CLINICAL—ALIMENTARY TRACT

Infliximab Prevents Crohn's Disease Recurrence After Ileal Resection

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Background & Aims: **Crohn's disease commonly recurs after intestinal resection. We evaluated whether the administration of infliximab after resective intestinal surgery for Crohn's disease reduces postoperative recurrence.** ***Methods:*** **We randomly assigned 24 patients with Crohn's disease who had undergone ileocolonic resection to receive intravenous infliximab (5 mg/kg), administered within 4 weeks of surgery and continued for 1 year, or placebo. The primary end point was the proportion of patients with endoscopic recurrence at 1 year. Secondary end points were clinical recurrence and remission and histologic recurrence.** ***Results:*** **The rate of endoscopic recurrence at 1 year was significantly lower in the infliximab group (1 of 11 patients; 9.1%) compared with the placebo group (11 of 13 patients; 84.6%) ($P = .0006$). There was a nonsignificant higher proportion of patients in clinical remission in the infliximab group (8 of 10; 80.0%) compared with the placebo group (7 of 13; 53.8%) ($P = .38$). The histologic recurrence rate at 1 year was significantly lower in the infliximab group (3 of 11 patients; 27.3%) compared with the placebo group (11 of 13 patients; 84.6%) ($P = .01$). The occurrence of adverse events was similar between the placebo and infliximab groups, and none occurred in the immediate postoperative period.** ***Conclusions:*** **Administration of infliximab after intestinal resective surgery was effective at preventing endoscopic and histologic recurrence of Crohn's disease.**

Crohn's disease most commonly involves the terminal ileum and proximal colon. Despite the advent of immunomodulator therapy, approximately 75% of Crohn's disease patients require an intestinal resection for complications related to stricturing or penetrating disease.[1,2] Intestinal resective surgery for Crohn's disease is not curative and most patients develop recurrent disease at or proximal to the surgical anastomosis. Histologic recurrence of Crohn's disease may occur as early as 1 week after surgery.[3] One year after intestinal resection, 70%–90% of patients have endoscopic evidence of recurrent Crohn's disease.[4,5] Clinical recurrence occurs in one third of patients 3 years after surgery and in 60% by 10 years.[6] The number of patients suffering recurrences severe enough to warrant repeat surgery is substantial, with approximately 70% undergoing repeat surgery by 20 years.[7] Endoscopic recurrence correlates with the likelihood of future clinical recurrence, and predicts the development of Crohn's disease–related complications and need for re-operation. Therefore, endoscopic follow-up evaluation 6–12 months after surgery has been advocated.[8]

There have been several studies evaluating the efficacy of medications for prevention of postoperative Crohn's disease recurrence. The results have been inconsistent, with most therapies showing little benefit. Although the nitroimidazole antibiotics have proved effective in reducing clinical and endoscopic recurrence after surgery, the rates of endoscopic recurrence are still high and exceed 50% at 1 year.[9,10] Results from trials of thiopurine analogues, such as azathioprine (AZA) and 6-mercaptopurine (MP), have been variable. Some studies suggested a reduction in clinical recurrence rates; however, the majority of these patients had endoscopically active disease 1 year after surgery.[11–13] Infliximab is effective for the induction and maintenance of moderate to severely active Crohn's disease. Data from open-label studies have suggested that it may be beneficial in preventing postoperative clinical and endoscopic recurrence.[14,15] To date, there have been no randomized controlled trials evaluat-

Abbreviations used in this paper: AZA, azathioprine; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; 6MP, 6-mercaptopurine.

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ing infliximab for postoperative Crohn's disease prophylaxis.

We undertook this randomized, placebo-controlled study to investigate the efficacy of infliximab to prevent endoscopic, clinical, and histologic Crohn's disease recurrence 1 year after intestinal resection.

Materials and Methods

Study Design

A randomized, two-armed, double-blind, placebo-controlled trial was conducted at the Inflammatory Bowel Disease Center at the University of Pittsburgh Medical Center. Eligible and consenting patients (described later) were assigned randomly in a blocked 1:1 manner to a regimen of either infusions of infliximab 5 mg/kg or placebo. Because of the blocking mechanism and small sample size, random assignment did not ensure exact 1:1 treatment allocation. The protocol was approved by the Institutional Review Board of the University of Pittsburgh Medical Center and all patients gave written informed consent. The study was registered with ClinicalTrials.gov (number NCT00688636).

Patients

Between 2005 and 2007 there were 24 adult patients with ileal or ileocolonic Crohn's disease undergoing resection who participated in the study. All patients were enrolled within 4 weeks of resection of macroscopically diseased bowel with anastomosis between normal ileum and colon (ie, ileocolonic anastomosis). Before formation of the anastomosis, the surgeon everted the ileal and colonic limbs to ensure no mucosally apparent lesions. All anastomoses were side to side and stapled. Exclusion criteria included the following: (1) more than 10 years of Crohn's disease requiring first resective surgery for short (<10 cm) fibrostenotic stricture, (2) macroscopically active disease not resected at the time of surgery, (3) presence of a stoma, and (4) prior severe reactions to infliximab.

