

## ORIGINAL ARTICLE

# Infliximab Maintenance Therapy for Fistulizing Crohn's Disease

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## ABSTRACT

**BACKGROUND**

Infliximab, a monoclonal antibody against tumor necrosis factor, is an effective maintenance therapy for patients with Crohn's disease without fistulas. It is not known whether infliximab is an effective maintenance therapy for patients with fistulas.

**METHODS**

We performed a multicenter, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of infliximab maintenance therapy in 306 adult patients with Crohn's disease and one or more draining abdominal or perianal fistulas of at least three months' duration. Patients received 5 mg of infliximab per kilogram of body weight intravenously on weeks 0, 2, and 6. A total of 195 patients who had a response at weeks 10 and 14 and 87 patients who had no response were then randomly assigned to receive placebo or 5 mg of infliximab per kilogram every eight weeks and to be followed to week 54. The primary analysis was the time to the loss of response among patients who had a response at week 14 and underwent randomization.

**RESULTS**

The time to loss of response was significantly longer for patients who received infliximab maintenance therapy than for those who received placebo maintenance (more than 40 weeks vs. 14 weeks,  $P < 0.001$ ). At week 54, 19 percent of patients in the placebo maintenance group had a complete absence of draining fistulas, as compared with 36 percent of patients in the infliximab maintenance group ( $P = 0.009$ ).

**CONCLUSIONS**

Patients with fistulizing Crohn's disease who have a response to induction therapy with infliximab have an increased likelihood of a sustained response over a 54-week period if infliximab treatment is continued every 8 weeks.

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**F**ISTULAS OCCUR IN 17 TO 43 PERCENT OF patients with Crohn's disease.<sup>1,2</sup> Perianal fistulas, the most common variant, decrease the quality of life and increase the likelihood of total colectomy.<sup>3</sup> Although widely used in the treatment of fistulas, antibiotics, immunomodulators, and dietary therapies have not been demonstrated to result in sustained closure of fistulas in Crohn's disease.<sup>4-9</sup> Surgical options are limited by the potential for compromise of anal continence. Surgical diversion of the fecal stream by a stoma often produces healing; however, many patients find a stoma to be undesirable, and the benefit of this approach is unlikely to endure once bowel continuity is restored.<sup>10</sup>

Infliximab, a monoclonal antibody against tumor necrosis factor (TNF), is an effective maintenance therapy in patients with luminal Crohn's disease without fistulas.<sup>11</sup> Although a short-term trial demonstrated that infliximab closed the fistulas in patients with fistulizing Crohn's disease, the median duration of response was 12 weeks.<sup>12</sup>

The ACCENT II trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn's Disease) evaluated the efficacy and safety of repeated infusions of infliximab in maintaining closure of draining fistulas among patients who had a response to a three-dose induction regimen of infliximab.

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## METHODS

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### PATIENTS

This multicenter, randomized, double-blind trial was conducted at 45 sites: 34 in North America, 9 in Europe, and 2 in Israel. The first patient was enrolled on January 21, 2000, and the last completed visit occurred on October 17, 2001. The institutional review board at each participating site approved the protocol. Written informed consent was obtained from all patients.

The members of the ACCENT II steering committee and Centocor staff members designed the study. The academic authors participated in data analysis and interpretation and had access to all the data. The article was written by a writing committee, which included authors from academic institutions and Centocor. No limits were placed on publication.

Eligible patients included men and women (patients 18 years of age or older) with Crohn's disease who had had single or multiple draining fistulas, including perianal fistulas and enterocutaneous fistu-

las, for at least three months. Women with rectovaginal fistulas were included if they had at least one other enterocutaneous draining fistula. Setons<sup>13</sup> were permitted at screening but were required to be removed by week 2. Concurrent therapies for Crohn's disease, including stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, methotrexate, and antibiotics, were permitted. Patients were excluded from the study if they had a stricture or abscess for which surgery might be indicated or if they had previously been treated with infliximab.

