Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection

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BACKGROUND & AIMS: Most patients with Crohn's disease (CD) eventually require an intestinal resection. However, CD frequently recurs after resection. We performed a randomized trial to compare the ability of infliximab vs placebo to prevent CD recurrence. **METHODS:** We evaluated the efficacy of infliximab in preventing postoperative recurrence of CD in 297 patients at 104 sites worldwide from November 2010 through May 2012. All study patients had undergone ileocolonic resection within 45 days before randomization. Patients were randomly assigned (1:1) to groups given infliximab (5 mg/kg) or placebo every 8 weeks for 200 weeks. The primary end point was clinical recurrence, defined as a composite outcome consisting of a CD Activity Index score >200 and a ≥70-point increase from baseline, and endoscopic recurrence (Rutgeerts score ≥i2, determined by a central reader) or development of a new or re-draining fistula or abscess, before or at week 76. Endoscopic recurrence was a major secondary end point. **RESULTS:** A smaller proportion of patients in the infliximab group had a clinical recurrence before or at week 76 compared with the placebo group, but this difference was not statistically significant (12.9% vs 20.0%; absolute risk reduction [ARR] with infliximab, 7.1%; 95% confidence interval: −1.3% to 15.5%; $P = .097$). A significantly smaller proportion of patients in the infliximab group had endoscopic recurrence compared with the placebo group (30.6% vs 60.0%; ARR with infliximab, 29.4%; 95% confidence interval: 18.6% to 40.2%; $P < .001$). Additionally, a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence based only on Rutgeerts scores ≥i2 (22.4% vs 51.3%; ARR with infliximab, 28.9%; 95% confidence interval: 18.4% to 39.4%; $P < .001$). Patients previously treated with anti-tumor necrosis factor agents or those with more than 1 resection were at greater risk for clinical recurrence. The safety profile of infliximab was similar to that from previous reports. **CONCLUSIONS:** Infliximab is not superior to placebo in preventing clinical recurrence after CD-related resection. However, infliximab does reduce endoscopic recurrence. ClinicalTrials.gov ID NCT01190839.

Keywords: PREVENT; Anti-TNF; Inflammatory Bowel Disease; CDAI.

Crohn's disease (CD) often requires intestinal resection, despite treatment with immunosuppressive and biologic therapies.[1,2] Historically, up to 70% of patients who undergo CD-related resection develop postoperative endoscopic recurrence at or proximal to the surgical anastomosis within 1 year.[3,4] Recent systematic reviews and meta-analyses have shown that approximately one-third of patients with CD who have a first resection require a second within 10 years, and the majority of these second intestinal resections occur within 5 years of the first. However, during the past few decades, the risk of a second resection has decreased.[5] Additionally, a decreasing trend has been found during the past 6 decades in the cumulative risk of resection 1, 5, and 10 years after CD diagnosis.[6]

Studies of probiotics, aminosalicylates, and budesonide[7–13] for prevention of postoperative recurrence have overall yielded negative results. Studies of nitroimidazole antibiotics have been positive for prevention of clinical recurrence. Studies of thiopurines have had mixed results for the prevention of clinical recurrence. Neither nitroimidazole antibiotics nor thiopurines have consistently

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prevented endoscopic recurrence.[14–16] Initial studies,[17,18] a small placebo-controlled trial,[19] and subsequent observational studies[20–25] suggested that tumor necrosis factor (TNF) antagonists might be effective for prevention of postoperative recurrence. In recent studies of CD treatment strategies after intestinal resection, therapy adjusted according to 6-month colonoscopy findings led to effective disease control.[26–28] Overall, optimal postoperative management is unclear.

Given these considerations, we evaluated the efficacy and safety of infliximab for prevention of postoperative CD recurrence.

Methods

Patients

The PREVENT (Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® [infliximab] and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence; ClinicalTrials.gov ID NCT01190839) study was a phase 3, multicenter, placebo-controlled, double-blind, randomized study conducted at 104 sites globally between November 2010 and May 2012. The Institutional Review Board or ethics committee at each site approved the protocol, and patients provided written informed consent. All authors had access to the study data and had reviewed and approved the final manuscript.

Enrolled patients were at least 18 years old with a confirmed diagnosis of CD who had undergone ileocolonic resection with ileocolonic anastomosis. An end or loop ileostomy within 1 year was permitted if stoma closure and ileocolonic anastomosis occurred within 45 days of randomization. Patients had no evidence of macroscopic CD, no known active CD elsewhere in the gastrointestinal tract, and were eligible for randomization within 45 days of resection. Patients were ineligible if the qualifying surgery occurred more than 10 years after CD diagnosis and was performed for stricturing disease involving <10 cm of bowel. Patients were also required to have a baseline CD Activity Index (CDAI)[29] score <200 and at least one of the following risk factors for disease recurrence: qualifying surgery that was their second intra-abdominal resection within 10 years; third or more intra-abdominal resection; resection for a penetrating CD complication (eg, abscess or fistula); a history of perianal fistulizing CD, provided the event had not occurred within 3 months; or smoking 10 or more cigarettes per day for the past year. The prespecified risk factors of smoking, perforating disease, and previous resection had been identified from previous studies and were utilized in a recent postoperative study.[28,30–35]

Patients receiving oral mesalamine or immunosuppressives (azathioprine, 6-mercaptopurine, or methotrexate) pre-surgery could continue treatment with maintenance of stable doses after resection. Patients not receiving these agents pre-surgery could not receive them post-surgery. Rectal mesalamine was discontinued at least 2 weeks before randomization. Initiation of corticosteroids or antibiotics for CD treatment was prohibited.

