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Timing of Last Preoperative Dose of infliximab Does Not Increase Postoperative Complications in Inflammatory Bowel Disease Patients

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Abstract

Background—The association between preoperative use of infliximab and postoperative complications in patients with inflammatory bowel disease (IBD) is a subject of continued debate. Results from studies examining an association between the timing of last preoperative dose of infliximab and postoperative complications remain inconsistent.

Aims—To assess if timing of last dose of infliximab prior to surgery affects the rate of postoperative complications in patients with Crohn's disease or ulcerative colitis

Methods—Retrospective chart review of IBD patients who have undergone surgery while receiving therapy with infliximab was conducted. Forty seven patients were included in the analysis.

Results—No significant association was found between timing of infliximab and the rate of postoperative complications. Age, gender, disease type, steroid use, preoperative status, surgery type or surgeon type were not associated with increased rate of postoperative complications.

Conclusion—Timing of last dose of infliximab does not affect the rate of postoperative complications in patients with Crohn's disease or ulcerative colitis.

Keywords

Post-operative complications; ulcerative colitis; Crohn's disease; infliximab

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Introduction

The introduction of anti-tumor necrosis factor α (anti-TNFα) agents for the treatment of inflammatory bowel disease (IBD) resulted in a non-surgical therapeutic option for steroid-dependent as well as steroid refractory patients, and those intolerant or not responsive to thiopurine monotherapy. Despite the efficacy of anti-TNFα agents in the treatment of IBD, these agents have not lead to a significant decline in the need for surgical intervention in either Crohn's disease (CD) or ulcerative colitis (UC) over the last decade[1–3]. About 75% of patients with CD and up to 40% of patients with UC will require surgery at some point in the course of their disease[4,5]. The continued need for surgical intervention may be due to the underlying phenotype, delayed onset of treatment or due to lack of or loss of response to therapy.

Tumor necrosis factor α plays a central role in the development of inflammation through direct action as a potent pyrogen and through its ability to stimulate IL-1 secretion, which explains the response to anti-TNFα inhibitors in the treatment of IBD. In addition, TNFα is responsible for the differentiation and activation of cells important for wound healing and prevention of infection. As such, giving an antibody to TNFα in the perioperative period raises concerns about increasing the risk for postoperative complications in this group of patients.

Multiple studies, including retrospective studies as well as numerous meta-analyses, have examined the possible risk for increased infectious and non-infectious postoperative complications among IBD patients on anti-TNFα therapies with varying results. Some studies have found an increased risk of postoperative complications in all IBD patients, however when the cohorts were divided by disease type, only the CD patients were noted to have an increased risk[6,7]. In other studies including only CD patients, some found an increased risk of complications[8–10], another reported an increased risk only in those with an anti-TNFα drug level above a certain cutoff[11], and another showed a protective effect of anti-TNFα therapy in CD patients with penetrating disease[12]. In contrast, other studies reported no increased risk for postoperative complications associated with anti-TNFα use in CD patients[4,13] or among all IBD groups[14]. In studies looking only at UC patients, one meta-analysis found an increase in short-term postoperative complications[5] while a retrospective study found an increased risk for pelvic sepsis associated with preoperative anti-TNFα use[15].

Several prior studies have examined the association between postoperative complications and the time from the last preoperative dose of anti-TNFα therapy. In some studies, the timing of the last dose is quantified as a range, such as within three months or 8 weeks of surgery[10, 13]. Some also include postoperative administration of anti-TNFα therapy, up to 4 weeks after surgery, into the study cohort [13, 16]. The aim of our study was to assess for an association between the duration of time, in days, between the last preoperative dose of anti-TNFα therapy (infliximab) and the risk for postoperative complications among IBD patients.

Methods

Study Population

We performed a search within the Medical College of Virginia/Virginia Commonwealth University Cerner electronic health record database for all IBD patients using ICD-9 codes for Crohn's disease (555.XX) and ulcerative colitis (556.XX). We cross-referenced these patients with pharmaceutical records in order to determine which patients were also infliximab during the period between 2004 and 2014 and 285 patients met our search criteria. These charts were reviewed by one author (AA) to confirm the diagnosis of IBD and to determine which patients had undergone surgery related to CD or UC while receiving infliximab therapy and 47 patients were identified. Three of these patients had more than one surgery while on anti-TNFα therapy and, in this case, data related to the first surgery only was included for analysis.