### STUDY DESIGN

Patients were screened for eligibility two weeks before enrollment. All eligible patients received an intravenous infusion of infliximab (Remicade, Centocor) at a dose of 5 mg per kilogram of body weight at weeks 0, 2, and 6. A response<sup>12</sup> was defined as a reduction of at least 50 percent from base line in the number of draining fistulas at consecutive visits four or more weeks apart. A patient was classified as having a response if a response was observed at both weeks 10 and 14. At week 14, those with a response were randomly assigned to receive an infusion of either placebo (placebo maintenance) or 5 mg of infliximab per kilogram (infliximab maintenance) at weeks 14, 22, 30, 38, and 46 and were followed until week 54. A computer-generated adaptive randomization scheme was used, which included the study site, the number of draining fistulas at base line (one vs. more than one), and the presence or absence of active bowel disease at base line (active bowel disease was considered to be present if the Crohn's Disease Activity Index<sup>14</sup> was at least 150) as stratification factors. Patients without a response were also randomly assigned to a maintenance regimen of either placebo or infliximab to permit a secondary analysis of the proportion of patients who had a response to continued treatment after having had no response to the initial treatment. A pharmacist prepared each infusion of infliximab or an identical-appearing placebo. Neither the patients nor the study investigators were aware of the treatment assignment. The dose of all concomitantly taken medications remained constant except for that of corticosteroids, which was to be tapered according to a defined schedule.<sup>11</sup>

Loss of response was defined by the recrudescence of draining fistulas, the need for a change in medication for Crohn's disease or the need for additional therapy for persistent or worsening luminal

disease activity, the need for a surgical procedure for Crohn's disease, or the discontinuation of the study medication owing to a perceived lack of efficacy. A complete response was defined as the absence of draining fistulas. Beginning at week 22, patients receiving placebo maintenance who had a loss of response were eligible to cross over to maintenance treatment with 5 mg of infliximab per kilogram, and patients in the infliximab maintenance group could cross over to treatment with 10 mg of infliximab per kilogram. Crossovers were masked so that patients and physicians remained unaware of the treatment assignment.

#### FOLLOW-UP SCHEDULE AND SAFETY AND EFFICACY EVALUATIONS

Patients were assessed at weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, and 54. Fistula examinations were conducted at each visit. The Crohn's Disease Activity Index was determined at weeks 0, 14, 30, and 54; scores range from 0 to 600, with higher scores indicating more severe disease activity. The Inflammatory Bowel Disease Questionnaire<sup>15</sup> was administered to assess the health-related quality of life at weeks 0, 2, 10, 14, 30, and 54. Scores can range from 32 to 224, and higher scores indicate a better quality of life. Data for all 282 randomized patients were included in the safety analysis. At each visit, adverse events were ascertained and samples were collected for laboratory evaluations.

#### STATISTICAL ANALYSIS

The primary analysis evaluated with the use of life-table methods the time to the loss of response among patients with a response at randomization. Since fistula examinations occurred only during study visits, so-called interval censoring was used for patients categorized as having a loss of response resulting from the recrudescence of fistulas, which used the interval between the last study visit at which the patient was found to have a response and the first visit at which a loss of response was noted. The log-rank test for grouped data was used to test the hypothesis that the outcome in the two groups would not differ significantly. A two-sided test was performed with an alpha level of 0.05. The data were analyzed according to the intention-to-treat principle. Data for patients who crossed over from placebo to infliximab were censored before crossover occurred. A response in disease activity was defined as a reduction from a base-line Crohn's Disease Activity Index score of 220 or higher by at least 25 per-

cent and 70 points. The last-value-carried-forward method was used for analyses involving the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire. The chi-square test or Fisher's exact test and analysis of variance for van der Waerden normal scores were used as appropriate to provide nominal P values for secondary end points. All statistical analyses were performed with SAS software, version 8.0.