Study Design

Patients were randomized equally to receive infliximab (Remicade; Janssen Biotech, Inc., Horsham Township, PA) 5 mg/kg or placebo every 8 weeks. Placebo and infliximab infusions were administered in a blinded manner. Randomization was stratified by the number of risk factors for recurrence (1 or >1) and current use of an immunosuppressive (yes/no). Unlike dosing regimens used previously and those described in the prescribing information for patients with CD,[36] every-8-weeks dosing without the 3-dose induction regimen was utilized in this study. This dosing regimen was chosen because patients in this study were in surgically-induced remission and did not have active CD at the time they entered the study; thus, every-8-weeks dosing for maintenance of remission was employed. Also, some patients might not have been naïve to infliximab, and data from an infliximab trial in patients with psoriasis showed a higher rate of serious infusion reactions at the week-2 infliximab infusion after a hiatus.[37]

CDAI scores were determined at each visit, and as required at interim assessments; baseline CDAI refers to the CDAI collected during the screening period (ie, no fewer than 10 days and no more than 45 days before randomization) that qualified the patient for the study. Patients who met CDAI criteria (ie, ≥200 and an increase of ≥70 points from the baseline CDAI score) for clinical recurrence or reached week 76 underwent a video ileocolonoscopy. Patients who discontinued study agent before week 76 had a video ileocolonoscopy at the time of discontinuation. If clinical recurrence was observed, patients could receive blinded infliximab doses at an increase of 5 mg/kg for each subsequent scheduled infusion visit, such that patients receiving placebo increased to 5 mg/kg and patients receiving 5 mg/kg to 10 mg/kg.

Serum samples were collected at baseline and week 72 for measurement of infliximab and antibodies to infliximab (ATI).[38] Adverse events, concomitant medications, and CD-related hospitalizations and surgeries were recorded throughout.

End Points

The primary end point was clinical recurrence before or at week 76, defined by a ≥70-point increase from baseline with a total CDAI score ≥200 and evidence of endoscopic recurrence defined by a Rutgeerts score[3] of ≥i2 (i0, no lesions; i1, ≤5 aphthous lesions; i2, >5 aphthous lesions or anastomotic ulcer <1 cm; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; i4, diffuse inflammation with large ulcers, nodules, and/or narrowing) at the anastomotic site or its equivalent elsewhere in the gastrointestinal tract or fistula/abscess development (ie, new draining external fistula, internal fistula, reopening and draining of a previously existing external fistula, perianal abscess, or intra-abdominal abscess >3 months after the index surgery). Patients were considered to have clinical recurrence if they had a treatment failure (ie, initiated a prohibited CD medication, had a prohibited use of a CD medication, or had CD-related surgery).

The major secondary end point was endoscopic recurrence of CD before or at week 76, defined as a Rutgeerts score of ≥i2 either at the anastomosis or elsewhere in the gastrointestinal tract, whether this occurred at the week 76 video ileocolonoscopy, or at a prior video ileocolonoscopy. Patients who

Table 1. Baseline Demographics, Disease Characteristics, and Concomitant Crohn's Disease Medications for Randomized Patients

