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ORIGINAL ARTICLE

Postoperative Infliximab Is Not Associated with An Increase in Adverse Events in Crohn's Disease

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Abstract
Background Infliximab is effective treatment for Crohn's disease and has been associated with rare, but serious infectious complications. Emerging data suggest a benefit of infliximab in preventing postoperative Crohn's disease recurrence. It is not known whether administration of infliximab shortly after resective surgery for Crohn's disease increases postoperative complications.
Aims To evaluate the risk of developing postoperative complications among Crohn's disease patients receiving infliximab within 4 weeks of intestinal resection.
Methods As part of a randomized placebo-controlled infliximab postoperative prevention study, adverse events were prospectively monitored. Crohn's disease patients undergoing intestinal resection were randomized to placebo or infliximab 2–4 weeks after surgery. Study infusions were administered at 0, 2, and 6 weeks then every 8 weeks for 1 year. To evaluate whether infliximab increased postoperative complications, we analyzed all adverse events for 1 year after surgery.
Results Twenty-four patients were randomized to infliximab or placebo after intestinal resection for Crohn's disease. Mean time to first postoperative infusion was 20 days (range 14–25 days). Over the course of 1 year, there were 22 total adverse events, but no difference between infliximab and placebo patients (12 versus 10, respectively, $P = 1.0$). In the immediate postoperative period, within 8 weeks of surgery, the number of adverse events was also similar between the two groups (3 infliximab and 5 placebo patients, $P = 0.68$). There were no serious adverse events and no complications related to wound healing or infection.
Conclusions Initiation of infliximab within 4 weeks of intestinal resection was not associated with postoperative complications.

Keywords Surgery · Crohn's disease · Infliximab · Safety · Postoperative · Adverse events

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Introduction

Crohn's disease (CD) is a chronic relapsing and remitting inflammatory disease of the gastrointestinal tract. There is no cure for Crohn's disease, and nearly two-thirds of patients will require surgery for a complication of the disease, e.g., fibrostenotic stricture, fistula, abscess or perforation. Disease recurrence after surgery is common, with 90% of patients having endoscopic evidence of Crohn's disease 1 year after surgery and over 50% of patients requiring additional surgery in their lifetime [1–3]. Administration of postoperative medications in an attempt to avoid disease recurrence is common. Several medications have been studied, with variable results. Despite treatment with 5-aminosalicylates, steroids, antibiotics, and immunomodulators, 1-year endoscopic recurrence rates are

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as high as 60% [4]. Recent, small, postoperative anti-tumor necrosis factor-α (TNF-α) prevention studies have shown promise in preventing Crohn's disease recurrence after surgery [5–7]. In our previously published study, we observed that the 1-year endoscopic recurrence rate was significantly lower than with placebo (9.1% versus 84.6%, $P = 0.0006$) [5].

While administration of anti-TNF-α agents shortly after surgery may be an effective preventative strategy, the risk of postoperative complications is not known. Tumor necrosis factor-α plays an important role in host defense, and suppression of this cytokine could result in humoral and cell-mediated immune complications. As such, anti-TNF-α agents have been associated with rare but serious infections, such as bacterial, viral, fungal, and mycobacterial [8]. Tumor necrosis factor-α may also be important in tissue repair and healing through stimulation of angiogenesis and fibroblast proliferation. Animal study has suggested that inhibiting TNF-α may inhibit wound repair and healing [9]. Similarly, human study has raised the concern of impaired wound healing by suppressing TNF-α in the perioperative period [10].

The aim of this study is to examine whether administration of infliximab within 4 weeks of intestinal resection for Crohn's disease is associated with increased postoperative adverse events. This is the first study to prospectively evaluate the safety of infliximab administered immediately after surgery.