## RESULTS

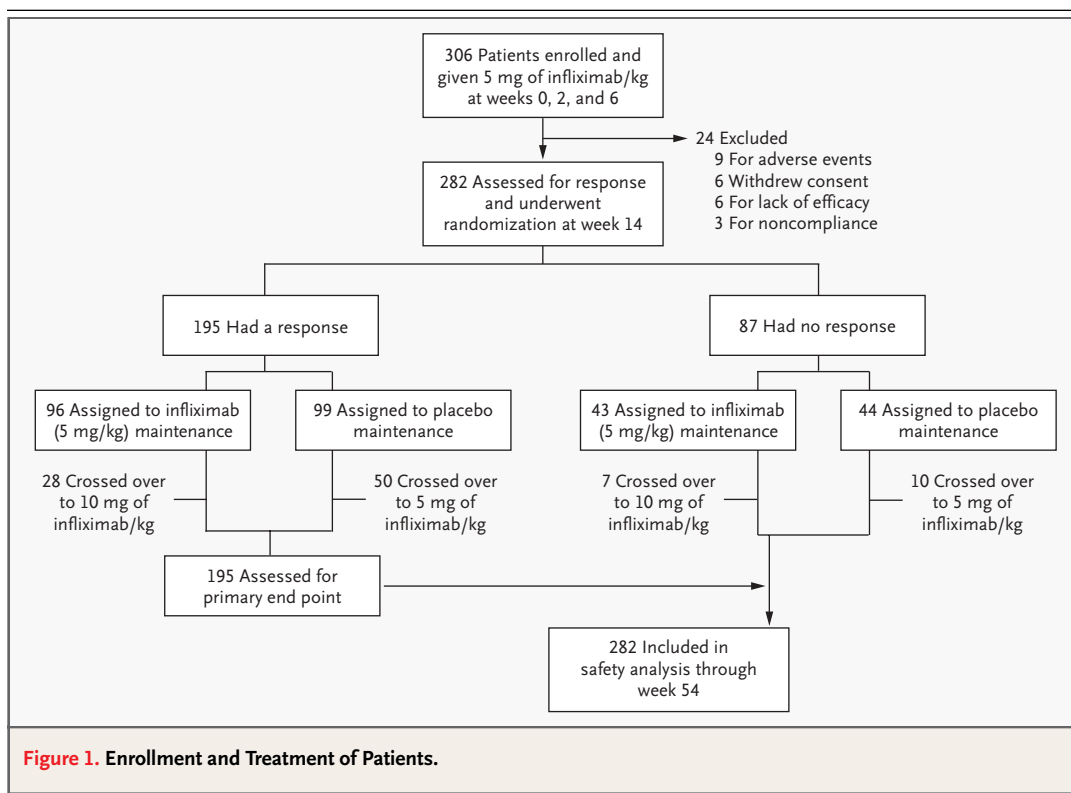
#### CHARACTERISTICS OF THE PATIENTS AND RESPONSE TO THE INDUCTION REGIMEN

Of 306 patients enrolled, 282 received 5 mg of infliximab per kilogram on weeks 0, 2, and 6 and were available for randomization at week 14 (Fig. 1). The 195 patients with a response were randomly assigned at week 14 to receive placebo maintenance (99 patients) or infliximab maintenance (96 patients). The remaining 87 patients, who had no initial response to infliximab administration, were also randomly assigned to receive placebo maintenance (44 patients) or infliximab maintenance (43 patients). The base-line characteristics of the patients who were classified as having a response at randomization were similar to those of patients classified as having no response (Table 1). The onset of response was rapid, with an increase in the response rate after each of the three induction infusions. Before randomization, a complete response was observed in 31 percent of patients (95 of 306) at week 2, 43 percent (130 of 305; 1 patient discontinued treatment before the third dose) at week 6, and 48 percent (147 of 305) at week 14.

#### EFFICACY

##### *Patients with a Response*

Among patients who had a response at the time of randomization, those assigned to receive infliximab maintenance therapy had a significantly longer time to the loss of response than those who received placebo ( $P < 0.001$ ) (Fig. 2A). After randomization, the median time to the loss of response was 14 weeks in the placebo maintenance group, as compared with more than 40 weeks in the infliximab maintenance group. Overall, 61 patients (62 percent) in the placebo maintenance group had a loss of response, as compared with 40 patients (42 percent) in the infliximab maintenance group. In both groups, the most common criterion met for the loss of response was a need for a change in the treatment of Crohn's



**Figure 1. Enrollment and Treatment of Patients.**

disease (38 percent of the placebo maintenance group and 25 percent of the infliximab maintenance group) — predominantly antibiotics or corticosteroids — followed by the recrudescence of fistulas (22 percent and 16 percent, respectively). One patient in the infliximab maintenance group required surgery — a small-bowel resection on day 340 — and one patient in the placebo maintenance group discontinued the study drug because of a lack of efficacy.

At week 54, 23 percent of patients in the placebo maintenance group still had a response (23 of 98), as compared with 46 percent of patients in the infliximab maintenance group (42 of 91,  $P=0.001$ ). In a multivariate regression model, no base-line characteristics were independent predictors of a sustained response at week 54. At week 54, 19 percent of patients in the placebo maintenance group had a complete response (19 of 98), as compared with 36 percent of patients in the infliximab maintenance group (33 of 91,  $P=0.009$ ) (Fig. 2B).