Characteristic	Placebo (N = 150)	Infliximab 5 mg/kg (N = 147)	Total (N = 297)
Sex, n (%)			
n	150	147	297
Male	81 (54.0)	77 (52.4)	158 (53.2)
Female	69 (46.0)	70 (47.6)	139 (46.8)
Race, n (%)			
n	150	147	297
White	138 (92.0)	138 (93.9)	276 (92.9)
Black or African American	4 (2.7)	3 (2.0)	7 (2.4)
Asian	2 (1.3)	1 (0.7)	3 (1.0)
Other	6 (4.0)	5 (3.4)	11 (3.7)
Age, y			
n	150	147	297
Mean (SD)	35.4 (12.41)	37.1 (13.49)	36.3 (12.96)
Median	34.0	35.0	34.0
Interquartile range	(25.0−44.0)	(26.0−45.0)	(26.0−44.0)
Range	(18−69)	(18−76)	(18− 76)
Weight, kg			
n	150	147	297
Mean (SD)	69.70 (16.083)	69.64 (17.716)	69.67 (16.883)
Median	67.30	66.00	66.80
Interquartile range	(58.10−78.10)	(57.20−79.50)	(58.00−78.30)
Range	(41.0−127.0)	(40.0−125.7)	(40.0−127.0)
Disease duration, y			
n	150	146	296
Mean (SD)	6.39 (7.457)	8.38 (8.651)	7.37 (8.115)
Median	3.32	6.49	5.17
Interquartile range	(0.74−9.71)	(1.45−11.07)	(0.80−10.61)
Range	(0.1−37.5)	(0.1−45.9)	(0.1−45.9)
CDAI score			
n	150	146	296
Mean (SD)	109.8 (54.75)	107.7 (52.75)	108.8 (53.69)
Median	109.5	102.5	105.5
Interquartile range	(66.0−153.0)	(64.0−148.0)	(65.0−152.5)
Range	(4−240)	(3−202)	(3−240)
Involved gastrointestinal areas, n (%)			
n	150	146	296
Ileum	146 (97.3)	144 (98.6)	290 (98.0)
Colon	76 (50.7)	89 (61.0)	165 (55.7)
Proximal small intestine, stomach and/or esophagus	6 (4.0)	6 (4.1)	12 (4.1)
Perianal	13 (8.7)	17 (11.6)	30 (10.1)
Extra intestinal manifestations	15 (10.0)	21 (14.4)	36 (12.2)
Findings at surgery, n (%)			
n	150	146	296
Stricture	86 (57.3)	84 (57.5)	170 (57.4)
Abscess	41 (27.3)	47 (32.2)	88 (29.7)
Internal fistula	86 (57.3)	67 (45.9)	153 (51.7)
Sinus tracts	10 (6.7)	7 (4.8)	17 (5.7)
Perforation	12 (8.0)	19 (13.0)	31 (10.5)
Prior intra-abdominal surgeries, n (%)			
n	150	146	296
0	91 (60.7)	79 (54.1)	170 (57.4)
1−2	51 (34.0)	63 (43.2)	114 (38.5)
>2	8 (5.3)	4 (2.7)	12 (4.1)
CD medication history, n (%)			
n	150	146	296
Any CD medication	144 (96.0)	136 (93.2)	280 (94.6)
Anti-tumor necrosis factor	30 (20.0)	37 (25.3)	67 (22.6)
Adalimumab	17 (11.3)	21 (14.4)	38 (12.8)
Infliximab	15 (10.0)	18 (12.3)	33 (11.1)
Certolizumab	0	3 (2.1)	3 (1.0)

Table 1. Continued

Characteristic	Placebo (N = 150)	Infliximab 5 mg/kg (N = 147)	Total (N = 297)
Corticosteroid (excluding budesonide)	96 (64.0)	104 (71.2)	200 (67.6)
Budesonide	67 (44.7)	63 (43.2)	130 (43.9)
Immunosuppressive drugs	88 (58.7)	85 (58.2)	173 (58.4)
6-MP	22 (14.7)	19 (13.0)	41 (13.9)
AZA	77 (51.3)	73 (50.0)	150 (50.7)
Methotrexate	7 (4.7)	11 (7.5)	18 (6.1)
Mesalamine	101 (67.3)	100 (68.5)	201 (67.9)
Antibiotics	88 (58.7)	94 (64.4)	182 (61.5)
Concomitant CD medications, n (%)			
n	150	147	297
Any CD medication	47 (31.3)	53 (36.1)	100 (33.7)
Corticosteroid (excluding budesonide)	4 (2.7)	10 (6.8)	14 (4.7)
≥20 mg/d P.Eq	0	1 (0.7)	1 (0.3)
<20 mg/d P.Eq	4 (2.7)	9 (6.1)	13 (4.4)
Budesonide	2 (1.3)	2 (1.4)	4 (1.3)
Immunosuppressive drugs	27 (18.0)	25 (17.0)	52 (17.5)
6-MP/AZA	27 (18.0)	21 (14.3)	48 (16.2)
Methotrexate	0	4 (2.7)	4 (1.3)
Mesalamine	27 (18.0)	28 (19.0)	55 (18.5)

AZA, azathioprine; 6-MP, 6-mercaptopurine; P.Eq, prednisone equivalent.

developed a fistula or abscess, or had a treatment failure were considered to have endoscopic recurrence.

Endoscopic recurrence before or at week 76 defined by endoscopic score only (Rutgeerts score ≥i2) was also analyzed. Endoscopy end points before or at week 76, including those for the primary end point, were evaluated by a central reader (P.R.).

A secondary efficacy end point was clinical recurrence before or at week 104.

Study Duration

Although treatment was planned for a maximum of 208 weeks, the study was terminated after week 104 because the primary outcome was not met.

Statistical Analysis

All randomized patients were included in efficacy analyses according to assigned treatment, regardless of actual treatment received. All patients who received at least 1 dose of study agent were included in safety and pharmacokinetic analyses based on actual treatment received.

For continuous outcomes, the last value before treatment failure was carried forward.

Seven sensitivity analyses were performed (5 prespecified and 2 post-hoc) on the primary end point.