Treatment

Patients received either infusions of infliximab 5 mg/kg or identical-appearing placebo at 0, 2, and 6 weeks, followed by every 8 weeks for 54 weeks. Treatment was started shortly after the 2-week postoperative visit and in all patients within 4 weeks of surgery.

Patients on corticosteroids and antibiotics at entry into the study discontinued these medications within 12 weeks of the surgery. Patients on concomitant immunomodulators (ie, AZA, 6MP) and mesalamines were included if the medication dose was stable 12 weeks before surgery and remained constant throughout the duration of study.

Study Outcomes

The primary study outcome was the proportion of patients with endoscopic recurrence at 1 year after surgery. Total ileocolonoscopy was performed 2–4 weeks after the final 54-week study infusion. A previously developed endoscopic recurrence score developed by Rutgeerts et al[5] was used. The scores were as follows: i0, no lesions; i1, 5 or fewer aphthous lesions; i2, more than 5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; and i4, diffuse inflammation with large ulcers, nodules, and/or narrowing.

Endoscopic recurrence was defined by an endoscopic score of i2, i3, or i4. Endoscopic remission was defined by a score of i0 or i1. In addition, the number of ulcers in the neoterminal ileum were counted and recorded as 0, 1–10, and greater than 10. All ileocolonoscopies were videorecorded. A pill camera enteroscopy was performed if ileal inspection was not possible on colonoscopy; only 1 patient required a pill endoscopy. An initial endoscopic score was recorded by the endoscopist (M.R.) at the time of the ileocolonoscopy. A blinded investigator (L.B.) reviewed each patient's videorecorded procedure and provided a separate endoscopic score. The colonoscopic videorecordings were placed on compact discs that were devoid of patient identifiers (ie, blinded). At the conclusion of the study, the principal investigator (M.R.) rescored each patient by re-reviewing the video recordings in a random and blinded fashion. Thus, 3 separate scores were collected on each patient. For those patients with scores that were not the same for the 3 readings, the investigators chose the score that matched in 2 readings and came to consensus agreement. This only occurred in 2 patients; 1 patient with 2 scores of 4 and a third score of 3, and 1 patient with 2 scores of 3 and a third score of 4.

Secondary outcomes of interest included clinical recurrence of Crohn's disease, histologic activity score, C-reaction protein (CRP) concentration, and erythrocyte sedimentation rate (ESR). Clinical recurrence was defined by a Crohn's Disease Activity Index (CDAI) score greater than 200 and clinical remission by a CDAI score of less than 150. An increase or decrease from baseline CDAI was not calculated because of symptoms related to recent surgery that would skew the baseline CDAI.

By using standard biopsy forceps, 6–8 biopsy specimens were taken from the neoterminal ileum and assessed blindly by a gastrointestinal pathologist (A.R.S.). The biopsy sites included the sites of endoscopically visualized lesions or, if no lesions were identified, a random sample of neoterminal ileum. Histologic recurrence was based on a histologic activity score and the presence of polymononuclear cells. The histology scoring system was modified from D'Haens et al.[3] The maximum score in the grading scheme was 14 per biopsy site (Table 1). A

Table 1. Histologic Grading of Ileal Biopsy Specimens

Histologic variable	Grading[a]
Epithelial damage	0 = normal; 1 = focal; 2 = extensive
Crypt architectural changes	0 = normal; 1 = moderate (<50%); 2 = severe (>50%)
Mononuclear cells in lamina propria	0 = normal; 1 = moderate increase; 2 = severe increase
Polymorphonuclear cells in lamina propria	0 = normal; 1 = moderate increase; 2 = severe increase
Polymorphonuclear cells in epithelium	1 = surface epithelium; 2 = deep cryptitis; 3 = crypt abscess
Erosion or ulceration	0 = no; 1 = yes
Granuloma	0 = no; 1 = yes
Pyloric gland metaplasia	0 = no; 1 = yes

[a]Moderate to severe disease activity: greater than 6 to 14 (requires at least grade 1 for polymorphonuclear scores (variables of polymorphonuclear cells in lamina propria and polymorphonuclear cells in epithelium).
The histology scoring system was modified from D'Haens et al.[3]

semiquantitative evaluation also was given for each case, as follows: inactive, 0; mildly active, 1–5; moderately active, 6–10; and severely active, 11–14. The ESR and CRP were obtained at each study visit as surrogate markers of inflammation. The ESR was recorded as millimeters per hour and the CRP level as milligrams per deciliter. A normal ESR was 0–20 mm/h; levels greater than 20 indicated inflammation. A normal CRP was 0–0.8 mg/dL; levels exceeding 0.8 mg/dL indicated inflammation.