Assessment of Clinical Characteristics

Demographic data collected includes gender and age at the time of surgery. Surgery specific data collected includes presence of infection at the time of surgery, type of surgeon who performed the surgery, surgical site (abdominal or perianal), and urgency of the surgical procedure (elective or urgent). Disease specific data collected includes disease type (CD or UC), duration of disease, and IBD medications used. Pharmacy charting was reviewed in order to determine the timing of the last dose. We also reviewed pharmacy records to determine if any other IBD medications were used, such as mesalamine or immunomodulators (including azathioprine/6MP or methotrexate). Steroid use included budesonide or corticosteroids which were divided into high dose (defined as IV dosing or oral dose ≥ 40 mg/day), moderate dose (defined as an oral dose ≥ 20 mg/day for > 2 months), or low dose (defined as oral < 20 mg/day or > 20 mg/day for < 2 months). We also collected data on the use of other medications which have been associated with postoperative complications, including proton-pump inhibitors and narcotics. Postoperative complications were divided into three categories: infectious, including wound Infection, intra-abdominal abscess, intra-abdominal leak and extra-abdominal infection; noninfectious, including small bowel obstruction, prolonged ileus, GI bleeding, VTE, readmission within 7 days and reoperation within 30 days; and other complications, including new end-organ failure and neurologic complications.

Statistical Analysis

Descriptive statistics were reported as the mean and the range for continuous variables and as frequencies and percentage for categorical variables. Group comparisons between patients with complications and patients without complications for those variables were carried out using either Fisher's exact test or Wilcoxon signed-rank test. The logistic regression model for the probability of having complications with forward and backward selection was considered for the association between complications and timing of last dose of infliximab, controlling for patient age, gender, preoperative infection status, surgery site, type and surgeon type.

Results

Patients

A total of 47 patients with confirmed inflammatory bowel disease on infliximab therapy had undergone surgery and were included for analysis (Table 1). The mean age was 35 years (10–63 years), 27 (57%) were males, 35 (74%) had CD, the mean time from last dose of infliximab to surgery was 40 days (3 days to >90 days). The dose and frequency of infliximab ranged between 5–10 mg/kg every 4 to 8 weeks. Fifteen patients (32%) had concomitant steroid use before surgery. Other IBD medication use is included in Table 2.

Surgeries

A majority of the surgeries (n=38, 81%) were performed for non-infectious causes, such as stricture or fistula formation (Table 1). Most surgeries were intra-abdominal (n=35, 74%) while the rest were perianal. Three quarters of the surgeries were performed on an elective basis (n=38, 81%). In addition, most surgeries (n=42, 89%) were performed by a colorectal surgeon, while the remaining operations were by general surgeons. Table 3 provides description of the procedures performed.

Postoperative Complications

Eight of the 47 patients (17%) had postoperative complications within thirty days (Table 4). Most of these patients had Crohn's disease (n=6,75%). All of the patients had undergone an intra-abdominal surgery for a non-infectious cause. Most surgeries were performed on an elective basis (n=6, 75%) and all were done by a colorectal surgeon. Six (67%) of the complications were early non-infectious (5 prolonged ileus, 1 required repeat surgery within 30 days for pneumoperitoneum and suspected ischemia (Table 5). Three (33%) were early infectious complications (one wound infection, one abscesses and one C. difficile colitis). One patient had both a wound infection and prolonged ileus. No patients died.

The infectious complications included one wound infection in a patient with CD on infliximab (last dose 44 days prior to surgery), low dose steroids and 6MP/AZA. One intra-abdominal abscess occurred in a CD patient being treated with infliximab (last dose 20 days prior to surgery) and 6MP/AZA. One case of *Clostridium difficile* colitis occurred in a CD patient being treated with infliximab (last dose 14 days prior to surgery) who underwent ileocecectomy.