Odds ratios for prespecified subgroup analyses (eg, demographics, disease characteristics, concomitant medications) of clinical recurrence were summarized.

Categorical data (eg, clinical or endoscopic recurrence) were compared using the Cochran-Mantel-Haenszel χ^2 test. Continuous measures were compared using analysis of variance on the van der Waerden normal scores. Time-to-event end points were analyzed using the log-rank test. A Cox model was used to evaluate predictors of clinical recurrence.

Statistical testing was performed at $\alpha = .05$ (2-sided) level of significance.

A fixed-sequence testing procedure controlled the overall type I error rate at the .05 level. If the test for the primary end point was not positive, statistical tests for other end points were not considered positive, even if the nominal P value reached the .05 level of significance.

In a study conducted with a patient population similar to that proposed for this study, approximately 40% of patients in the placebo group experienced clinical recurrence by week 52.[19] For calculation of sample size, 50% and 30% of placebo- and infliximab-treated patients, respectively, were expected to develop clinical recurrence by week 76. A sample size of 290 patients, 145 per treatment, provided 93% power to detect a 20% between-group difference in clinical recurrence before or at week 76.

Results

Patients

Demographics, qualifying characteristics, and risk factors of the 297 randomized patients (placebo, N = 150; infliximab, N = 147) were similar between treatment groups. The most common risk factor for intestinal resection was penetrating complication (Table 1, Supplementary Tables 2 and 3). Approximately 20% of randomized patients received concomitant immunosuppressives (Table 1). Antibiotics were administered for CD to 6 patients in the placebo group and 2 patients in the infliximab 5 mg/kg group; these patients were considered treatment failures.

Patient disposition is shown in Supplementary Figure 1. Approximately one-third of randomized patients discontinued study drug before week 76, most commonly for adverse events.
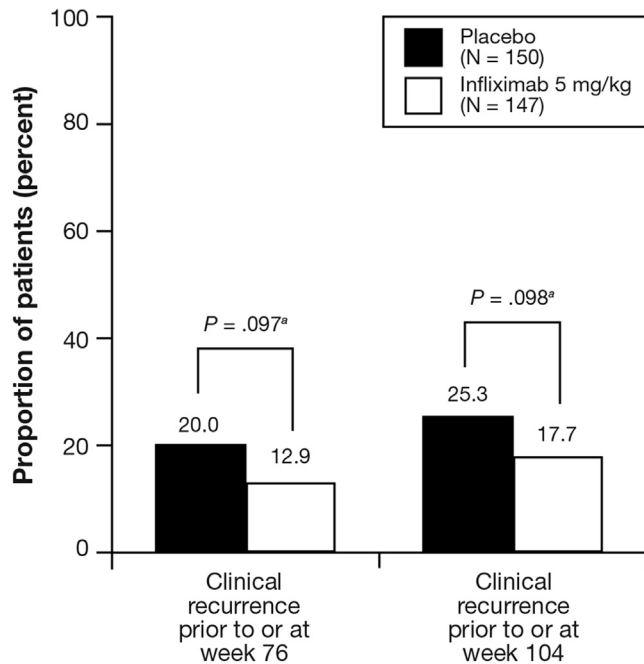
Figure 1. Clinical recurrence before or at week 76 and before or at week 104. P values based on the Cochran-Mantel-Haenszel χ^2 test stratified by the number of risk factors for recurrence of active Crohn's disease (1 or >1) and baseline use (yes/no) of an immunosuppressives (ie, azathioprine, 6-mercaptopurine, or methotrexate). [a]Nominal P value.

Primary End Point

Clinical recurrence rates before or at week 76 were 12.9% and 20.0% for the infliximab and placebo groups, respectively (absolute risk reduction [ARR] with infliximab, 7.1%; 95% confidence interval [CI]: −1.3% to 15.5%); these results were not statistically significant (P = .097) (Figure 1). Of note, clinical recurrence rates before or at week 76 among patients who met both CDAI and endoscopic criteria were 4.1% and 9.3% (P = .056) for the infliximab and placebo groups, respectively (Table 2).

In general, the results of the sensitivity analyses were consistent with the results of the primary end point analysis (Supplementary Table 1).

Time to clinical recurrence is summarized in Figure 2 for the infliximab and placebo groups (log rank P = .141).

Results observed in prespecified subgroups were generally consistent with the overall results, with a few exceptions, including CD duration, baseline CDAI score, prior TNF therapy, race, geographic location, disease location in gastrointestinal tract, and patients undergoing their second intra-abdominal operation (Supplementary Figure S2A−D).

Secondary End Points

Endoscopic recurrence. Endoscopic recurrence, as defined by Rutgeerts score ≥i2; or abscess, fistula recurrence, or development; or treatment failure, before or at week 76 for the infliximab and placebo groups was 30.6%

and 60.0%, respectively (ARR with infliximab = 29.4%; 95% CI: 18.6%−40.2%; P < .001; Figure 3A).