Methods

Study Subjects

Twenty-four adult patients were enrolled in a randomized double-blind placebo-controlled study to evaluate the effectiveness of infliximab in preventing postoperative recurrence of CD [5]. All 24 patients underwent ileocolonic resection with primary anastomosis and were then randomized to placebo or infliximab. The first infusion was administered between 2 and 4 weeks from the time of surgical resection and then 2, 6, and every 8 weeks thereafter for 1 year. The primary outcome of the study was 1-year endoscopic recurrence defined by Rutgeerts ileal score of i2, i3 or i4 [2].

An important secondary outcome of the study was the rate of postoperative adverse events. Patients were prospectively monitored for adverse events, temporally recorded as "in the immediate postoperative period," defined as any event within 8 weeks of surgery, and those "outside of the immediate postoperative period," as any event that occurred greater than 8 weeks from surgery. All adverse events were recorded, but special attention was paid to such complications as bacterial and opportunistic infections, anastomotic leak, sepsis, intra-abdominal abscess, wound infection and dehiscence, cardiac events, small bowel obstruction, bleeding, and death.

Statistical Analysis

Acknowledging small sample size, baseline characteristics of study patients were compared by random assignment (infliximab versus placebo) using Fisher exact tests for categorical variables and Wilcoxon tests (exact methods) for continuous variables. The occurrence of adverse events after surgery was documented by random assignment and is presented on a per patient basis. Thus, patients could have experienced more than one different type of adverse event, and no competing risk methods were used for adverse events that would tend to predispose to, or alternatively reduce the likelihood of experiencing, a particular adverse event.

The original trial was designed as a proof-of-concept (of active treatment) study with the primary goal of estimating the likely effect size to be achieved from infliximab therapy for subsequent evaluation in a large definitive trial. Thus, the trial was not designed or powered to detect small differences (or equivalence) in rates of adverse events by random assignment. Nonetheless, Fisher's exact test of proportions was used to compare adverse event rates by random assignment, recognizing that with the sample size of 24 trial participants, only large differences in event rates would be detectable statistically at the conventional $P < 0.05$ level.

Results

Baseline Characteristics

Eleven patients were randomized to infliximab and 13 to placebo (Table 1). All patients had end-of-study colonoscopy. Infliximab patients did not differ statistically from placebo patients at baseline in relation to age (median 43 versus 32 years, $P = 0.34$), female gender (45.5% versus 23.1%, $P = 0.39$), duration of Crohn's disease (median 13 versus 9 years, $P = 0.35$) or prior infliximab exposure (30.0% versus 38.5%, $P = 1.0$). However, in the infliximab group, there were more active smokers (45.5% versus 7.7%, $P = 0.06$). All patients had an indication for surgery for a complication: 22 of the patients for penetrating disease and 2 for small bowel obstruction related to a stricture. Nearly half of the patients (four infliximab, seven placebo) were on an immunomodulator at time of surgery and continued these medications throughout the duration of the study. None of the patients were taking antibiotics for their

Crohn's disease, and aside from intravenous antibiotics at time of surgery, no patients received antibiotics in the postoperative setting. Seven patients (four infliximab, three placebo) were taking corticosteroids at the time of surgery, and all were weaned off completely by 2 weeks postoperatively.

Occurrence of Adverse Events by Follow-Up Interval

In the 8-week interval after surgery, the occurrence of adverse events was infrequent in both the placebo and infliximab groups (Table 2). Two of 13 patients in the placebo arm (15.4%) experienced infusion reaction compared with 1 of 11 patients (9.1%) in the infliximab group ($P = 1.0$). Other events that occurred in just a single patient in one or both study groups included viral upper respiratory infection, small bowel obstruction, arthralgia, and abdominal pain. In aggregate, 5 of 13 patients in the placebo group (38.5%) compared with 3 of 11 patients in the infliximab group (18.2%) experienced at least one adverse event in the 8-week period after surgery ($P = 0.39$).

