings.

Level of evidence: Retrospective comparative study, Level III.

Since the Federal Drug Administration's (FDA) approval of infliximab for the treatment of inflammatory bowel disease (IBD), biologic therapy has replaced corticosteroids as the cornerstone of medical management for IBD. The anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, and certolizumab pegol) remain the most widely studied and utilized biologics to treat IBD. Unfortunately, their use is limited as one third of patients experience primary nonresponse [1–4] and another third have secondary loss of response [5,6]. In addition, their safety profile is tarnished by increased risk of skin cancers [7] and serious infections [8]. These findings have driven a search for alternative biologic therapies.

Vedolizumab, a humanized monoclonal antibody to the α4β7 integrin that selectively blocks T cells from reaching the gastrointestinal tract, was approved by the FDA in 2014 for the treatment of moderate to severe ulcerative colitis (UC) and Crohn's disease (CD) following demonstration of safety and efficacy in the GEMINI studies [9,10]. Since then, there has been a rapid surge in its use given the alternative

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mechanism of action for patients who have lost response to anti-TNF therapy, and theoretically improved safety profile related to its gut selectivity. This wave of enthusiasm has not spared the pediatric population, especially now that recent reports confirm safety and efficacy in the pediatric population [11–14].

Despite the growing number of effective biologic therapies for IBD, 19% of pediatric patients with UC will undergo colectomy within 5 years of diagnosis [15], and more than 80% of patients with CD [16,17] will undergo an abdominal operation in their lifetime. While the increased risk of postoperative infectious complications with preoperative exposure to infliximab has been well documented [18–20], only one study regarding postoperative outcomes in the setting of vedolizumab has been published to date. This study, from our center, found a significantly increased risk in infectious complications among adult IBD patients who received vedolizumab within 12 weeks of an abdominal operation [21]. However, these findings remain controversial with some presented abstracts confirming our findings [22], one even representing a multicenter study [23], while others have refuted these findings [24–26]. As the incidence of pediatric IBD increases worldwide [27], there are an increased number of patients exposed to vedolizumab in the preoperative period, thus underscoring the importance of studying the postoperative outcomes in this patient population. We therefore sought to determine 1) the rate of postoperative infectious complications after preoperative exposure to vedolizumab in the pediatric surgery population, and 2) determine the rate of unplanned 30-day readmission and return to the operating room among pediatric surgery patients who received vedolizumab within 12 weeks of a major abdominal operation.

1. Materials and methods

Following institutional review board approval, a retrospective chart review of the Mayo Clinic, Rochester, MN electronic medical records between May 20, 2014 and June 1, 2017 was performed. A list of all pediatric IBD patients who underwent a major abdominal operation was obtained. Study patients included pediatric patients (aged 18 years or younger) with IBD who received vedolizumab within 12 weeks of a major abdominal operation. The control cohort included those patients exposed to anti-TNF agents within 12 weeks of a major abdominal operation. Patients were excluded if they had nonabdominal surgery (e.g., exam under anesthesia for perianal disease), did not have 30 days of follow-up after their operation, or if their operation was performed at an outside hospital. Data abstracted included patient demographics, IBD subtype, smoking history, diabetes mellitus status, preoperative serum laboratories, date and type of surgery, anastomoses performed and diversion if anastomosis was constructed, concomitant immunosuppressive medications, and postoperative complications and mortality. The primary outcome was a 30-day postoperative surgical site infection (SSI), including superficial and deep space SSI, mucocutaneous separation at the stoma border, and anastomotic leak. Secondary outcomes included 30-day postoperative rate of non-SSI infectious complications (pneumonia, *Clostridium difficile* infection, urinary tract infection, cholangitis), small bowel obstruction (SBO)/ileus with radiographic confirmation and/or requirement of nasogastric tube for decompression, 30-day unplanned readmission to the hospital, and 30-day unplanned return to the operating room (ROR). An adult cohort of vedolizumab treated patients (>18 years) was collected as previously described, and was used to compare to the pediatric vedolizumab treated patients and perform an analysis of SSI by age stratification.

