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## INFLIXIMAB FOR THE TREATMENT OF FISTULAS IN PATIENTS WITH CROHN'S DISEASE

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### ABSTRACT

**Background** Enterocutaneous fistulas are a serious complication of Crohn's disease and are difficult to treat. Infliximab, a chimeric monoclonal antibody to tumor necrosis factor  $\alpha$ , has recently been developed as a treatment for Crohn's disease. We conducted a randomized, multicenter, double-blind, placebo-controlled trial of infliximab for the treatment of fistulas in patients with Crohn's disease.

**Methods** The study included 94 adult patients who had draining abdominal or perianal fistulas of at least three months' duration as a complication of Crohn's disease. Patients were randomly assigned to receive one of three treatments: placebo (31 patients), 5 mg of infliximab per kilogram of body weight (31 patients), or 10 mg of infliximab per kilogram (32 patients); all three were to be administered intravenously at weeks 0, 2, and 6. The primary end point was a reduction of 50 percent or more from base line in the number of draining fistulas observed at two or more consecutive study visits. A secondary end point was the closure of all fistulas.

**Results** Sixty-eight percent of the patients who received 5 mg of infliximab per kilogram and 56 percent of those who received 10 mg per kilogram achieved the primary end point, as compared with 26 percent of the patients in the placebo group ( $P=0.002$  and  $P=0.02$ , respectively). In addition, 55 percent of the patients assigned to receive 5 mg of infliximab per kilogram and 38 percent of those assigned to 10 mg per kilogram had closure of all fistulas, as compared with 13 percent of the patients assigned to placebo ( $P=0.001$  and  $P=0.04$ , respectively). The median length of time during which the fistulas remained closed was three months. More than 60 percent of patients in all the groups had adverse events. For patients treated with infliximab, the most common were headache, abscess, upper respiratory tract infection, and fatigue.

**Conclusions** Infliximab is an efficacious treatment for fistulas in patients with Crohn's disease. (N Engl J Med 1999;340:1398-405.)

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**C**ROHN'S disease is a chronic inflammatory bowel disease of unknown cause, which is characterized by segmental transmural inflammation and granulomatous lesions of the intestinal mucosa. The disease is complicated by the development of fistulas in approximately one third of patients.<sup>1</sup> Fistulas may be internal (e.g., bowel to

bowel, bowel to bladder, or rectovaginal) or enterocutaneous (extending through the abdominal wall or into the perineum). These fistulas rarely heal spontaneously or as a result of drug treatment and frequently require surgery. According to anecdotal evidence, antibiotics have short-term efficacy in their treatment. Although the use of immunomodulatory agents is associated with improvement and closure of fistulas, no significant effect has been demonstrated in prospective, placebo-controlled studies.<sup>2-4</sup>

The local production of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) is thought to have a key role in the initiation and propagation of Crohn's disease.<sup>5-7</sup> Production of TNF- $\alpha$  in the intestinal mucosa is increased in patients with Crohn's disease.<sup>7-9</sup> Neutralization of TNF- $\alpha$  has been suggested as a therapeutic intervention in inflammatory diseases, such as inflammatory bowel disease and rheumatoid arthritis.<sup>5,10</sup>

Infliximab (formerly known as cA2) is a genetically constructed IgG1 murine-human chimeric monoclonal antibody that binds both the soluble subunit and the membrane-bound precursor of TNF- $\alpha$ .<sup>11,12</sup> Infliximab inhibits a broad range of biologic activities of TNF- $\alpha$ , presumably by blocking the interaction of TNF- $\alpha$  with its receptors, and it may also cause lysis of cells that produce TNF- $\alpha$ .<sup>12,13</sup> Infliximab has been found to be efficacious and safe in the treatment of moderate-to-severe Crohn's disease in several clinical trials.<sup>14-17</sup> Anecdotal reports of the closure of fistulas in these trials prompted us to evaluate the efficacy of infliximab in healing enterocutaneous fistulas.