In weeks 9–54 of follow-up, again, the occurrence of adverse events was infrequent in both study groups and did not differ statistically. During this interval, 4 of 13 patients in the placebo group (30.8%) compared with 6 of 11 patients in the infliximab group (54.5%) experienced at least one adverse event ($P = 0.41$). Similarly, when considering the entire 54-week follow-up period after surgery, there was no evidence of higher occurrence of adverse events in infliximab patients compared with those in the placebo group (Table 3). In aggregate, for the full 1-year follow-up period, 6 of 13 patients in the placebo group (46.2%) compared with 7 of 11 patients in the infliximab group (63.6%) experienced at least one adverse event ($P = 0.44$). In terms of the total number of adverse events (i.e., considering more than one event per patient), there were 10 among the placebo patients and 12 among the infliximab patients. Although the sample size was too small to perform multivariate analysis, there were no differences in adverse events based on cigarette smoking status, disease behavior or phenotype, preoperative infliximab administration or concomitant immunomodulator treatment.

The occurrence of severe adverse events was rare and not statistically different between the placebo and infliximab patients (Fig. 1). Notably, there were two patients (one infliximab, one placebo) who developed a perianal abscess, and there was one placebo patient who developed a small bowel obstruction. The small bowel obstruction was due to aggressive recurrence of Crohn's disease 8 weeks after surgery and ultimately required another small bowel resection. There were no other adverse events that would be of potential concern regarding administration of postoperative infliximab, e.g., bacterial or opportunistic infections, anastomotic leak, sepsis, intra-abdominal abscess, wound infection and dehiscence, cardiac events, small bowel obstruction, bleeding or death.

Table 1 Baseline demographics at study entry

Baseline demographic	Infliximab ($n = 11$)		Placebo ($n = 13$)		P value[a]
	n	%	n	%	
Female	5	45.5	3	23.1	0.39
Age ≥40 years	6	54.5	5	38.5	0.68
Active smoker	5	45.5	1	7.7	0.06
Duration of Crohn's disease >10 years	7	63.6	5	38.5	0.41
Disease location at surgery					0.78
Ileum only	2	18.2	3	23.1	
Ileum and colon	9	81.8	10	76.9	
Phenotype					0.48
B2 (stricture)	0	0.0	2	15.4	
B3 (fistula)	11	100.0	11	84.6	
Prior infliximab	3	30.0	5	38.5	1.0
Surgical resections, n[b]					1.0
1	7	63.6	9	69.2	
2	3	27.3	3	23.1	
3	1	9.1	1	7.7	
Concomitant immunomodulator	4	36.4	7	53.8	.44
Mesalamine agent	1	9.1	4	30.8	.33
CDAI >200[c]	6	54.5	4	30.8	0.41
Age (years)	43	28, 49	32	26, 45	0.34
Duration of Crohn's disease (years)[d]	13	1, 19	9	2, 12	0.35

CDAI Crohn's Disease Activity Index

[a] P values were calculated by exact methods: chi-square tests for categoric variables; Wilcoxon tests for continuous variables

[b] Includes surgical resection related to study enrollment

[c] One placebo patient had assessment at 2 weeks

[d] Duration of less than 1 year was coded as 0.5 years

Discussion

Infliximab is effective in inducing and maintaining remission in patients with Crohn's disease [11]. Small studies suggest that infliximab is also effective at preventing postoperative recurrence of Crohn's disease [5, 6]. This prospective, randomized, double-blind placebo-controlled study evaluated the safety of infliximab administered within 4 weeks of abdominal surgery for Crohn's disease. Adverse events were common in patients receiving infliximab and placebo, but serious adverse events, e.g., infectious complications, were rare and did

Table 2 Adverse events (AE) per subject by random assignment and follow-up interval