Among the patients who had a response at the time of randomization and who had a base-line Crohn's Disease Activity Index score of 220 or higher, 6 percent of patients in the placebo maintenance

group had a response in disease activity at week 54 (2 of 31), as compared with 36 percent of patients in the infliximab maintenance group (12 of 33,  $P=0.004$ ). Among all randomized patients, the median decreases from the base-line score at weeks 30 and 54 were 16 and 15, respectively, in the placebo maintenance group and 42 and 40, respectively, in the infliximab maintenance group ( $P=0.004$  and  $P=0.04$  for the comparisons between groups at weeks 30 and 54, respectively). The median increases from base line in the score for the Inflammatory Bowel Disease Questionnaire at weeks 30 and 54 were 4 and 5, respectively, in the placebo maintenance group and 14 and 10, respectively, in the infliximab maintenance group ( $P=0.002$  and  $P=0.03$  for the comparisons between groups at weeks 30 and 54, respectively).

#### *Patients with No Response*

Among the patients who had no response at the time of randomization, 7 of 44 patients who subsequently received placebo had a response (16 percent), as compared with 9 of 43 patients who subsequently received infliximab (21 percent,  $P=0.6$ ).

**Table 1. Base-Line Characteristics of the Patients Who Had a Response and Those Who Had No Response at the Time of Randomization.**

Characteristic	Response and Assignment to Placebo Maintenance (N=99)	Response and Assignment to Infliximab Maintenance (N=96)	P Value*	No Response (N=87)
Male sex — no. (%)	48 (48)	53 (55)	0.35	43 (49)
Age — yr			1.00	
Median	36	37		40
Interquartile range	29–46	28–47		31–48
Disease duration — yr			0.85	
Median	12.3	10.5		11.7
Range	0.5–31.6	0.2–32.2		0.3–49.8
Involved intestinal area — no. (%)				
Ileum	16 (16)	18 (19)	0.71	14 (16)
Colon	30 (30)	34 (35)	0.54	28 (32)
Ileum and colon	53 (54)	44 (46)	0.32	45 (52)
Previous segmental resection — no. (%)	54 (55)	55 (57)	0.70	47 (54)
Crohn's Disease Activity Index — total no. (%) <sup>†</sup>				
Score ≥150	57 (59)	57 (59)	0.97	56 (64)
Score ≥220	31 (32)	33 (34)	0.72	30 (34)
IBDQ score <sup>‡</sup>			0.16	
Median	168	155		161
Interquartile range	145–193	135–187		136–176
C-reactive protein — mg/dl			0.17	
Median	0.7	0.6		0.9
Interquartile range	0.4–2.2	0.4–1.5		0.5–2.1
Concomitant medication — no. (%)				
5-Aminosalicylates (oral or rectal)	49 (49)	41 (43)	0.34	42 (48)
Mercaptopurine or azathioprine	35 (35)	29 (30)	0.44	28 (32)
Methotrexate	2 (2)	1 (1)	1.00	2 (2)
Antibiotics	26 (26)	28 (29)	0.35	29 (33)
Corticosteroids				
Any	30 (30)	25 (26)	0.51	26 (30)
>20 mg per day	8 (8)	8 (8)	1.00	7 (8)
Prior medication — no. (%)				
Antibiotics	92 (93)	92 (96)	0.38	80 (92)
Mercaptopurine or azathioprine	63 (64)	69 (72)	0.22	53 (61)
Cyclosporine or tacrolimus	7 (7)	3 (3)	0.21	7 (8)
Methotrexate	8 (8)	5 (5)	0.42	11 (13)
Fistula location — no. (%)				
Perianal	86 (87)	89 (93)	0.18	71 (82)
Abdominal	15 (15)	7 (7)	0.08	17 (20)
Rectovaginal	6 (6)	10 (10)	0.27	9 (10)
Draining fistulas			0.58	
Median	2	2		2
Range	1–11	1–6		1–8
No. (%) with 1 fistula	42 (42)	38 (40)	0.69	43 (49)
No. (%) with >1 fistula	57 (58)	58 (60)		44 (51)
Smoking history — no. (%)				
Nonsmoker	41 (41)	34 (35)	0.24	32 (37)
Former smoker	20 (20)	19 (20)	0.86	30 (34)
Current smoker	38 (38)	43 (45)	0.66	25 (29)

\* P values are for the comparison of patients with a response who were randomly assigned to placebo maintenance with patients with a response who were randomly assigned to infliximab maintenance.

<sup>†</sup> Scores for the Crohn's Disease Activity Index can range from 0 to 600; higher scores indicate more severe disease activity. Data were missing for two patients in the placebo maintenance group.

<sup>‡</sup> Scores for the Inflammatory Bowel Disease Questionnaire (IBDQ) can range from 32 to 224; higher scores indicate a better quality of life.