Schedule of Study Events

Patients were assessed at each study infusion (weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54), at colonoscopy (weeks 56–60 or withdrawal from study), and at the final study visit at week 66. The CDAI was determined at each study visit. In addition, adverse events were ascertained and samples were collected for laboratory evaluations at each visit.

Statistical Analysis

To assess balance of presenting profiles achieved by randomization, baseline characteristics of study patients were compared by random assignment using the Fisher exact test for categoric variables and Wilcoxon tests (exact methods) for continuous variables. Similarly, to evaluate efficacy of treatment assignment, Fisher exact tests and Wilcoxon tests (exact methods) were used based on the intent-to treat principle. With the small sample size of 24 patients, adjusted analyses were feasible using only continuous outcome measures and a limited number of covariates. Thus, analysis of covariance was used to compare adjusted mean levels of CDAI, histologic activity score, CRP level, and ESR at study completion by random assignment. The analysis was adjusted for baseline measures of the outcomes of interest duration of Crohn's disease (in years), and baseline concomitant use of immunomodulator and/or mesalamine agent. For outcome measures, up to 4 values were incomplete at week 54 of follow-up evaluation because of either early patient withdrawal or missed measurement. In most instances, analyses were performed using the last observation carried forward (see Tables 2, 3, and 4 footnotes).

The trial was designed as proof-of-concept (of active treatment) as opposed to a definitive evaluation of infliximab therapy. Therefore, the primary goal was to estimate the likely effect size to be achieved from infliximab therapy for subsequent evaluation in a large definitive trial. Nonetheless, on the basis of prior endoscopic postoperative studies suggesting that 80% of patients without treatment or on placebo would have an endoscopic recurrence at 1 year, the study was powered to be able to detect a very large treatment effect. Specifically, with anticipated 1:1 randomization of 24 patients, and an endoscopic recurrence of 80% in the placebo group, the study provided 80% power (2-sided type I error rate of 0.05) to detect an absolute difference of 59% associated with infliximab therapy (ie, 80.0% recurrence in the placebo group, 20.7% recurrence in the infliximab group).

Results

Baseline Demographics

Twenty-four patients were included in the study: 11 in the infliximab group and 13 in the placebo arm. Three patients withdrew before 1 year of follow-up evaluation; 1 patient in the placebo group and 2 patients in the infliximab group. All patients had end-of-study colonoscopic evaluation and were included in the intention-to-treat analysis.

The baseline characteristics of the 2 groups are summarized in Table 2. Characteristics were relatively similar for sex, age, duration of Crohn's disease, disease behavior, disease location, prior infliximab exposure, and prior surgical resection. The 8 patients with prior infliximab exposure had received between 1 and 4 doses before surgery; the indication for surgery in these patients included small-bowel obstruction and penetrating complications related to intra-abdominal abscess formation. None of the patients in the study were taking antibiotics. In the infliximab group, there were significantly more active smokers (45.5% vs 7.7%; $P = .06$), and a trend for less concomitant immunomodulators use (36.4 vs 53.8%; $P = .44$) or mesalamine use (9.1% vs 30.8%; $P = .33$). In addition, the median baseline ESR was significantly higher in the infliximab group (40 vs 11; $P = .004$), as was the median CRP concentrations (0.5 vs 0.1; $P = .05$).

Table 2. Baseline Demographics at Study Entry

Baseline demographic	Infliximab (n = 11) n	Infliximab (n = 11) %	Placebo (n = 13) n	Placebo (n = 13) %	*P* value[a]
Female	5	45.5	3	23.1	.39
Age ≥40 (*y*)	6	54.5	5	38.5	.68
Active smoker	5	45.5	1	7.7	.06
Duration of Crohn's disease > 10 (*y*)	7	63.6	5	38.5	.41
Disease location at surgery					.78
Ileum only	2	18.2	3	23.1	
Ileum and colon	9	81.8	10	76.9	
Phenotype					.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	.41
	Median	25%, 75%	Median	25%, 75%	
Age (*y*)	43	28, 49	32	26, 45	.34
Duration of Crohn's disease (*y*)[d]	13	1, 19	9	2, 12	.35
ESR	40	19, 46	11	8, 19	.0004
CRP[e]	0.5	0.1, 0.8	0.1	0.1, 0.2	.049
CDAI[c]	202	120, 232	112	68, 202	.18

[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 rather than at baseline.
[d]Duration of less than 1 year was coded as 0.5 years.
[e]Concentrations of less than 0.1 were coded as 0.05.

Endoscopic and Clinical Outcomes

Primary outcome parameter: endoscopic recurrence. Ileocolonoscopy with biopsy was performed 2–4 weeks after the final study infusion. Therefore, 22 patients underwent ileocolonoscopy 56–58 weeks after the first study infusion. Two patients had ileocolonoscopies at weeks 32 and 39 because of early withdrawal.