### METHODS

#### Patients

We enrolled patients who were 18 to 65 years of age and who had single or multiple draining abdominal or perianal fistulas of at least three months' duration as a complication of Crohn's disease that had been confirmed by radiography, endoscopy, or pathological examination. Patients could receive concomitant therapy. Acceptable regimens were aminosalicylates at a dosage that had been stable for more than four weeks before screening; oral cortico-

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Other participants in the study are listed in the Appendix.

steroids at a dosage of 40 mg or less per day that had been stable for more than three weeks; methotrexate given for at least three months at a dosage that had been stable for more than four weeks; azathioprine or mercaptopurine given for at least six months at a dosage that had been stable for more than eight weeks; and antibiotics at a dosage that had been stable for more than four weeks. If patients were not currently receiving treatment with any of these medications, they had to have discontinued therapy at least four weeks before enrollment. Patients treated concurrently with cyclosporine were excluded from the study. Treatment with investigational agents or the use of any medication to reduce the concentration of TNF- $\alpha$  was not allowed within three months before enrollment. Additional exclusion criteria were other complications of Crohn's disease, such as current strictures or abscesses; the presence of a stoma created less than six months before enrollment; a history of allergy to murine proteins; and previous treatment with infliximab. Men and women with reproductive potential were required to use an acceptable form of birth control throughout the study and for six months after the final infusion.

One hundred twenty patients were screened at 12 centers in the United States and Europe, of whom 94 were enrolled. The protocol was approved by the institutional review boards and ethics committees at all sites, and all patients gave written informed consent before enrolling in the study.

### Protocol

The screening procedures included a physical examination, routine laboratory analyses, assessment of the severity of disease according to the Crohn's Disease Activity Index and, for patients who had perianal disease at base line, a Perianal Disease Activity Index. The Crohn's Disease Activity Index incorporates eight related variables: the number of liquid or very soft stools per day, the severity of abdominal pain or cramping, general well-being, the presence or absence of extraintestinal manifestations of disease, the presence or absence of an abdominal mass, the use or nonuse of antidiarrheal drugs, the hematocrit, and body weight.<sup>18</sup> These items yield a composite score ranging approximately from 0 to 600; scores below 150 indicate remission, whereas scores above 450 indicate severe illness. The Perianal Disease Activity Index incorporates five elements: the presence or absence of discharge, pain or restriction of activities of daily living, restriction of sexual activity, the type of perianal disease, and the degree of induration, yielding a composite score ranging from 0 to 20, with higher scores indicating more severe disease.<sup>19</sup> All fistulas had to be distinctly identifiable; drawings as well as photographs were used to document the sites of disease.

Within seven days of screening, eligible patients were randomly assigned to receive one of three treatments: placebo, 5 mg of infliximab per kilogram of body weight, or 10 mg of infliximab per kilogram, all to be given intravenously at weeks 0, 2, and 6. Randomization was performed by an independent organization (PPD Pharmaco, Austin, Tex.), using a stratified treatment assignment<sup>20</sup> with the investigational site and the number of fistulas (one or more than one) as the stratification variables. Patients were enrolled from May 30 through October 1, 1996.

Infliximab was administered intravenously. Infliximab (Chimeric A2 [cA2] IgG, Centocor, Malvern, Pa.) was supplied as a lyophilized solid containing 250 mg of cA2 IgG, 2.5 g of sucrose, 61.0 mg of dibasic sodium phosphate dihydrate, 21.7 mg of monobasic sodium phosphate monohydrate, and 2.5 mg of polysorbate 80 in a 100-ml vial for reconstitution in 50 ml of sterile water. The medication was added to the diluent directly from the 100-ml vial with a 15- $\mu$ m filter, then infused slowly over a two-hour period.

The placebo preparation was supplied as a lyophilized solid containing 25 mg of human serum albumin, 2.5 g of sucrose, 61.0 mg of dibasic sodium phosphate dihydrate, 21.7 mg of monobasic sodium phosphate monohydrate, and 2.5 mg of polysorbate 80 in a 100-ml vial for reconstitution in 50 ml of sterile water. The placebo was identical in appearance to the infliximab solution.