*Crossover Treatment*

Among randomized patients with a response during maintenance therapy who subsequently lost their response because of a recrudescence of draining fistulas, 61 percent of patients (25 of 41) who crossed over from placebo maintenance to infliximab (5 mg per kilogram) maintenance reestablished a response. Similarly, 57 percent of patients (12 of 21) reestablished a response on crossing over from an infliximab dose of 5 mg per kilogram to a dose of 10 mg per kilogram.

**ANTIBODIES AGAINST INFLIXIMAB**

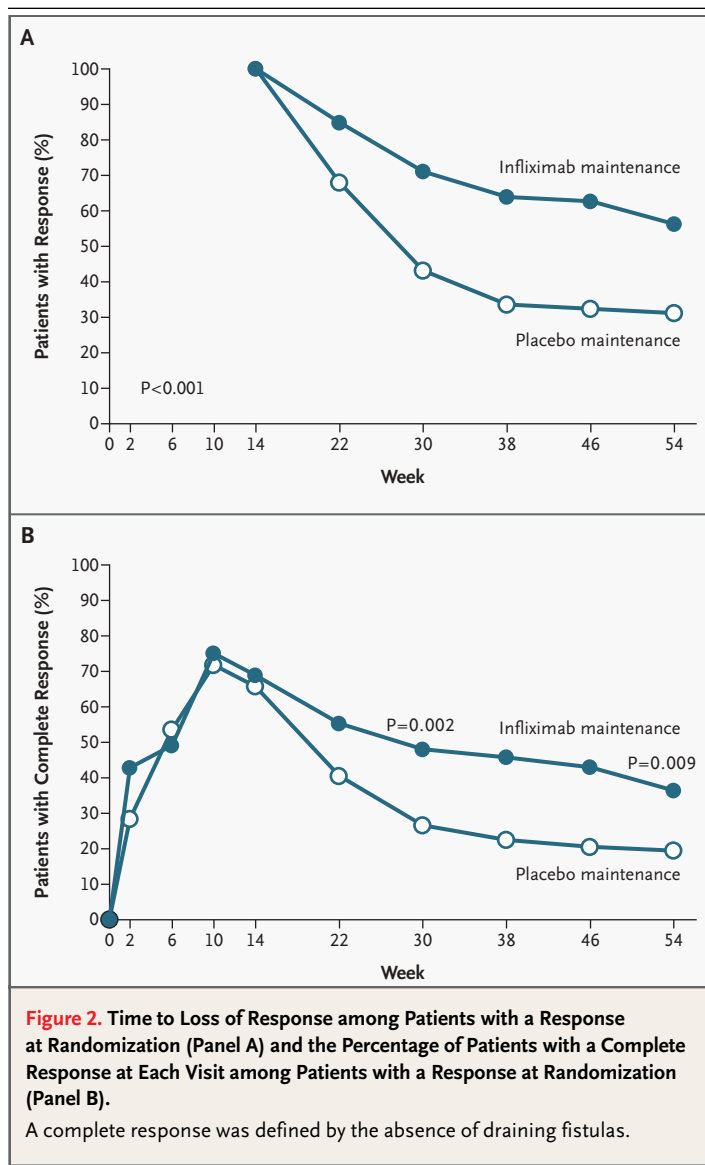
Response rates were similar among patients with antibodies against infliximab (32 percent), those without antibodies (31 percent), and those with inconclusive antibody tests (29 percent). In contrast to the absence of an association between antibody status and efficacy, patients who were positive for antibodies against infliximab were two to three times as likely to have infusion reactions as those who were negative or who had inconclusive results (Table 2).

The concomitant administration of corticosteroids and immunomodulators at base line appeared to prevent the development of antibodies against infliximab. Antibodies developed in 1 of the 27 patients receiving corticosteroids in combination with immunomodulators (4 percent), as compared with 6 of 46 patients receiving corticosteroids alone (13 percent), 7 of 62 patients receiving immunomodulators alone (11 percent), and 30 of 123 patients receiving neither corticosteroids nor immunomodulators (24 percent).

**SAFETY**

Adverse events occurred in 92 percent of patients in the placebo maintenance group and 89 percent of patients in the infliximab maintenance group. Few patients discontinued treatment because of an adverse event (8 percent of patients in the placebo maintenance group and 4 percent of those in the infliximab maintenance group). The most frequently reported adverse events in both groups were similar in nature and incidence to those described previously in patients with Crohn's disease.<sup>14,16</sup> Slightly more patients assigned to placebo maintenance than to infliximab maintenance reported a new fistula-related abscess (Table 3).