One of 11 (9.1%) patients treated with infliximab had endoscopic recurrence, defined as a score of i2, i3, or i4, compared with 11 of 13 (84.6%) patients in the placebo group ($P = .0006$; Table 3 and Figure 1). The 1 infliximab-treated patient who experienced recurrence had an endoscopic grade score of i3. Among the placebo-treated patients who experienced recurrence, 4 had the maximum endoscopic grade score of i4 (Figure 2). Similarly, there were significantly more infliximab-treated patients who had no evidence of Crohn's disease on colonoscopy (0 ulcers and i0) compared with those receiving placebo (81.8% vs 7.7%; $P = .0005$). In addition, fewer patients in the infliximab group had severe endoscopic recurrence (i3 or i4) and more than 10 ulcers in the ileum compared with placebo (9.1% vs 53.8%; $P = .0008$).

Clinical recurrence. The CDAI was used to determine clinical recurrence and was calculated on 23 of 24 patients (Table 3). One patient developed abdominal pain 8 weeks into the study and asked to be withdrawn and unblinded (see Safety of Therapy section). Because of the early drop-out, this patient did not have the last CDAI observation score (assessed at 2 weeks) carried forward, and thus was not included in the 1-year analysis of clinical recurrence or remission. Among the remaining 23 patients, 0 of 10 (0%) in the infliximab group had a clinical recurrence compared with 5 of 13 (38.5%) in the placebo group ($P = .046$). The clinical recurrence (CDAI > 200) in the 5 placebo patients correlated with endoscopic recurrence (i2, 1; i3, 2; and i4, 2) and serologic evidence of inflammation (4 with ESR > 20 mm/h and 4 with CRP > 0.8 mg/dL). There were 8 of 10 (80%) patients in the infliximab group with a clinical remission compared with 7 of 13 in the placebo group (53.8%; $P = .38$). As seen in Figure 3, most patients in the infliximab group showed reductions in CDAI scores from baseline to study completion, whereas no discernable pattern of change was observed in the placebo group. Despite the fact that CDAI scores correlated with clin-

Table 3. Unadjusted Estimates of Clinical Efficacy at the 1-Year Follow-Up Evaluation by Random Assignment to Infliximab Versus Placebo

	Infliximab (n = 11)		Placebo (n = 13)		
Measure of efficacy	(*n*)	(%)	(*N*)	(%)	*P* value[a]
Early termination	2	18.2	1	7.7	.58
Endoscopic grade					.0006
0–1	10	90.9	2	15.4	
2–4	1	9.1	11	84.6	
Endoscopic grade					.0005
0	9	81.8	1	7.7	
1	1	9.1	1	7.7	
2	0	0.0	4	30.8	
3	1	9.1	3	23.1	
4	0	0.0	4	30.8	
Ulcers					.0008
None	9	81.8	1	7.7	
1–10	1	9.1	5	38.5	
>10	1	9.1	7	53.8	
CDAI score					.38
≤150	8	80.0	7	53.8	
>150	2	20.0	6	46.2	
CDAI score					.046
≤200	10	100.0	8	61.5	
>200	0	0.0	5	38.5	
	Median	25%, 75%	Median	25%, 75%	
CDAI[b]	104	89, 118	85	67, 237	1.0
ESR[b]	30	10, 43	19	9, 34	.42
CRP[b]	0.5	0.05, 0.8	0.6	0.2, 1.5	.23

NOTE. Three patients had early endoscopic evaluation (2 infliximab patients: weeks 32 and 48; 1 placebo patient: week 39).
[a]*P* values were calculated by exact methods; chi-square tests for categoric variables; Wilcoxon tests for continuous variables.
[b]Early assessment: CDAI (2 infliximab patients: weeks 30 and 46; 1 placebo patient: week 36); ESR (1 infliximab patient: week 36; 1 placebo patient: week 37); CRP (1 infliximab patient: week 36; 1 placebo patient: week 36).

ical recurrence, only 1 patient had a Crohn's disease exacerbation that was clinically significant and required treatment. This patient withdrew from the study at week 36 and received open-label infliximab; the data through week 36 were included in the intention-to-treat analysis.

