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Gastrointestinal Conditions

# Postoperative complications of pediatric patients with inflammatory bowel disease treated with vedolizumab

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ABSTRACT

*Background:* Vedolizumab is a biologic, which inhibits leukocyte adhesion in the gut and is used to treat ulcerative colitis (UC) and Crohn's disease (CD). Little is known of the surgical outcomes in patients treated with vedolizumab. We reviewed the postoperative complications in a cohort of pediatric UC and CD patients treated with vedolizumab.
*Methods:* We identified pediatric UC and CD patients treated with vedolizumab at our institution from 2014 to 2016. We compared postoperative outcomes in the vedolizumab exposed group to a cohort of vedolizumab naïve patients who required diverting ileostomy.
*Results:* Of the 31 patients who were treated with vedolizumab, 13 patients required surgery. Eight of 13 (62%) vedolizumab exposed patients had a postoperative complication, including mucocutaneous separation at the stoma (3), readmission for pain/dehydration (2), bowel obstruction at the ostomy, and intraoperative colonic perforation. In comparison, four of 16 (25%) vedolizumab naive patients had a postoperative complication, including readmission for ileus and for high stoma output with mucocutaneous separation. $p = 0.07$.
*Conclusions:* At our institution, patients treated with vedolizumab prior to surgery have a high prevalence of postoperative complications, notably mucocutaneous separation of the stoma. A prospective, multicenter study is needed to determine if these observed complications are attributable to vedolizumab.
*Level of evidence:* Level III.



Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing and remitting inflammatory conditions that occur in children and adults. Over the past decade, significant advances have been made in the medical treatment of CD and UC with the addition of biologic therapies. Most recently, vedolizumab, an α4β7 integrin inhibitor, has been approved for treatment of children and adults with CD and UC. This biologic therapy works by inhibiting leukocyte migration in the gut epithelium, a process important for wound healing. Given that about 15%–45% of children still require abdominal operations to treat their CD within 5 years of their diagnosis [1–4], and about 20%–30% UC patients require colectomy [5,6], concern exists around surgical outcomes, and in particular wound healing, in children and adolescents treated with vedolizumab prior to surgery.

Data on the risk of surgical complications in patients who are treated with vedolizumab are very limited. The initial trials of vedolizumab in patients with CD and UC excluded surgical patients [7,8]. A recent retrospective review of adults with CD and UC patients who underwent surgery at a single center reported an increase in overall complications and surgical site infections in the group treated with vedolizumab prior to surgery, compared to patients treated with infliximab or other non-biologic therapies prior to surgery [9]. No studies to date have been published in the pediatric population. We hypothesized that patients treated with vedolizumab would have a higher rate of complications based on our anecdotal experience. The present study aims to examine the surgical complications in a group of pediatric patients with CD or UC treated with or without vedolizumab prior to surgery.

## 1. Material and methods

Boston Children's Hospital (BCH) is a 395-bed tertiary care pediatric hospital. The electronic medical record was queried to identify all patients who had been treated with vedolizumab in our institution. The medical record was then reviewed for these patients using a standardized case report form, and any discrepancies in data interpretation were resolved by consensus. Patients were included in the study if they had Crohn's disease or chronic ulcerative colitis, were treated with vedolizumab, and had at least 3 months of follow-up after initiation of therapy. A comparison group of patients with CD or UC who underwent a total abdominal colectomy with diverting end ileostomy,

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by a single surgeon at our institution was evaluated. This comparison group was selected as it included a group of patients with medically refractory disease and other baseline surgical risk factors who were too sick to include J pouch creation in the initial surgery for UC patients or had severe, debilitating Crohn's disease requiring permanent diversion.

Data extracted included age, gender, disease (UC or CD), presence of operation, type of surgical procedure performed, surgical indications, preoperative medical therapy, albumin, hematocrit, Pediatric Ulcerative Colitis Activity Index (PUCAI), length of hospital stay, and postoperative complications. Complications were identified during the postoperative hospital stay or during outpatient or inpatient visits documented after surgery. Complications were defined *a priori* as any infection, abscess, bowel obstruction, anastomotic leak, or any complication requiring re-operation, inpatient level care, or unplanned outpatient visits. The duration between the last administration of vedolizumab and the day of operation was recorded for those who received this agent. The primary outcome of interest was surgical complication in patients treated with vedolizumab prior to surgery. Surgical complications were compared between the vedolizumab exposed group and the comparison group of patients using the two-tailed Fisher's exact test.

This review was approved by the BCH Institutional Review Board.

## 2. Results

Overall 31 pediatric patients with CD and UC were treated with vedolizumab from 2014 to 2016. This group included 21 patients with CD and 10 patients with UC. Vedolizumab was given using standard dosing (300 mg or 5 mg/kg per infusion at 0, 2, and 6 weeks and then every 8 weeks). Of the patients treated with vedolizumab, 30 of 31 (97%) failed a TNF inhibitor and 21 of 31 (65%) had failed two TNF inhibitors.

Of these 31 patients treated with vedolizumab, 13 required surgery. In the surgical cohort, seven patients had CD and six had UC. The mean age of these 13 patients was 16.6 ± 2.9 years (age range 9–24). The types of surgical procedures performed included laparoscopic diverting ileostomy (n = 4), laparoscopic proctocolectomy, ileoanal pouch anastomosis & diverting ileostomy (n = 4), laparoscopic colectomy with ileostomy (stage one of a three stage IAP procedure) (n = 2), laparoscopic ileocolic resection with ileostomy (n = 2), and laparoscopic subtotal colectomy with an ileosigmoid anastomosis (n = 1). Twelve of the 13 patients had a diverting ileostomy at the time of surgery. The mean hospital length of stay among patients treated with vedolizumab who required surgery was 6.7 days ± 3.9 days. In the cohort that required surgery, vedolizumab was used after disease was refractory to other medications. Almost half of the cohort was dependent on steroids at the time of surgery. (Table 1).