After the first infusion of study medication, patients returned

for clinical and laboratory assessments at weeks 2, 6, 10, 14, and 18. Blood samples were drawn at each study visit and at weeks 26 and 34 to determine the serum concentration of infliximab.

### Evaluation of Efficacy

The primary efficacy end point was defined a priori as a reduction of 50 percent or more from base line in the number of draining fistulas observed at two or more consecutive study visits. Treatment was considered to have failed in patients who had changes in medication that were not permitted in the protocol, who underwent surgery related to Crohn's disease, or who did not return for follow-up visits.

The primary end point was based on the investigators' physical evaluation of the patient; a fistula was considered to be closed when it no longer drained despite gentle finger compression. Draining fistulas of less than three months' duration at base line were excluded from the primary analysis. In order for a patient to reach the primary end point, a minimum of 21 days between consecutive visits was required.

Secondary analyses of efficacy evaluated the number of patients with a complete response (defined as the absence of any draining fistulas at two consecutive visits), the length of time to the beginning of a response, and the duration of the response. Changes in scores on the Crohn's Disease Activity Index and the Perianal Disease Activity Index were also evaluated.

### Evaluation of Safety

Safety was assessed in terms of the incidence of adverse events and changes in vital signs and routine laboratory measures. Patients were monitored for adverse events during each infusion and at each study visit.

### Immunologic Evaluation

We conducted assays to detect the formation of antinuclear antibodies, antibodies against double-stranded DNA, and human antichimeric antibodies. Antinuclear antibodies were measured by means of a standard immunofluorescence technique in HEP-2 cells, with a screening dilution of the sample of 1:40 (negative results were defined as less than 1:40). Patients who were positive for antinuclear antibodies were evaluated for antibodies against double-stranded DNA with the *Critidia luciliae* immunofluorescence technique and a screening dilution of 1:10. Antibodies against double-stranded DNA were measured in patients with positive results by means of the Farr radioimmunoassay. Patients were considered positive for antibodies against double-stranded DNA if they had positive results on both the *C. luciliae* immunofluorescence assay and the Farr radioimmunoassay. Human antichimeric antibodies were measured with use of a double-antigen enzyme immunoassay.

### Statistical Analysis

The primary analysis was performed according to the intention-to-treat principle and included all patients who were screened and randomly assigned to treatment. The analysis was performed in two stages. We performed the Mantel-Haenszel chi-square test for a linear dose response in the proportion of patients in whom the primary end point occurred. If the result was significant at an alpha level of 0.05, Fisher's exact test was then used to compare the proportion of patients achieving the primary end point in each of the two infliximab groups with that in the placebo group. Odds ratios were used to assess the consistency of benefit of infliximab treatment in subgroups of patients.

Analysis of the proportion of patients who had a complete response was performed with the same methods used for the analysis of the primary end point. Continuous variables (e.g., scores on the Crohn's Disease Activity Index and Perianal Disease Activity Index) were compared by analysis of variance of the van der Waerden normal scores. For patients who discontinued regularly scheduled follow-up, underwent a surgical procedure, or had a change in medication that was not permitted by protocol, the measurements

from the last evaluation were carried forward. All reported P values are two-sided.

**RESULTS**

Ninety-four patients were randomly assigned to treatment with infliximab or placebo. Demographic and clinical characteristics and rates of use of concomitant medications were similar in all treatment groups at base line (Table 1). Six patients discontinued treatment (four in the placebo group and two treated with infliximab); all had received two of the three scheduled infusions. The reasons for withdrawal were lack of efficacy (three patients in the placebo group), administrative reasons (one in the placebo group), withdrawal of consent (one patient assigned to 5 mg of infliximab per kilogram), and adverse events (one patient treated with 10 mg of infliximab per kilogram).