Histologic Activity

Histologic recurrence was based on a histologic activity score and the presence of neutrophils. Three of

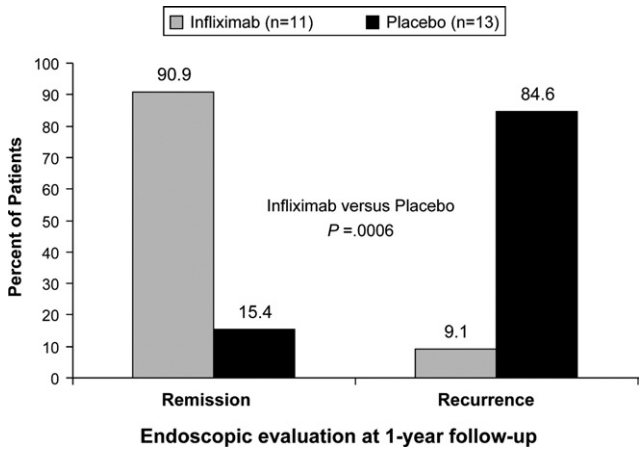

Figure 1. Percentage of patients in remission (endoscopic grade score of i0 or i1) vs recurrence (endoscopic grade score of i2, i3, or i4) of Crohn's disease at the 1-year endoscopic evaluation by random assignment to infliximab or placebo. Infliximab vs placebo: $P = .0006$.

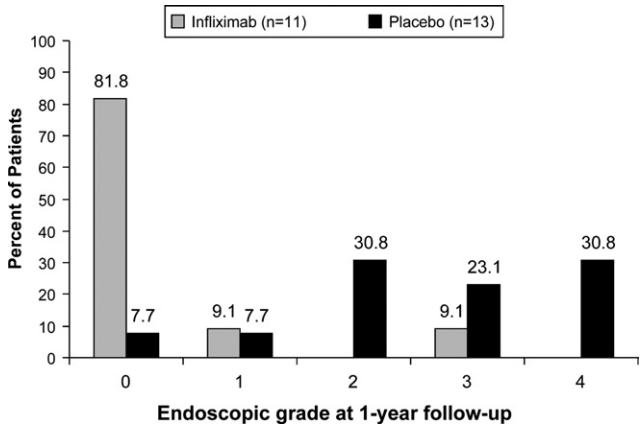

Figure 2. Endoscopic grade and percentage of patients with endoscopic recurrence of Crohn's disease at 1-year follow-up evaluation by random assignment to infliximab or placebo.

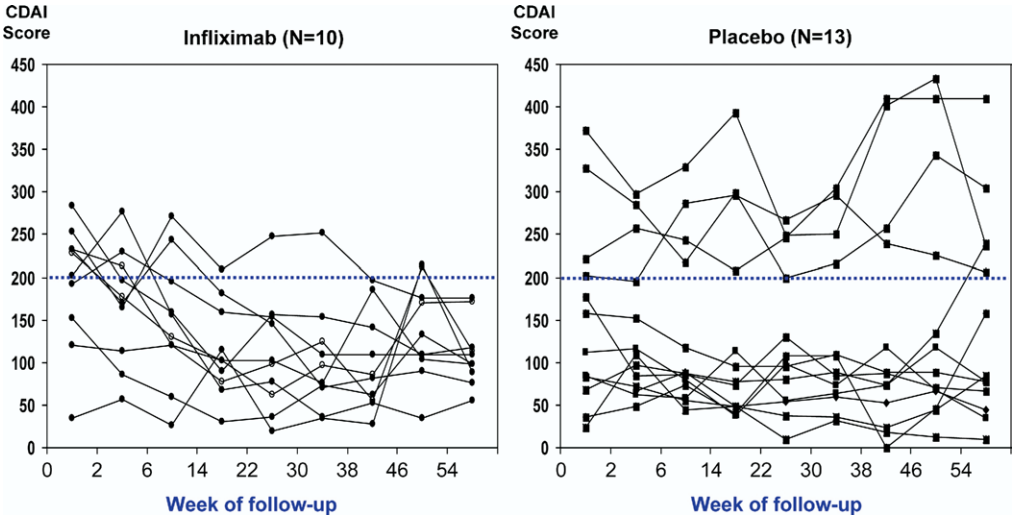

Figure 3. CDAI scores of individual study patients at baseline and throughout the 1-year follow-up period by random assignment to (*A*) infliximab (n = 10) vs (*B*) placebo (n = 13). Two infliximab patients had their last CDAI score carried forward beginning at weeks 30 and 46; 1 placebo patient had the last CDAI score carried forward beginning at week 36.

11 (27.3%) infliximab-treated patients had evidence of neutrophil infiltration compared with 11 of 13 (84.6%) patients in the placebo group (Table 4; $P = .01$). In analyses adjusted for the duration of Crohn's disease, concomitant use of immunomodulators/mesalamine agents, and baseline CDAI, the mean histologic activity score was lower in the patients treated with infliximab compared with placebo (1.9 vs 5.9; $P = .01$) (supplementary Table 1; see supplementary Table 1 online at www.gastrojournal.org).

CRP and ESR

In analyses adjusted for the duration of Crohn's disease, concomitant use of immunomodulators/mesalamine agents, and baseline CRP or ESR, concentrations of CRP (log-transformed) at study completion were significantly lower (−1.8 vs −0.04; $P = .01$) among the infliximab group compared with placebo. Similarly, there was a trend towards lower adjusted mean ESR at study completion in the infliximab group (18.4 vs 28.4; $P = .28$), collectively indicating lower levels of inflammation after infliximab therapy.