Similarly, endoscopic recurrence defined only by Rutgeerts scores ≥i2 for the infliximab and placebo groups was 22.4% and 51.3%, respectively (ARR with infliximab = 28.9%; 95% CI: 18.4% −39.4%; P < .001; Figure 3A).

Classification of patients by Rutgeerts score i1 (<5 aphthous ulcers) and i2 (≥5 aphthous ulcers or anastomotic ulcer <1 cm) endoscopic recurrence may be of negligible clinical significance and potentially separated by only 1 aphthous ulcer. Classifying patients by normal mucosa (i0) or aggressive endoscopic recurrence (i3/i4) provides a more meaningful distinction.

Central endoscopic results before or at week 76 are presented in Figure 3B. Of 73 patients with an i0 Rutgeerts score before or at week 76, 54 (74.0%) and 19 (26.0%) patients were in infliximab and placebo groups, respectively (Supplementary Figure S3). Of 59 patients with an i3 or i4 Rutgeerts score before or at week 76, 11 (18.6%) and 48 (81.4%) patients were in the infliximab and placebo groups, respectively (Supplementary Figure S3).

Among patients with endoscopy results before or at week 76, the distribution of Rutgeerts scores are summarized in Figure 3B.

Clinical recurrence at week 104. Clinical recurrence rates before or at week 104 were 17.7% and 25.3% for the

Table 2. Reasons for Clinical Recurrence[a] Before or at Week 76

Reasons	Placebo (N = 150)	Infliximab, 5 mg/kg (N=147)
Met CDAI and endoscopic criteria	14 (9.3)	6 (4.1)
Met fistula/abscess criteria	7 (4.7)	3 (2.0)
Developed a new draining external fistula	2 (1.3)	0
Reopened and drained a previously existing external fistula	0	1 (0.7)
Developed a new internal fistula	3 (2.0)	2 (1.4)
Developed a new perianal abscess	6 (4.0)	1 (0.7)
Developed a new intra-abdominal abscess >3 mo after the date of the index surgery	0	1 (0.7)
Had a treatment failure	14 (9.3)	14 (9.5)
Initiated a prohibited CD medication	7 (4.7)	4 (2.7)
Had a prohibited use of a CD medication	12 (8.0)	12 (8.2)
Had a surgery for CD	2 (1.3)	2 (1.4)
Met at least 1 of the following criteria	1 (0.7)	0
Discontinued study agent due to recurrent symptoms of CD	0	0
Met CDAI criteria at the time of discontinuation of study agent	1 (0.7)	0
Did not have sufficient data to evaluate clinical recurrence status at both wk 72 and wk 76	0	0

NOTE. Values are n (%).
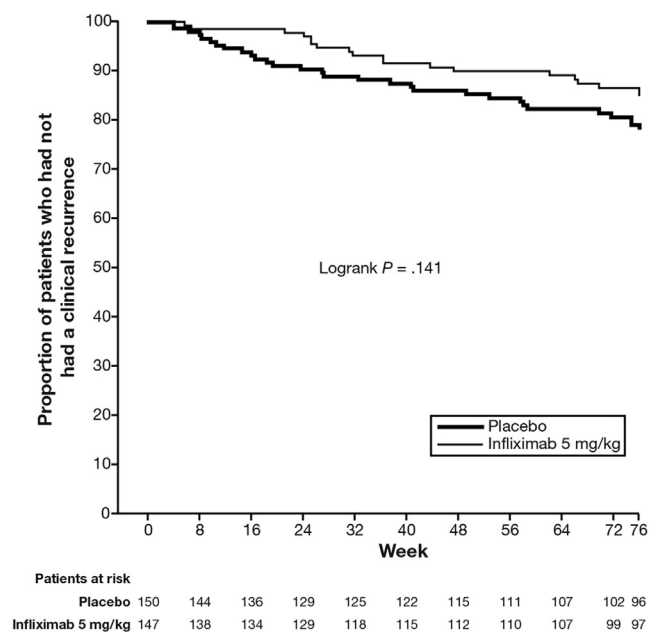[a]Patients could have more than one reason for clinical recurrence.

Figure 2. Time to first clinical recurrence before or at week 76; all randomized patients.

infliximab and placebo groups, respectively (ARR with infliximab = 7.6%, 95% CI: −1.7%, to 17.0%; $P = .098$) (Figure 1).

Crohn's Disease Activity Index scores at week 104. Median changes from baseline in CDAI score at the last visit before or at week 104 were −15.0 and −22.0 for placebo and infliximab 5 mg/kg, respectively ($P = .058$). Median CDAI scores through week 104 are shown in Supplementary Figure S4.

Hospitalizations and Surgeries

Hospitalizations and surgeries were uncommon, with no statistically significant differences observed between groups through week 104 (Supplementary Table 4).

Predictors of Clinical Recurrence

Patients with more than one resection or who received anti-TNF therapy pre-surgery were more likely to have a clinical recurrence (Supplementary Table 5).