The most frequently reported serious adverse events were related to the gastrointestinal system. Worsening of Crohn's disease was the most com-



mon individual serious adverse event, occurring in 6 percent of all randomized patients. No deaths or cancers occurred during the study; however, two deaths have been reported during the long-term follow-up. One patient (a 78-year-old woman) died of sepsis related to advanced Crohn's disease approximately nine months after her last (fourth) study infusion of infliximab. She also received an infusion of infliximab seven months before her death. The other patient (a 52-year-old man) died from multisystem organ failure (heart failure, pneumonia, renal failure, and amyloidosis) 18 months after receiving the three-dose induction regimen of infliximab. This patient did not receive any additional infliximab.

**Table 2. Incidence of Infusion Reactions According to Infliximab Antibody Status up to Week 54.\***

Variable	Antibody Status			All Patients
	Positive†	Negative‡	Inconclusive§	
No. of patients with appropriate samples who could be evaluated (%)¶	44 (17)	80 (31)	134 (52)	258 (100)
Infusion reaction				
No. of patients/total no. (%)	13/44 (30)	13/80 (16)	15/134 (11)	41/258 (16)
No. of infusions/total no. (%)	20/226 (9)	16/332 (5)	24/971 (2)	60/1529 (4)

\* An infusion reaction was defined as any adverse event that occurred during or within one hour after infusion. Samples for the measurement of antibodies against infliximab were collected before the infusion at weeks 0, 14, 30, and 54 and were measured as previously described.<sup>11</sup>

† The analysis includes all patients with appropriate samples who had at least one positive sample at any time.

‡ The analysis includes all patients with appropriate samples who had a negative sample after the last infusion, excluding patients who had a positive sample at any time.

§ The analysis includes all patients with appropriate samples who had only inconclusive samples (samples with detectable infliximab concentration) after the last infusion, excluding those who had a positive sample at any time.

¶ Patients with appropriate samples either had antibodies against infliximab at some time after the first infusion or had one or more samples obtained after the last infusion.

Two cases of cancer have also been reported during long-term follow-up. One patient (a 42-year-old man with a 20-year history of colonic Crohn's disease) received a diagnosis of rectal carcinoma approximately 2 years after his last infliximab infusion. The second patient (a 36-year-old man with a 22-year history of ileal Crohn's disease and perianal fistula) received a diagnosis of rectal adenocarcinoma approximately 19 months after his last (sixth) infliximab infusion.

Multiple sclerosis developed in one patient who was assigned to placebo maintenance, approximately one month after an infliximab infusion that was not related to the study. Infections requiring antimicrobial treatment occurred in nearly one third of patients. Five percent of all randomized patients had a serious infection. The only serious infection reported in more than two patients was abscess. Opportunistic infections included one case of cytomegalovirus infection reported 39 days after the third induction infusion and one case of cutaneous nocardia infection reported 8 days after the first induction infusion.

The proportion of infusions accompanied by an infusion reaction was low. Infusion reactions occurred more frequently in association with infliximab infusions (70 of 1728 infusions [4 percent]) than with placebo infusions (4 of 419 infusions [1 percent],  $P < 0.001$ ). In general, the reactions were not severe enough to warrant the discontinuation of treatment, and only one infusion reaction met the definition for a serious adverse event.<sup>11</sup>

Patients assigned to infliximab maintenance therapy were more than twice as likely to have antinuclear antibodies and nearly four times as likely to have antibodies against double-stranded DNA than patients assigned to placebo maintenance. A lupus-like syndrome developed in one patient; however, the results of tests for antinuclear antibodies and antibodies against double-stranded DNA were negative in this patient.

## DISCUSSION

Fistulas remain a common yet challenging complication of Crohn's disease, causing complications that are distinct from the major manifestations of diarrhea and abdominal pain. Our results indicate that maintenance treatment with infliximab every eight weeks is superior to a placebo infusion in patients who had a response to induction infliximab infusions at weeks 0, 2, and 6. Nearly twice as many patients who received infliximab maintenance therapy, as compared with placebo maintenance therapy, had complete and durable closure of fistulas over the 54-week study. In addition, as previously reported in patients with Crohn's disease without fistulas,<sup>11</sup> superior control of disease activity and an improved quality of life were associated with infliximab maintenance therapy.