**Efficacy**

With respect to the primary efficacy end point, response rates were significantly greater among the patients receiving infliximab (68 percent in the group

assigned to 5 mg per kilogram and 56 percent in the group receiving 10 mg per kilogram) than in the placebo group (26 percent; P=0.002 and P=0.02, respectively) (Table 2). Response rates in the two infliximab groups were not significantly different (P=0.35). The results of treatment are summarized in Table 2. Photographs of the healing of fistulas over time in two patients are shown in Figure 1. There was a complete response, defined as the absence of any draining fistulas, in 55 percent of the patients treated with 5 mg of infliximab per kilogram, in 38 percent of those treated with 10 mg per kilogram, and in 13 percent of patients receiving placebo (P=0.001 and P=0.04, respectively). Complete responses occurred both in patients with single fistulas and in those with multiple fistulas; of the 29 infliximab-treated patients with a complete response, 15 had a single fistula and 14 had multiple fistulas at base line.

In patients who reached the primary end point, the length of time to the beginning of a response was calculated as the number of days from the initial infusion to the first of the two or more consecutive

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS, ACCORDING TO STUDY GROUP.\***

| CHARACTERISTIC                            | PLACEBO<br>(N=31) | INFLIXIMAB        |                    | ALL<br>PATIENTS<br>(N=94) |
|---|-------------------|-------------------|--------------------|---------------------------|
|   |                   | 5 mg/kg<br>(N=31) | 10 mg/kg<br>(N=32) |                           |
| Age — yr                                  | 35.4±8.6          | 41.2±12.2         | 35.0±12.3          | 37.2±11.4                 |
| Weight — kg                               | 69.4±12.0         | 70.4±14.5         | 66.2±15.0          | 68.6±13.9                 |
| Race — no. (%)                            |                   |                   |                    |                           |
| White                                     | 29 (94)           | 28 (90)           | 29 (91)            | 86 (91)                   |
| Black                                     | 2 (6)             | 3 (10)            | 3 (9)              | 8 (9)                     |
| Sex — no. (%)                             |                   |                   |                    |                           |
| Male                                      | 17 (55)           | 15 (48)           | 12 (38)            | 44 (47)                   |
| Female                                    | 14 (45)           | 16 (52)           | 20 (62)            | 50 (53)                   |
| Duration of Crohn's disease — yr          | 12.0±7.9          | 13.6±9.5          | 11.5±8.2           | 12.4±8.5                  |
| Area of involvement — no. (%)             |                   |                   |                    |                           |
| Ileum                                     | 3 (10)            | 7 (23)            | 4 (12)             | 14 (15)                   |
| Colon                                     | 9 (29)            | 7 (23)            | 10 (31)            | 26 (28)                   |
| Ileum and colon                           | 19 (61)           | 17 (55)           | 18 (56)            | 54 (57)                   |
| Previous segmental resection — no. (%)    | 12 (39)           | 21 (68)           | 17 (53)            | 50 (53)                   |
| No. of enterocutaneous fistulas — no. (%) |                   |                   |                    |                           |
| 1   | 13 (42)           | 15 (48)           | 14 (44)            | 42 (45)                   |
| >1  | 18 (58)           | 16 (52)           | 18 (56)            | 52 (55)                   |
| Location of fistula                       |                   |                   |                    |                           |
| Perianal                                  | 29 (94)           | 27 (87)           | 29 (91)            | 85 (90)                   |
| Abdominal                                 | 2 (6)             | 4 (13)            | 3 (9)              | 9 (10)                    |
| Previous medication — no. (%)             |                   |                   |                    |                           |
| Corticosteroids                           | 11 (35)           | 12 (39)           | 10 (31)            | 33 (35)                   |
| Mercaptopurine or azathioprine            | 9 (29)            | 12 (39)           | 17 (53)            | 38 (40)                   |
| Aminosalicylates                          | 19 (61)           | 17 (55)           | 16 (50)            | 52 (55)                   |
| Antibiotics                               | 11 (35)           | 6 (19)            | 11 (34)            | 28 (30)                   |
| Score on Crohn's Disease Activity Index†  | 192.9±92.0        | 184.4±98.5        | 184.9±97.5         | 187.3±95.0                |

\*Plus-minus values are means ±SD.