Safety

Among 297 randomized patients, 291 received at least 1 dose of study drug. The average duration of treatment before a dose increase was similar for infliximab and placebo (74.3 weeks and 75.9 weeks, respectively; Table 3).

Adverse and serious adverse event rates were similar between groups. Infection rates, including serious infections, were also similar. More patients in the infliximab than placebo group discontinued therapy because of an adverse event through the final visit, most commonly for adverse events related to the gastrointestinal or infection and infestation system organ class (Supplementary Table 6).

There were no deaths or malignancies (excluding non-melanoma skin cancer) in infliximab-treated patients (Table 3).

Infusion reactions occurred in 8.2% of placebo-treated compared with 19.4% of infliximab-treated patients (Table 3).

Pharmacokinetics and Immunogenicity

For patients in the infliximab 5 mg/kg group, median trough serum infliximab concentrations were 0.00 μg/mL and 2.18 μg/mL at week 0 and week 72, respectively.

At week 72, median serum infliximab concentration for patients receiving immunosuppressives was numerically greater than those not receiving immunosuppressives (4.89 μg/mL vs 1.83 μg/mL, respectively). The proportion of infliximab-treated patients with endoscopic recurrence before or at week 76 decreased with increasing serum infliximab concentration. This effect was not observed for clinical recurrence (Supplementary Figure S5).

Overall, ATIs were present in 16.2% of patients, none of whom were receiving immunosuppressives at baseline. This ATI incidence was based on an antigen-bridging enzyme immunoassay in which detectable levels of circulating infliximab can interfere with the ability to assess the presence of ATI. Endoscopic recurrence before or at week 76 was seen in 64.7% (11 of 17), 46.7% (7 of 15), and 30.1% (22 of 73) of patients who were positive, negative, or inconclusive for ATI, respectively. This effect was not observed for clinical recurrence.

Discussion

This study evaluating infliximab for prevention of post-surgical CD recurrence after ileocolonic resection did not meet the primary end point of clinical recurrence and was prematurely terminated at week 104. The endoscopic recurrence rate in infliximab-treated patients is consistent with those of small randomized controlled trials.[18,19]

We also found that patients with a prior resection and use of anti-TNF therapy pre-surgery were at higher risk for postoperative CD recurrence. However, it is possible that these factors reflect disease severity and/or complicated disease course rather than independent risk factors for recurrence. These results should be interpreted with caution due to the small sample size.

The PREVENT trial is the first large, multicenter, placebo-controlled postoperative CD study with a biologic. Assumptions on postoperative clinical and endoscopic recurrence were extrapolated from the collective results of several smaller studies, including the trial by Regueiro et al.[19] Patients enrolled in that small study may have had a higher risk of postoperative CD recurrence, most with penetrating disease and a high proportion having undergone at least 2 resections. The intent of the PREVENT study was to enroll a similar high-risk population of patients; however, 69.6% had only one risk factor for recurrence, and 57.4% were undergoing their first
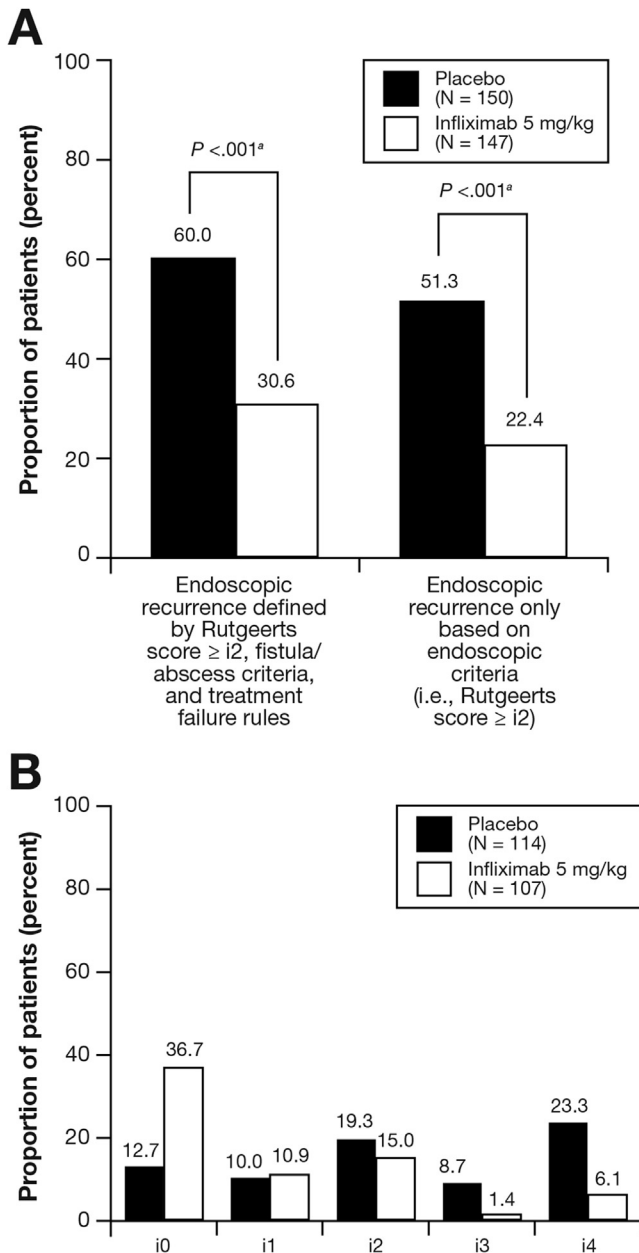
A