1.1. Statistical analysis

Continuous variables were expressed as median (range). Differences in the means between subgroups were compared using the t-test. Comparisons between categorical variables were analyzed using the Fisher's exact test and Chi square. A p-value of <0.05 was considered statistically significant.

2. Results

A total of 49 patients were included in this study: 13 patients received vedolizumab and 36 patients received anti-TNF agents within 12 weeks of an abdominal operation between May 20, 2014 and June 1, 2017 at Mayo Clinic in Rochester, Minnesota. Within the vedolizumab group, 5 (38%) patients were female, the median age was 15 years (range, 5–18 years), and the median body mass index was 17 kg/m^2 (range, 14–34 kg/m^2). No patients smoked or had diabetes mellitus. Five patients (39%) and 4 patients (31%) were receiving corticosteroid therapy and immunomodulator (IMM) therapy, respectively, at the time of operation, compared to 14 (38%) and 7 (19%) in the anti-TNF group. Within 14 days of surgery, the median leukocyte count was 10.2 g/dL, hemoglobin was 11.9 g/dL, platelet count was 391 × 10 (9)/L, serum albumin was 3.6 g/dL, and C reactive protein (CRP) was 15.8 mg/dL, all not significantly different from the TNF inhibitor and nonbiologic groups (Table 1).

When comparing operative characteristics, vedolizumab patients underwent equivalent use of laparoscopy (62% versus 56% in the anti-TNF inhibitor; $p = 0.7837$), had equivalent number of anastomoses constructed at the time of surgery (38% versus 42% in the anti-TNF inhibitor; $p = 1.000$), and equivalent use of proximal diversion in the setting of an anastomosis (8% versus 8% in the anti-TNF inhibitor; $p = 1.000$) (Table 2).

Within the vedolizumab treated cohort, the reasons for operation in patients with CD included medically refractory inflammatory disease ($n = 6$), stricturing disease with obstructive or failure to thrive symptoms ($n = 3$), restoration of intestinal continuity ($n = 2$), and stoma revision for obstruction ($n = 1$). The patient with UC had an operation for medically refractory disease (Table 3).

Postoperatively, none of the patients in the vedolizumab group experienced a postoperative infectious complication within 30 days of surgery. Two patients (13%) had a 30-day unplanned hospital readmission, one for an ileus and the other for a stoma revision, and one patient (7%) had a return to the operating room (ROR) for a missed enterotomy and stoma revision. ROR for both the vedolizumab treated cohort ($n = 1$) and anti-TNF treated cohort ($n = 3$) was primarily performed for local stoma repair/revision ($n = 4$). There was no 30-day mortality in either cohort (Table 4).

Table 1
Preoperative characteristics of pediatric patients with IBD.

	N	TNFα inhibitors (n = 36)	Vedolizumab (n = 13)	P-value
Female sex, n (%)	49	20 (56%)	5 (38%)	0.3451
Median age at surgery, years (range)	49	16 (10–18)	15 (5–18)	0.6639
IBD Type				0.2461
Crohn's disease	49	26 (72%)	12 (91%)	
Ulcerative colitis		10 (28%)	1 (8%)	
Median duration of IBD at surgery, years (range)	49	3 (0–12)	6 (0–10)	0.1228
Median BMI, kg/m^2 (range)	49	19 (9–33)	17 (14–34)	0.6457
Median hemoglobin, g/dL*	34	10.6	11.9	0.7170
Median leukocyte, g/dL*	34	8.5	10.2	0.4445
Median platelet count, ×10(9)/L*	34	369	391	0.8095
Median albumin, g/dL*	21	3.9	3.6	0.4428
Median CRP mg/L*	26	4.5	15.8	0.6637
Steroid use, n (%)	49	14 (39%)	5 (39%)	1.0000
IMM use, n (%)	49	7 (19%)	4 (31%)	0.4509
Median number of prior biologics (range)	49	0 (0–2)	3 (1–3)	<**0.0001**

All p-values are generated by the Fisher's exact test and t-test for categorical and continuous variables, respectively.
TNF, tumor necrosis factor-alpha; BMI, body mass index; CRP, C-reactive protein; IMM, immunomodulator.
* TNF inhibitors: 15 adalimumab, 18 infliximab, 4certolizumab.

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