Our findings have important implications for the care of patients with fistulizing Crohn's disease. We confirmed that the onset of fistula response to infliximab is rapid. With infliximab maintenance ther-

**Table 3. Summary of Safety Analysis for All Randomized Patients up to Week 54.\***

Variable	Placebo Maintenance (N=144)	Infliximab Maintenance (N=138)	Total (N=282)	P Value†
Extent of infliximab exposure over 54-wk period				
No. of infliximab infusions	4.3±1.7	7.5±1.3	5.9±2.2	<0.001
Total dose — mg/kg	21.4±8.3	41.1±10.9	31.1±13.8	<0.001
Adverse events leading to discontinuation of study agent — no. of patients (%)	12 (8)	5 (4)	17 (6)	0.1
Serious adverse events — no. of patients (%)				
All events	33 (23)	19 (14)	52 (18)	0.05
Reasonably related events‡	9 (6)	3 (2)	12 (4)	0.09
Infections — no. of patients (%)				
Infections requiring antimicrobial treatment§	39 (27)	47 (34)	86 (30)	0.20
Serious infections¶	9 (6)¶	4 (3)¶	13 (5)	0.18
New fistula-related abscesses — no. of patients (%)	25 (17)	17 (12)	42 (15)	0.25
Infusion reactions — no. of patients (%)**	24 (17)	22 (16)	46 (16)	
During induction	11 (8)	9 (7)	20 (7)	
During maintenance	4 (3)	13 (9)	NA	0.02
During treatment after crossover††	14 (23)	3 (9)	17 (18)	
Development of antinuclear antibodies — no. of patients/total no. (%)‡‡	24/132 (18.2)	56/122 (45.9)	80/254 (31.5)	<0.001
Development of antibodies against double-stranded DNA — no. of patients/total no. (%)§§	8/127 (6.3)	27/116 (23.3)	35/243 (14.4)	<0.001

\* Plus-minus values are means ±SD.

† P values are for the comparison between the placebo maintenance and infliximab maintenance groups.

‡ Events deemed by the investigator to be possibly, probably, or definitely related to the study agent (or that had an unknown relation) were recorded as "reasonably related."

§ The analysis does not include one patient who was found to have a positive skin test with purified protein derivative (who was asymptomatic and had negative findings on chest radiography) before the week 30 infusion. Isoniazid therapy was initiated, and the patient subsequently received all remaining study infusions.

¶ The analysis includes three patients with an intraabdominal abscess, one patient with parastomal and retroperitoneal abscesses, and one patient with parastomal and perianal abscesses.

¶ The analysis includes one patient with an ischioanal abscess and one patient with a perianal abscess.

\*\*Some patients had infusion reactions during more than one period.

††A total of 60 patients in the placebo maintenance group crossed over to receive 5 mg of infliximab per kilogram, and 35 patients in the infliximab maintenance group crossed over to receive 10 mg of infliximab per kilogram.

‡‡Among patients with antinuclear antibodies who were evaluated at base line and at week 54, 132 were assigned to the placebo maintenance group and 122 were assigned to the infliximab maintenance group.

§§Among patients with antibodies against double-stranded DNA who were evaluated at base line and at week 54, 127 were assigned to the placebo maintenance group and 116 were assigned to the infliximab maintenance group.

apy, sustained closure of fistulas was observed in patients who had had no response to treatment with other agents.

An alternative approach to maintenance therapy is intermittent treatment with infliximab when there is loss of response, as defined by the recrudescence of fistulas. Although we did not examine this strategy directly, patients who had an initial response to infliximab and who were then assigned to placebo maintenance were permitted to cross over to infliximab maintenance if they had disease flare. Although 61 percent of these patients reestablished a response, they had a temporary increase in disease

activity and a decrease in the quality of life. In addition, intermittent therapy may predispose patients to the formation of antibodies against infliximab and may increase the likelihood of the loss of response.<sup>17</sup> For these reasons, we believe that fixed-interval maintenance therapy is the optimal choice for this group of patients.

Our findings also suggest that many patients who have a loss of response during maintenance therapy with 5 mg of infliximab per kilogram may again have a response when the dose is increased to 10 mg per kilogram every eight weeks. It is important to note that we found that patients who did

not have a response to induction therapy were unlikely to have a response to continued maintenance treatment.

Patients with fistulas tolerated infliximab maintenance therapy well. Although all patients received infliximab induction therapy, more patients assigned to placebo maintenance than to infliximab maintenance therapy discontinued treatment because of adverse events.

The proportion of patients in whom antibodies against infliximab developed was similar to that in other studies of this agent.<sup>11</sup> However, more than half of patients had inconclusive results of assays to detect antibodies against infliximab. The presence of antibodies was associated with a higher incidence of infusion reactions. No association was observed between antibodies against infliximab and closure of fistulas.