B

Figure 3. Endoscopic recurrence before or at week 76; all randomized patients (*A*) and central endoscopic results before or at week 76 (Rutgeerts score i0, i1, i2, i3, i4) (*B*). *P* values based on the Cochran-Mantel-Haenszel χ^2 test stratified by the number of risk factors for recurrence of active Crohn's disease (1 or >1) and baseline use (yes/no) of an immunosuppressives (ie, azathioprine, 6-mercaptopurine, or methotrexate). [a]Nominal *P* value. i0, no lesions; i1, ≤5 aphthous lesions; i2, >5 aphthous lesions or anastomotic ulcer <1 cm; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; i4, diffuse inflammation with large ulcers, nodules, and/or narrowing.

intestinal resection. This may account for the difference in the placebo clinical recurrence rate before or at week 76 in PREVENT (20.0%) and the 12-month rate reported previously (38.5%).[19]

It should be noted that although the risk factors for postoperative recurrence, that is, cigarette smoking,

recurrent surgery, and penetrating disease, have been included in numerous previous studies,[4,26,30–35] these factors have never been formally validated or replicated. Likewise, the combination of factors would presume a higher risk of postoperative recurrence; this additive effect has also not been replicated. Therefore, the stratification of risk based on the small sample size of the Regueiro trial may have resulted in an overestimation of effect in PREVENT.

The low baseline median CDAI score of 105.5 required many patients to double their CDAI score during the course of the study to meet the clinical recurrence criterion of CDAI ≥200. This possibly contributed to the small proportions of patients (infliximab, 4.1%; placebo, 9.3%) who met both CDAI and endoscopic criteria for clinical recurrence before or at week 76. Furthermore, only 17.5% of patients received concomitant immunosuppressives compared with 45.8% of patients in the Regueiro trial.[19] Administration of immunosuppressives increases infliximab levels, reduces immunogenicity, and increases efficacy of infliximab.[39]

Patients in PREVENT underwent a video ileocolonoscopy at week 76, when CDAI criteria met the definition of clinical recurrence, or when they discontinued the study. Week 76, rather than week 24 or 48, was selected as the primary time point due to the combined clinical and endoscopic end point. Clinical recurrence within the first year after resection is low, as endoscopic recurrence often occurs initially without clinical symptoms.[3,40–43]

We hypothesized that waiting 18 months after resection for primary composite end point assessment would be sufficient to detect clinical recurrence without endoscopic recurrence causing severe, irreversible bowel damage. Additionally, when the PREVENT study was designed (2009), only one small proof-of-concept study[19] and an open-label experience[18] in postoperative patients with CD treated with anti-TNF therapies were published to guide the timing and definition of clinical end points.

Our selection of a composite end point appeared to be supported by a subsequent publication by Walters et al,[44] who explored the utility of the CDAI in determining symptomatic disease recurrence in patients having previously undergone ileocolonic resection for CD, and concluded that "a combination of symptom assessment plus endoscopic evidence of recurrence should remain the gold standard definition for assessing outcomes in postoperative CD trials." However, it must be acknowledged that the composite end point prospectively implemented here was not formally validated in this clinical setting.

Because early endoscopic recurrence appears to correlate with future clinical recurrence and the need for resection,[3] it is currently recommended that patients with CD undergo a surveillance ileocolonoscopy 6 to 12 months postoperatively to assess for endoscopic recurrence.[40–43] Recent studies have suggested that TNF-antagonists are effective in this setting based on therapy adjusted according to 6-month postoperative colonoscopy findings.[26–28]

There are limitations to the study. Infliximab might have been started as late as 45 days after resection, by which

Table 3. Key Safety Findings Through Week 104 for Treated Patients

			Infliximab (dose increase)		
Variable	Placebo[a] (N = 146)	Infliximab, 5 mg/kg[a,b] (N = 145)	Placebo/infliximab, 5 mg/kg[c] (n = 25)	Infliximab 5 mg/kg/infliximab, 10 mg/kg[c] (n = 9)	All infliximab[d] (N = 170)
Mean duration of follow-up, *wk*	85.4	85.7	50.6	39.4	82.6
Mean duration of treatment, *wk*	75.9	74.3	32.4	13.9	68.9
Patients with ≥1 adverse events, n (%)	132 (90.4)	133 (91.7)	19 (76.0)	7 (77.8)	152 (89.4)
Patients with ≥1 serious adverse events, n (%)	32 (21.9)	28 (19.3)	3 (12.0)	2 (22.2)	32 (18.8)
Patients who discontinued study agent because of ≥1 adverse events, n (%)	13 (8.9)	35 (24.1)	10 (40.0)	5 (55.6)	50 (29.4)
Patients who died, n (%)	1 (0.7)	0	0	0	0
Patients with 1 or more malignancies,[e] n (%)	2 (1.4)	0	0	0	0
Patients with ≥1 infections, n (%)	85 (58.2)	84 (57.9)	8 (32.0)	4 (44.4)	93 (54.7)
Patients with ≥1 serious infections, n (%)	9 (6.2)	7 (4.8)	1 (4.0)	1 (11.1)	9 (5.3)
Patients with ≥1 infusion reaction,[f] n (%)	12 (8.2)	26 (17.9)	7 (28.0)	1 (11.1)	33 (19.4)