The average time between last vedolizumab infusion and surgery was seven weeks (range 16–154 days). Overall, eight of 13 (62%) of patients treated with vedolizumab prior to their operation had a significant complication; specifically 23% had mucocutaneous separation of the ileostomy (n = 3).

In the cohort of patients with postoperative complications, five of eight patients required operation after first or second induction doses (62%). Two patients had surgery after a third induction dose, and one patient had four doses of vedolizumab prior to surgery. This is in comparison to the cohort without complications, where all patients had three or more doses of vedolizumab prior to surgery (Fig. 1). The range of time from last dose of vedolizumab to surgery in patients who had a postoperative complication was 17–63 days (mean 40 days). Mean time from vedolizumab to operation in patients without complication was 60 days (range 16–154 days). Of the eight patients who had a complication, six patients had surgery within the eight weeks of last vedolizumab infusion (Fig. 2).

The cohort of patients with postoperative complications included four patients with CD and four patients with UC. All patients had a diverting ileostomy as part of the procedure. The postoperative complications in the patients with CD included mucocutaneous separation of ileostomy (n = 2) with one patient requiring repeat operation to resite the stoma (Fig. 3), postoperative seizure, and readmission for dehydration and pain. The complications in the UC patients included mucocutaneous separation of the ileostomy & skin separation of peristomal striae, pain and dehydration, partial small bowel obstruction at the stoma requiring ostomy takedown, and intraoperative colonic perforation with fecal spillage and abscess. (Fig. 4).

The comparison group of patients included two CD and 14 UC patients who required total abdominal colectomy with end ileostomy for medically refractory disease. All patients had failed at least one biologic therapy, and four had failed two biologics (25%). Nine of the 16 patients were on steroids at the time of surgery. The mean age of the patients in the comparison cohort was 12.6 ± 4 years (range 5–21 years). The mean hospital length of stay among patients treated without

**Table 1**
Demographics of patients treated with and without Vedolizumab who require surgery.

| | Vedolizumab n = 13 | No Vedolizumab n = 16 | p value |
|---|---|---|---|
| Mean Age ± SD (years) | 16.6 ± 2.9 | 12.6 ± 4 | 0.99 |
| Female n (%) | 10 (77) | 13 (81) | 1 |
| IBD phenotype n (%) | | | |
| Crohn's disease | 7 (54) | 2 (12) | 0.04* |
| Ulcerative colitis | 6 (46) | 14 (88) | 0.04* |
| Types of surgery n (%) | | | |
| Laparoscopic diverting ileostomy | 4 (31) | | *0.03** |
| Laparoscopic assisted proctocolectomy, ileoanal pouch & diverting ileostomy | 4 (31) | | *0.03** |
| Laparoscopic colectomy & ileostomy | 2 (15) | 16 (100) | *<0.001** |
| Laparoscopic ileocolic resection & ileostomy | 2 (15) | | 0.19 |
| Laparoscopic subtotal colectomy w/ ileosigmoid anastomosis | 1 (8) | | 0.45 |
| Steroids at time of surgery n (%) | 6 (46) | 9 (56) | 0.71 |
| Preoperative medication history (%) | | | |
| 6-mercaptopurine | 11 (85) | 9 (56) | 0.13 |
| Methotrexate | 3 (23) | 2 (13) | 0.63 |
| Infliximab | 13 (100) | 15 (94) | 1 |
| Adalimumab | 10 (77) | 1 (6) | *0.001** |
| Certilizumab | 3 (23) | 0 (0) | 0.08 |
| Thalidomide | 3 (23) | 1 (6) | 0.30 |
| Tacrolimus | 1 (8) | 4 (25) | 0.34 |
| Preoperative albumin (mean ± SD) | 3.9 ± 0.4 | 3.4 ± 0.7 | 0.91 |
| Preoperative Hematocrit (mean ± SD) | 36 ± 4.4 | 31.2 ± 4 | 0.99 |
| Mean (range) last PUCAI prior to surgery[a] | 36 (15-65) | 44 (5-75) | 0.7 |

PUCAI = Pediatric Ulcerative Colitis Activity Index.
[a] For last PUCAI in vedolizumab exposed group n = 6, for non-vedolizumab exposed group n = 14.
* $p < 0.05$.

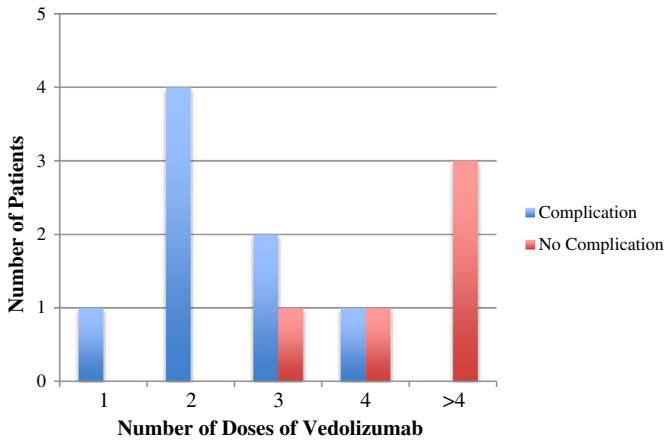


**Fig. 1.** Complications based on number of Vedolizumab doses prior to surgery.