Safety of Therapy

The occurrence of adverse events was similar between the placebo and infliximab groups (Table 5). Two patients in the infliximab group and 1 in the placebo group discontinued therapy because of adverse events. One patient receiving infliximab developed severe abdominal pain 2 weeks after the third induction dose (at 6 weeks). The patient was admitted to the hospital and underwent abdominal/pelvic computed tomography scan, upper endoscopy, ileocolonoscopy, and blood testing for complete blood count, liver, pancreas, and kidney function. All testing was normal and the pain resolved spontaneously. Although an etiology for the pain was never identified, the patient requested to be withdrawn from the study. After unblinding, the patient was found to

Table 4. Unadjusted Estimates of Histologic Efficacy at Follow-Up Evaluation by Random Assignment to Infliximab Versus Placebo

	Infliximab (n = 11)		Placebo (n = 13)		
Measure of efficacy	(*n*)	(%)	(*n*)	(%)	*P* value[a]
Histologic activity (wk 56–58)					.10
0–3	8	72.7	4	30.8	
4–6	1	9.1	2	15.4	
≥7	2	18.2	7	53.8	
Histologic activity					.10
0–6	9	81.8	6	46.2	
≥7	2	18.2	7	53.8	
Neutrophils (wk 56–58)					.01
No	8	70.0	2	15.4	
Yes	3	27.3	11	84.6	
	Median	25%, 75%	Median	25%, 75%	
Histologic activity score (wk 56–58)	0	0, 4	7	3, 8	.02

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

Table 5. Adverse Events During the 12-Month Treatment Period

Adverse events	Infliximab (n = 11)	Placebo (n = 13)
Bronchitis	1	0
Nasopharyngitis	1	2
Lung nodules	0	1
Abdominal pain	1[a]	0
Partial small-bowel obstruction	0	1
Gastroenteritis	0	1
Arthralgia	0	2
Pyelonephritis	1	0
Fever	0	1
Lupus-like reaction	1	0
Infusion reaction:		
Flushing	0	1
Hives	1	0
Chest tightness	1[a]	0
Abscess:		
Abdominal wall	1	0
Perianal	0	1
Crohn's disease exacerbation	0	1[a]
Total adverse events	8	11

[a]Withdrew from study because of adverse event.

have received infliximab. Infliximab was continued in an open-label fashion every 8 weeks. There were no further episodes of pain and at the end of 1 year the patient remained in endoscopic remission. Another patient receiving infliximab developed a significant infusion reaction at week 30 with symptoms of chest pain, arthralgias, and shortness of breath. The patient had not received infliximab before the study. The symptoms resolved after cessation of the infusion and treatment with intravenous corticosteroids and antihistamine. Because of this reaction, the patient elected to withdraw from the study. A patient in the placebo group developed a severe exacerbation of Crohn's disease at week 36 with diarrhea, weight loss, abdominal pain, and perianal fistula. Because of the severity of the Crohn's disease recurrence the patient was withdrawn from the study and treated with open-label infliximab. This patient quickly improved with complete resolution of Crohn's disease symptoms.

Discussion

We found infliximab to effectively prevent Crohn's disease relapse in the neoterminal ileum after resective surgery. Infliximab prevented endoscopic, clinical, and histologic recurrence of Crohn's disease 1 year after surgery in this cohort of patients. The proportion of patients with endoscopic recurrence at 1 year was only 9.1% in the infliximab group compared with 84.6% in the placebo group. In addition, proportions of patients with clinical and histologic recurrence at 1 year were much lower in the infliximab group (0% and 27.3%, respectively) than in the placebo group (38.5% and 84.6%, respectively). Although there were more smokers and fewer patients on immunomodulators and mesalamines in the infliximab group, the Crohn's disease recurrence rates were significantly lower than those of the placebo group. There were no apparent safety concerns identified in this study and the rates of adverse events were similar between the infliximab and placebo groups.

We elected to use endoscopic recurrence as the primary study end point and measure of Crohn's disease relapse. Rutgeerts et al have reported a correlation between endoscopic Crohn's disease recurrence and future clinical and surgical relapses. Specifically, they reported that an endoscopic score of i0 or i1 correlated with a low risk of endoscopic progression and had clinical recurrence rates of less than 10% over 10 years. Endoscopic scores of i2 correlated with clinical recurrence rates of 20% over 5 years, whereas scores of i3 and i4 correlated with clinical recurrence rates of 50%–100% and a high likelihood of requiring a re-operation. In our study all but 2 of the patients in the infliximab group had completely normal ileal mucosa, defined as an endoscopic score of i0. Among the placebo-treated patients, using this measure only 1 patient had normal mucosa. Conversely, severe endoscopic recurrence, defined as an endoscopic score of i3 or i4, occurred in only 1 actively treated patient compared with more than half of those who received placebo. Most published postoperative studies have reported 1-year endoscopic recurrence rates between 40% and 60% with active treatment (eg, mesalamine, antibiotics, or 6MP/AZA). To date, no other randomized controlled trials have shown the profound endoscopic remission rates observed in this study.