[a]Includes data up to the time of dose increase for those who increased dose. Six patients were randomized but not treated and analyzed for efficacy only, and 2 patients inadvertently received infliximab 5 mg/kg and analyzed for safety as infliximab-treated patients.
[b]Two patients were randomized to the placebo group, but received one infusion of infliximab. These patients were analyzed in the infliximab 5 mg/kg group for safety.
[c]Includes data from the time of dose increase onward.
[d]Includes data from the time of the first infliximab dose onward.
[e]Malignancies excluding nonmelanoma skin cancers were defined by individual event terms in neoplasms benign, malignant, and unspecified (including cysts and polyps) system organ class.
[f]An infusion reaction was defined as any adverse event that occurred during or within 1 hour of the administration of the study agent infusion.

time there could have been early endoscopic recurrence. This would mean that treatment was initiated in response to active inflammation rather than prevention of CD recurrence. The rationale for waiting 45 days was to ensure at least 14 to 21 days passed with no surgical resection complication, and to allow enough time for the CDAI collection and additional patient screening. The median time between resection and first study infusion was 36.5 days for placebo and 35 days for infliximab 5 mg/kg, and is unlikely to have altered the results significantly. While we designed the study to use every-8-weeks maintenance infusions after resection, it is possible that the 3-dose induction and concomitant use of immunosuppressants could have led to even lower recurrence rates, as described previously,[40] and reduced immunogenicity.

While prevention of clinical recurrence was not achieved, infliximab-treated patients achieved a lower endoscopic recurrence rate than those assigned to placebo. Consistent with other studies using anti-TNF therapies,[17,18,25,45] infliximab-treated patients had lower recurrence defined by endoscopic criteria only.

The primary end point of clinical recurrence may be influenced by symptom-based CDAI score, which consists of diarrhea, abdominal pain, and general well-being components that might be neither sensitive nor specific for mucosal inflammation, which is integral to disease recurrence.[46] Regueiro and colleagues[47] also found no correlation between CDAI scores and endoscopic disease activity 1 year after ileocolonic resection, with the majority of patients in clinical remission (CDAI <150) despite endoscopic recurrence.

The severity of endoscopic recurrence has a high predictive value for the need for future resection.[3,48] If the goal of mucosal healing and maintenance of intestinal normalcy, rather than symptom control alone, are relevant inflammatory bowel disease management targets, then a postoperative strategy for prevention of endoscopic recurrence may be clinically relevant, especially for high-risk patients.[49,50] Given the high rates of clinically silent, but endoscopically active, CD within 2 years of resection, we suggest that future postoperative studies utilize objective rather than subjective criteria for active CD, and have the primary assessment no more than 1 year after resection.

A postoperative strategy of escalating treatment for endoscopic recurrence at 6 months was evaluated in the POCER (Post-Operative Crohn's Disease Endoscopic Recurrence) study.[28] Patients were risk-stratified (high vs low) for CD recurrence then randomized to have an initial colonoscopy at 6 months or no colonoscopy until 18 months. All patients received 3 months of metronidazole, if tolerated, and high-risk patients were treated with postoperative thiopurine, or if previously intolerant, adalimumab. Patients undergoing a 6-month colonoscopy were

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started on or received additional treatment for endoscopic recurrence. The primary end point of the POCER study was postoperative endoscopic recurrence at 18 months. The 18-month endoscopic recurrence rate in patients previously undergoing a colonoscopy at 6 months was 49% compared with 67% in those who had not had a 6-month colonoscopy. The 6-month endoscopic recurrence rate in high-risk patients receiving thiopurine was 45% compared with 21% with anti-TNF therapy and is similar to the 18-month endoscopic recurrence rate in the PREVENT trial (51.3% in placebo and 22.4% in infliximab). Therefore, it may be reasonable to approach low-risk patients undergoing their first resection for CD conservatively and initiate treatment only if there is endoscopic recurrence at 6 months. High-risk patients with recurrent intestinal resection for CD should be considered for postoperative anti-TNF therapy.

In conclusion, infliximab was not significantly superior for prevention of clinical recurrence after CD ileocolonic resection, but did reduce endoscopic recurrence.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.02.072.

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Conflicts of interest

Funding