Discussion

In this retrospective study, we did not find any association between the timing of the last preoperative dose of infliximab and the rate of overall postoperative complications. Age, gender, disease type, preoperative steroid use, surgery type, surgeon type or preoperative infection were not statistically different between the patients with and without complications. All complications were associated with intra-abdominal surgeries (table 5). Our sample size is consistent with most similar previous studies which have included from 48 up to 195 patients[17,18].

Our complication rate of 17% is much lower than the 42.3% total complication rate and lower than the 27.2% infectious complication rate reported in a recent meta-analysis[8]. Our complication rate is also on the lower end of the expected postoperative complication rates for patients with IBD. The surgical literature reports the postoperative complication rate for Crohn's disease patients, in the absence of immunosuppressive therapy, to range from 6 to 45%[19,20]. The rates are estimated to range from 19 to 58% for UC patients undergoing ileal pouch-anal anastomosis procedures with the rates decreasing with increasing experience of the performing surgeon[21–23]. Our low complication rate may be because the majority of the surgeries were performed by an experienced colorectal surgeon and due to the inclusion of perianal surgeries in the final analysis.

The lack of an association between preoperative infliximab use and postoperative complications in our study is consistent with most previous studies in this area[13,14,16–18,24]. One study showed a protective effect of preoperative anti-TNFα use, which lead to a decrease in the risk for surgical site infections in patient with penetrating Crohn's disease (OR 0.1, $p<0.01$)[12]. Syed et al. reported that preoperative anti-TNFα use was an independent predictor for overall postoperative infections (OR 2.43; 95% CI 1.18–5.03) and surgical site complications (OR 1.96; 95% CI 1.02 – 3.77) among patients with Crohn's disease undergoing abdominal surgery[25]. In the study consisting of 150 Crohn's disease patients who received anti-TNFα therapy within 8 weeks of undergoing abdominal surgery, 36% in the anti-TNF group developed an infection compared to 25% in the TNF naïve group, which is much higher than our complication rate as well as higher than the reported infectious complication rate in the recent meta-analysis[8]. Appau et al. also reported an increased risk of postoperative complications in Crohn's disease patients who received infliximab within three months of undergoing an ileocolonic resection, noting an increased 30-day postoperative readmission rate ($p=0.045$), sepsis ($p=0.027$), and intra-abdominal abscess ($p=0.005$)[10]. Interestingly, the authors note that there were no differences in outcomes among a subset of patients who had received infliximab within 2 months of surgery compared to the group who received infliximab within 3 months. This finding suggests either that the subset is too small of a sample size or that some other confounding variable is responsible for the increased risk of complications as the patients with a likely higher drug level, given more recent dosing, did not have any increase in complications.

Looking specifically at drug levels, Lau et al. found an increased odds of postoperative morbidity (OR 2.5, $p=0.03$) and infectious complications (OR 3.0, $p=0.03$) among Crohn's disease patients with preoperative infliximab drug levels of > 3 μg/mL[11]. In UC patients, the authors did not find any increase in postoperative complications regardless of preoperative infliximab drug levels, which suggests that the increased complication rate may be due to the surgery or underlying disease severity as the influence of the drug on wound healing and ability to fight infections should not vary by disease type. Waterman et al. also examined the association between drug levels and postoperative complications and found that patients with detectable preoperative infliximab levels had similar complication rates compared with those without detectable levels[18]. A prospective, multi-center, observational study designed to determine if preoperative exposure to anti-TNF agents is an independent risk factor for post-operative infectious complications within 30 days of surgery in subjects with IBD is

currently underway with an estimated completion date of January 2017 (https://clinicaltrials.gov/ct2/show/NCT02054533).

Our study is limited by the retrospective study design however we were only able to locate one prospective cohort study in this area, which found a protective effect of anti-TNFα agents[12]. Our sample size and results are similar to most of the prior studies in this area. Our study is limited to one tertiary care center however this should result in patients with more severe disease, more complicated surgeries and more complications, which did not occur. We report a 17% complication rate, however we found no association between the time from the last preoperative infliximab dose and postoperative complication rates. In our study, the majority of our cases were non-emergent with almost all performed by a colorectal surgeon. Prior studies have shown lower postoperative complication rates associated with increased surgical experience. Our study reaffirms the safety of these medications in preoperative setting with appropriate timing of surgery and with experienced surgeons.