Although we documented lower rates of clinical recurrence in the infliximab-treated patients, this was based exclusively on the CDAI score and should be interpreted with caution. In fact, only 1 patient in the study had a recurrence that required therapy. Four of the 5 placebo-treated patients with clinical recurrence had increased CDAI scores shortly after surgery; whereas 6 infliximab-treated patients had increased CDAI scores at the same time point and none of these patients had increased CDAI scores at the end of the follow-up period. These data highlight the imperfect nature of the CDAI, particularly in the postoperative setting, and is another reason that we elected to use endoscopic findings as our primary outcome. Although one can anticipate that there would be higher rates of clinical recurrence requiring medical therapy in the placebo-treated patients, larger studies with longer follow-up periods are required to assess this.

There have been several risk factors associated with postoperative Crohn's disease recurrence. Cigarette smoking has been studied the most extensively and associated consistently with endoscopic, clinical, and surgical Crohn's disease recurrence. The risk for re-operation 5 and 10 years after the first surgery for Crohn's disease is significantly higher in smokers compared with nonsmokers (36% vs 20% at 5 years and 70% vs 41% at 10 years).[16] In

our study nearly half (5 of 11) of our infliximab-treated patients were active smokers at baseline and throughout the study compared with only 1 smoker in the placebo group. Despite this fact, the endoscopic and clinical recurrence rates were significantly lower in the infliximab group than in the placebo group of mainly nonsmokers. There was 1 infliximab-treated patient who had significant endoscopic recurrence (i3). This patient was a smoker and it is conceivable that the cigarette smoking contributed to this patient's disease recurrence. Although smoking cessation remains of paramount importance in prevention of Crohn's disease recurrence, our findings suggest that infliximab may negate the detrimental effect of cigarette smoking on postoperative disease relapse. The Group d'Etude Therapeutique des Affections Inflammatories du Tube Digestif (GETAID) group reported a similar reduction in the effects of smoking on relapse in those treated with immunosuppression.[17]

Other risk factors for Crohn's disease recurrence after surgery include disease behavior, specifically penetrating/fistulizing disease, young age, short disease duration before first surgery, and ileocolonic disease.[18–22] In our cohort of patients there were no significant differences in these risk factors between infliximab- and placebo-treated patients. All 11 patients in the infliximab group and 11 of 13 in the placebo group had penetrating Crohn's disease. Patient ages and the duration of Crohn's disease before surgery also were similar between the 2 groups. The number of prior resections also has been suggested as a possible correlate of disease recurrence; however, the number of prior surgical resections did not differ between treatment groups.

There was a high endoscopic recurrence rate (84.6%) in our placebo-treated group. This occurred despite 11 of 13 of these patients also being on concomitant mesalamine or immunomodulator therapy. This high endoscopic recurrence rate is similar to what has been reported previously in postoperative natural history studies and placebo arms of randomized controlled trials.[5,9,10,31] The patients in our study previously treated with mesalamines and immunomodulators had progressed to surgery despite these treatments. Therefore, continuing these medications after surgery probably afforded little benefit in preventing active Crohn's disease and explains the high placebo recurrence rate. Given this information and the rare, but fatal, reports of hepatosplenic T-cell lymphoma in patients treated concomitantly with infliximab and 6MP/AZA, we would not recommend continuing immunomodulators with infliximab postoperatively.

There have been several medications that have been evaluated for the prevention of postoperative Crohn's disease recurrence. Sulfasalazine and mesalamine have been studied most extensively and often used as first-line therapy after surgery. There have been 3 placebo-controlled sulfasalazine studies but only 1 showed a modest reduction of radiographic and surgical recurrence at 1 year.[23–25] There have been 4 placebo-controlled and several uncontrolled mesalamine studies.[26–29] Only 1 showed a statistically significant decrease in clinical recurrence at 72 months.[26] There have been 3 randomized controlled trials using 6MP/AZA for prevention of postoperative Crohn's disease.[11,12,30] Two were placebo-controlled studies that reported lower endoscopic recurrence rates with 6MP/AZA compared with placebo. The third was an open-label study by Ardizzone et al[12] that did not find that AZA reduced postoperative clinical recurrence more than mesalamine. There have been 2 placebo-controlled studies evaluating the efficacy of nitroimidazole antibiotics in the prevention of postoperative Crohn's disease.[9,10] Both showed a reduction in clinical and endoscopic recurrence in the nitroimidazole-treated group. Although nitroimidazole antibiotics appeared to reduce postoperative Crohn's disease recurrence, the benefit was attenuated over time and medication intolerance limited long-term administration. Although 6MP/AZA and nitroimidazole antibiotics may have modest benefits in the prevention of postoperative Crohn's disease recurrence, endoscopic recurrence rates remained significant, ranging from 37.5% to 52%.