Adverse event	Placebo 0–8 Weeks ($n = 13$)	Infliximab 0–8 Weeks ($n = 11$)	*P* value**	Placebo 9–54 Weeks ($n = 13$)	Infliximab 9–54 Weeks ($n = 11$)	*P* value**
Infections						
Viral upper respiratory infection	1	1	1.0	0	0	1.0
Abscess[a]	0	0	1.0	1	1	1.0
Pyelonephritis	0	0	1.0	0	1	0.46
Viral gastroenteritis	0	0	1.0	1	0	1.0
Infusion reactions	2	1	1.0	1	2	0.58
Other						
Benign lung nodules	0	0	1.0	1	0	1.0
Small bowel obstruction	1	0	1.0	0	0	1.0
Elevated liver enzymes	0	0	1.0	0	1	0.46
Renal calculus	0	0	1.0	0	1	0.46
Lupus-like reaction	0	0	1.0	0	1	0.46
Gastric ulcer	0	0	1.0	0	1	0.46
Arthralgia	1	0	1.0	0	1	0.46
Abdominal pain	0	1	0.46	0	0	1.0
Poor wound healing	0	0	1.0	0	0	1.0
Crohn's disease exacerbation	0	0	1.0	1	0	1.0
Total number of subjects ≥1 AE	5	2	0.39	4	6	0.41
Total events[b]	5	3		5	9	

For timeframe from week 0 (baseline infusion) through week 54

** Based on Fisher's exact test

[a] Both perianal abscesses were related to perianal fistula, no surgery-related abscesses

[b] Accounts for total number of adverse events (more than one adverse event per subject)

Table 3 Adverse events (AE) per subject by random assignment (1-year follow-up)

	Placebo ($n = 13$)	Infliximab ($n = 11$)	Total	*P* value**
Infections				
Viral upper respiratory infection	1	1	2	1.0
Abscess[a]	1	1	2	1.0
Pyelonephritis	0	1	1	0.46
Viral gastroenteritis	1	0	1	1.0
Infusion reactions	3	3	6	1.0
Other				
Benign lung nodules	1	0	1	1.0
Small bowel obstruction	1	0	1	1.0
Elevated liver enzymes	0	1	1	0.46
Renal calculus	0	1	1	0.46
Lupus-like reaction	0	1	1	0.46
Gastric ulcer	0	1	1	0.46
Arthralgia	1	1	2	1.0
Abdominal pain	0	1	1	0.46
Poor wound healing	0	0	0	1.0
Crohn's disease exacerbation	1	0	1	1.0
Death	0	0	0	1.0
Total number of subjects ≥1 AE	6	7	13	0.44
Total events[b]	10	12	22	

For timeframe from week 0 (baseline infusion) through week 54

** Based on Fisher's exact test

[a] Both perianal abscesses were related to perianal fistula, no surgery-related abscesses

[b] Accounts for total number of adverse events (more than one adverse event per subject)

not differ between the two groups. There was also no difference in adverse events in the immediate (within 8 weeks of surgery) or long-term (up to 1 year) period. There were no abdominal abscesses or sepsis in either the placebo or infliximab-treated patients, and one perianal abscess in each group. There were no complications

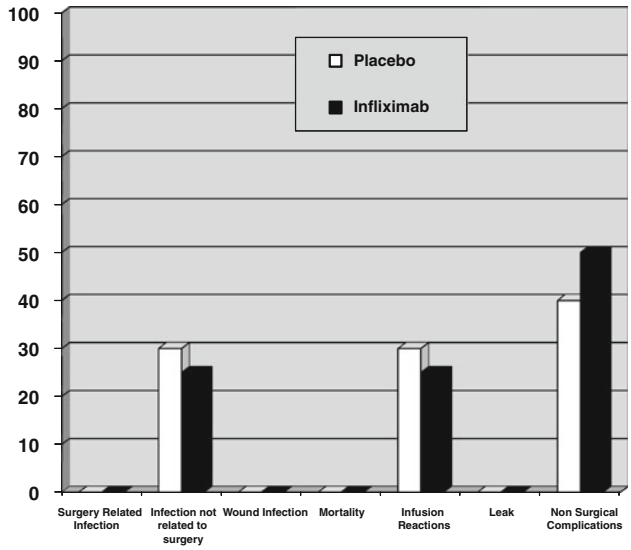

Fig. 1 Postoperative adverse events within 1 year of surgery. *All comparisons nonsignificant with $P > 0.05$

related to wound healing, cardiac events or death. Based on this small study, infliximab appears to be safe when administered within 1 month of intestinal resection for Crohn's disease.