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Table 1

Patient and surgery characteristics (N=47)

Age, Mean (range)		34.57 years (10–63 years)
Gender, total (%)	Male	27 (57.45%)
	Female	20 (42.55%)
Disease type, total (%)	Crohn's	35 (74.47%)
	UC	12 (25.53%)
Preoperative steroid use, total (%)	Yes	15 (31.91%)
	No	32 (68.09%)
Time between last dose and surgery, Mean (range)		39.81 days (3 days to > 90 days)
Preoperative status, total (%)	Infection	9 (19.15%)
	No infection	38 (80.85%)
Surgery site, total (%)	Intra-abdominal	35 (74.47%)
	Perianal	12 (25.53%)
Surgery type, total (%)	Elective	38 (80.85%)
	Urgent	9 (19.15%)
Surgeon type, total (%)	Colorectal	42 (89.36%)
	General	5 (10.64%)
Complications, total (%)	Yes	8 (17.02%)
	No	39 (82.98%)

Note: All 47 subjects are on Infliximab.

Table 2

Other Medications

Steroid use, total (%)	High Dose (any IV or oral ≥ 40 mg/day)	4 (9)
	Moderate (oral ≥ 20 mg/day for > 2 months)	6 (13)
	Low (oral < 20 mg /day or > 20 mg/day for < 2 months)	6 (13)
	Budesonide	1 (2)
Other IBD medications, total (%)	Mesalamine	22 (47)
	Antibiotics	16 (34)
	6MP/Azathioprine	16 (34)
	Sulfa	2 (4)
	Methotrexate	0 (0)
Other medications, total (%)	PPI	10 (21)
	Narcotics	18 (38)

IV = intravenous, 6MP = 6-mercatopurine, PPI = proton-pump inhibitors.

Table 3

Surgery characteristics

Surgery type		**Number**
Perianal (abscess drainage, seton placement)		12
Abdominal	Ileocolonic resection	17
	Small bowel resection	4
	Colonic resection	11
	Ostomy takedown	2
	Appendectomy	1

Table 4

Summary of complications

	Complication	Number of patients	Timing after surgery
Septic	Wound Infection	1*	developed within 6–7 days
	Intra-abdominal /pelvic abscess	1	developed 12–14 days
	Intra-abdominal leak	0	
	Extra-abdominal infection	1$	diagnosed after 7 days
Non-septic	Small bowel obstruction	0	
	Prolonged ileus	5*	resolved within 5–10 days
	GI bleeding	0	
	VTE	0	developed after 2 days
	Readmission within 7 days	0	
	Reoperation Rates within 30 days	1&	1 day
Other	Cardiac	0	
	Acute renal failure	0	
	Neurologic	0	

VTE= venothromboembolism;

*One patient had both prolonged ileus and a wound infection;

$Clostridium difficile colitis;

&Ex lap the day after the procedure for pneumoperitoneum and suspected ischemia

Table 5

Patients with vs without complications

	w/ complications (N=8)	**w/o complications (N=39)**	**P-value**
Age in years, mean (range)	37.63 (16–58 years)	33.94 (10–63 years)	0.561
Male, n (%)	4 (50.00%)	23 (58.97%)	0.707
Crohn's disease, n (%)	6 (75.00%)	29 (74.36%)	0.999
Preoperative steroid use, n (%)	2 (25.00%)	13 (33.33%)	0.999
Timing of last dose of anti-TNFα agent, in days, mean (range)	43.87 (14 to > 90 days)	38.97 (3 to > 90 days)	0.776
Preoperative infection, n (%)	0 (0%)	9 (23.08%)	0.323
Intra-abdominal surgery, n (%)	8 (100%)	27 (69.23%)	0.093
Elective surgery, n (%)	6 (75.00%)	32 (82.05%)	0.639
Colorectal surgeon, n (%)	8 (100%)	34 (87.18%)	0.571

Note: p-values are either based on Fisher's exact test or Wilcoxon signed-rank test.