To date, there have been no placebo-controlled studies of anti–tumor necrosis factor antibodies as prophylactic postoperative therapy. In an open-label study by Sorrentino et al, seven Crohn's disease patients were treated with standard induction and maintenance dosing consisting of infliximab (5 mg/kg) and oral methotrexate 10 mg/wk, and compared with a group of 16 patients treated only with mesalamine 2.4 g/day.[15] At the end of 2 years, none of the infliximab/methotrexate-treated patients had clinical or endoscopic recurrence, whereas 75% of the patients treated with mesalamine alone had clinical or endoscopic recurrence.

Limitations to our study included a small sample size, a disproportionate number of smokers in the infliximab group, more patients on immunomodulators in the placebo group, and inclusion of patients who had previously received infliximab. Although our sample size was small, the a priori power calculation considered a potential large endoscopic difference; 80% recurrence in the placebo group and 20% or lower in the infliximab group. Thus, despite the small sample size, statistical significance was achieved with the observed endoscopic recurrence rate of 84.6% in the placebo group vs only 9.1% in the infliximab group. More active smokers were assigned to the infliximab group despite randomization. We would normally expect this imbalance, and the higher recurrence rates associated with smoking to bias our results against infliximab, a finding that was not observed in this trial. Most postoperative studies to date have discontinued all nonstudy medications after surgery. Aside from antibiotics and corticosteroids, we elected to include patients who already were taking immunomodulators or mesalamine therapy and continue

these medications throughout the study. Concomitant immunomodulator use, however, did not appear to impact recurrence. Of the 7 patients in the placebo group who were taking concomitant immunomodulators, 5 had endoscopic recurrence at 1 year. Lastly, although 3 of 24 patients (12.5%) withdrew early from the study, they represented both treatment groups (2 patients from the infliximab group, 1 patient from the placebo group). Furthermore, imputed analyses were based on at least 30 weeks of observed data carried forward. Thus, incomplete and imputed study data are unlikely to be an appreciable source of bias.

We elected to include patients who had received prior infliximab to mimic a real-world experience. That is, there are many patients in whom anti–tumor necrosis factor therapy is used as an attempt at preventing inevitable surgery. Many of these patients probably already have developed a complication (eg, fibrostenotic stricture or severe penetrating disease), for which any medical therapy would be ineffectual. In our cohort of patients, 8 had received infliximab before surgery. All had received the infusions within 6 months of surgery and the number of infliximab infusions ranged from 1 to 4. All of these patients required surgery for a fibrostenotic or penetrating complication. We surmise that these patients were not true primary nonresponders to infliximab, but rather had a complication of Crohn's disease that required surgery. Therefore, unlike primary nonresponders to infliximab, it is not surprising that the 3 patients who were randomized to infliximab after surgery did well.

In summary, there are a significant number of patients with Crohn's disease who undergo 2 or more resective surgeries and/or require rapid abdominal re-operation. Our study provides strong evidence that infliximab is effective at preventing endoscopic, clinical, and histologic postoperative recurrence of Crohn's disease and provides a rationale for aggressive postoperative chemoprevention with biologic therapy. Our study was designed as a proof-of-concept trial and larger studies are warranted. In our practice, we now consider patients with a high risk for postoperative recurrence of Crohn's disease, such as ileal penetrating disease and recurrent resective surgery, for postoperative infliximab prophylaxis. The duration of postoperative infliximab maintenance and appropriate endoscopic follow-up evaluation remains a subject for future study.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2008.10.051.

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Supplementary Table 1. Adjusted Estimates of Clinical and Histologic Efficacy by Random Assignment to Infliximab Versus Placebo

	Unadjusted				Adjusted[b]				
	Infliximab		Placebo		Infliximab		Placebo		
Measure of efficacy[a]	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*P* value
CDAI (wk 56–58)	111	38	150	121	109	53–165	151	103–199	.27
ESR (wk 56–58)	26.9	17.7	21.9	13.3	18.4	6.2–30.7	28.4	18.2–38.7	.28
Log CRP (wk 56–58)	−1.2	1.3	−0.5	1.4	−1.8	−2.8 to −0.9	−0.04	−0.8 to 0.8	.01
Histologic activity score[c]	2.3	3.4	5.8	3.2	1.86	0–3.89	5.88	3.94–7.82	.01

[a]Refer to footnotes in Table 3.

[b]Adjusted for baseline level of the efficacy measure, duration of CD (in years), and baseline concomitant use of immunomodulator and/or mesalamine agent.

[c]Adjusted for baseline CDAI score rather than baseline histologic activity score.