Safety data for anti-TNF treatment in the perioperative period have been limited and only retrospective. There is one large prospective safety study, the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT), but postoperative adverse events were not separately analyzed [8]. To date, there have been 10 retrospective perioperative safety studies with infliximab: 5 in Crohn's disease and 5 in ulcerative colitis. For the most part, the inflammatory bowel disease (IBD) studies assessed postoperative safety outcomes in patients administered *preoperative* infliximab. Our study is unique in that we are the first to describe infusion of infliximab immediately after surgery and prospectively compare placebo outcomes.

The TREAT registry includes the largest safety data experience with infliximab and prospectively follows over 6,000 Crohn's disease patients, approximately 50% receiving infliximab. There has been no difference in mortality rates or malignancy between those receiving infliximab and those who are not. There has been a higher rate of infections in the infliximab group, but on multivariate analysis, corticosteroids, narcotics, and disease severity were the associating factors.

There have been five perioperative infliximab safety studies in Crohn's disease [12–16]. Only one of the five studies showed a higher rate of postoperative complications [16]. The four studies that did not show an increased postoperative risk associated with infliximab were those by Colombel et al. (52 patients), Kunitake et al. (188 patients), Indar et al. (17 patients), and Marchal et al. (40 patients) [12–15]. Of the 297 patients in these four studies, all but 2 received infliximab prior to surgery. The two who did not receive preoperative infliximab received the infusion 1 week after surgery (Colombel). None of the 297 patients had postoperative complications related to infection or wound healing. The study by Appau et al. (60 patients) did conclude that there was an increased rate of postoperative readmission, sepsis, and intra-abdominal abscess (10–20% of infliximab patients compared with 1–6% no infliximab). Although these studies were retrospective with relatively small numbers (357 total patients), the infrequent postoperative complications related to preoperative infliximab are consistent with our findings.

There are also five perioperative infliximab safety studies of patients with ulcerative colitis undergoing ileal pouch anal anastomosis [17–21]. Similar to the Crohn's disease publications, the patients received *preoperative* infliximab and the studies were retrospective analyses on relatively few patients. Three of the studies showed no increase in adverse events [17–19]. Unlike the Crohn's disease studies, two of the studies associated an increased risk of postoperative complications in the setting of preoperative infliximab [20, 21]. Most of the reported complications were related to early postoperative pelvic sepsis and anastomotic leak. Given these findings, most IBD surgeons now perform three-stage ileal pouch anal anastomosis procedures in patients receiving preoperative infliximab.

The greatest limitation to our study is the small sample size. Nonetheless, the trial was prospective and included a placebo comparison group with rigorous assessment for postoperative complications. Although a type 2 error may have occurred with such a small number of patients, there was not even a trend toward increased complications from postoperative infliximab. If anything, the most serious adverse event was a small bowel obstruction due to Crohn's disease recurrence in a placebo patient. This patient ultimately did require another surgery, but this occurred after 1 year and was therefore not included in initial safety data. The results of our study are supported by our continued experience in which patients administered early postoperative anti-TNFs do not have increased rates of infections or other complications (unpublished data).

In conclusion, there was no increased risk of postoperative complications associated with infliximab. This is the first prospective, placebo-controlled trial to evaluate the safety of administration of postoperative infliximab within 4 weeks of intestinal resection. A large international postoperative Crohn's disease prevention study is underway and should definitively assess the safety and efficacy of postoperative infliximab. Until then, it is our practice to

initiate postoperative anti-TNF-α treatment for patients at high risk for Crohn's disease recurrence.

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