Fistula-related abscesses were uncommon despite concern that this might occur as a result of the recurrence of inflammation beneath a superficially healed fistula tract. Others have reported radiographic evidence of persistent fistula tracts in patients who have a clinical response to infliximab.<sup>16,18</sup> These observations, along with the high rate of recurrent drainage of fistulas after the cessation of infliximab induction therapy, suggest that infliximab suppresses the inflammatory factors associated with disease activity and fistula drainage but may not eradicate these epithelialized tracts.

Infection remains an important consideration in assessing the risk-benefit ratio of infliximab maintenance therapy, with important consequences for those at risk for intracellular pathogens, particularly tuberculosis.<sup>19</sup> It is noteworthy that one of our patients had cytomegalovirus infection and another had cutaneous nocardia. Another important safety consideration is the possibility of autoimmune phenomena, including drug-induced lupus and demyelinating disease. Although there is no clear evi-

dence to date that anti-TNF therapy is a risk factor for cancer, the possibility has not been excluded.<sup>20-22</sup> Clinicians need to maintain a high index of suspicion for these conditions, as well as abscess, to ensure early detection and treatment.

In conclusion, among patients with fistulizing Crohn's disease whose fistulas closed after infliximab induction therapy, continued infliximab infusions at fixed intervals maintained closure for a longer period than did placebo infusions.

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#### APPENDIX

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## REFERENCES

1. Sands BE. Crohn's disease. In: Feldman M, Friedman LS, Sleisenger MH, eds. *Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management*. 7th ed. Vol. 2. Philadelphia: Saunders, 2002:2005-38.
2. Schwartz DA, Pemberton JH, Sandborn WJ. Diagnosis and treatment of perianal fistulas in Crohn disease. *Ann Intern Med* 2001;135:906-18.
3. Lapidus A, Bernell O, Hellers G, Löfburg R. Clinical course of colorectal Crohn's disease: a 35-year follow-up study of 507 patients. *Gastroenterology* 1998;114:1151-60.
4. Schneider MU, Laudage G, Guggenmoos-Holzmann I, Riemann JF. Metronidazol in der Behandlung des Morbus Crohn: Ergebnisse einer kontrollierten randomisierten prospektiven studie. *Dtsch Med Wochenschr* 1985;110:1724-30.
5. Jakobovits J, Schuster MM. Metronidazole therapy for Crohn's disease and associated fistulae. *Am J Gastroenterol* 1984;79:533-40.
6. Egan LJ, Sandborn WJ, Tremaine WJ. Clinical outcome following treatment of refractory inflammatory and fistulizing Crohn's disease with intravenous cyclosporine. *Am J Gastroenterol* 1998;93:442-8.
7. Sandborn WJ, Present DH, Isaacs KL, et al. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. *Gastroenterology* 2003;125:380-8.
8. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine: a long-term, randomized, double-blind study. *N Engl J Med* 1980;302:981-7.
9. Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease: a meta-analysis. *Ann Intern Med* 1995;123:132-42.
10. Yamamoto T, Allan RN, Keighley MRB. Effect of fecal diversion alone on perianal Crohn's disease. *World J Surg* 2000;24:1258-63.
11. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541-9.
12. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-405.
13. Koganei K, Sugita A, Harada H, Fukushima T, Shimada H. Seton treatment for perianal Crohn's fistulas. *Surg Today* 1995;25:32-6.
14. Best WR, Beckett JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index: National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;70:439-44.
15. Irvine EJ, Feagan BG, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. *Gastroenterology* 1994;106:287-96.
16. van Bodegraven AA, Sloots CEJ, Felt-Bersma RJF, Meuwissen SGM. Endosonographic evidence of persistence of Crohn's disease-associated fistulas after infliximab treatment, irrespective of clinical response. *Dis Colon Rectum* 2002;45:39-46.
17. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601-8.
18. van Assche G, Vanbeckevoort D, Bielen D, et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. *Am J Gastroenterol* 2003;98:332-9.
19. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor  $\alpha$ -neutralizing agent. *N Engl J Med* 2001;345:1098-104.
20. Cohen RB, Dittrich KA. Anti-TNF therapy and malignancy — a critical review. *Can J Gastroenterol* 2001;15:376-84.
21. Bickston SJ, Lichtenstein GR, Arseneau KO, Cohen RB, Cominelli F. The relationship between infliximab treatment and lymphoma in Crohn's disease. *Gastroenterology* 1999;117:1433-7.
22. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002;46:3151-8.

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