†Data were available for 25 patients in the placebo group, 27 assigned to 5 mg of infliximab per kilogram, and 27 assigned to 10 mg per kilogram (total, 79 patients).

**TABLE 2.** OUTCOME OF TREATMENT, ACCORDING TO STUDY GROUP.

| VARIABLE                                | PLACEBO   | INFLIXIMAB |            |                  |
|---|-----------|------------|------------|------------------|
|   |           | 5 mg/kg    | 10 mg/kg   | 5 OR<br>10 mg/kg |
| <b>End points</b>                       |           |            |            |                  |
| Primary end point — no./total no. (%)*  | 8/31 (26) | 21/31 (68) | 18/32 (56) | 39/63 (62)       |
| P value vs. placebo                     | —         | 0.002      | 0.02       | 0.002            |
| Complete response — no./total no. (%)†  | 4/31 (13) | 17/31 (55) | 12/32 (38) | 29/63 (46)       |
| P value vs. placebo                     | —         | 0.001      | 0.04       | 0.001            |
| Time to onset of response (days)‡       |           |            |            |                  |
| Median                                  | 42        | 14         | 14         | 14               |
| Interquartile range                     | 15–72     | 14–42      | 14–42      | 14–42            |
| Duration of response (days)‡            |           |            |            |                  |
| Median                                  | 86        | 84         | 99         | 86               |
| Interquartile range                     | 56–104    | 31–113     | 86–113     | 57–113           |
| <b>Crohn's Disease Activity Index§</b>  |           |            |            |                  |
| Base-line score                         |           |            |            |                  |
| Median                                  | 162       | 163        | 203        | 168              |
| Interquartile range                     | 126–265   | 99–284     | 112–254    | 112–258          |
| P value vs. placebo                     | —         | 0.71       | 0.66       | 0.64             |
| Score at week 2                         |           |            |            |                  |
| Median                                  | 171       | 108        | 111        | 108              |
| Interquartile range                     | 114–252   | 83–203     | 89–164     | 84–179           |
| P value vs. placebo                     | —         | 0.04       | 0.06       | 0.02             |
| Score at week 18                        |           |            |            |                  |
| Median                                  | 160       | 104        | 123        | 117              |
| Interquartile range                     | 72–206    | 47–177     | 58–175     | 49–177           |
| P value vs. placebo                     | —         | 0.23       | 0.32       | 0.21             |
| <b>Perianal Disease Activity Index¶</b> |           |            |            |                  |
| Base-line score                         |           |            |            |                  |
| Median                                  | 9.0       | 8.0        | 10.0       | 9.0              |
| Interquartile range                     | 7.0–10.5  | 7.0–10.0   | 8.0–12.0   | 7.0–11.0         |
| P value vs. placebo                     | —         | 0.69       | 0.31       | 0.73             |
| Score at week 2                         |           |            |            |                  |
| Median                                  | 8.0       | 6.0        | 6.0        | 6.0              |
| Interquartile range                     | 6.0–10.0  | 3.0–7.0    | 4.0–8.0    | 3.5–8.0          |
| P value vs. placebo                     | —         | 0.02       | 0.04       | 0.01             |
| Score at week 18                        |           |            |            |                  |
| Median                                  | 7.0       | 4.0        | 5.0        | 5.0              |
| Interquartile range                     | 4.0–9.0   | 1.0–7.0    | 3.0–8.0    | 2.0–7.5          |
| P value vs. placebo                     | —         | 0.05       | 0.14       | 0.05             |

\*The primary end point was defined as a reduction of 50 percent or more from base line in the number of open fistulas observed at two or more consecutive visits.

†A complete response was defined as the absence of any draining fistulas at two or more consecutive visits.

‡Only patients achieving the primary end point were included.

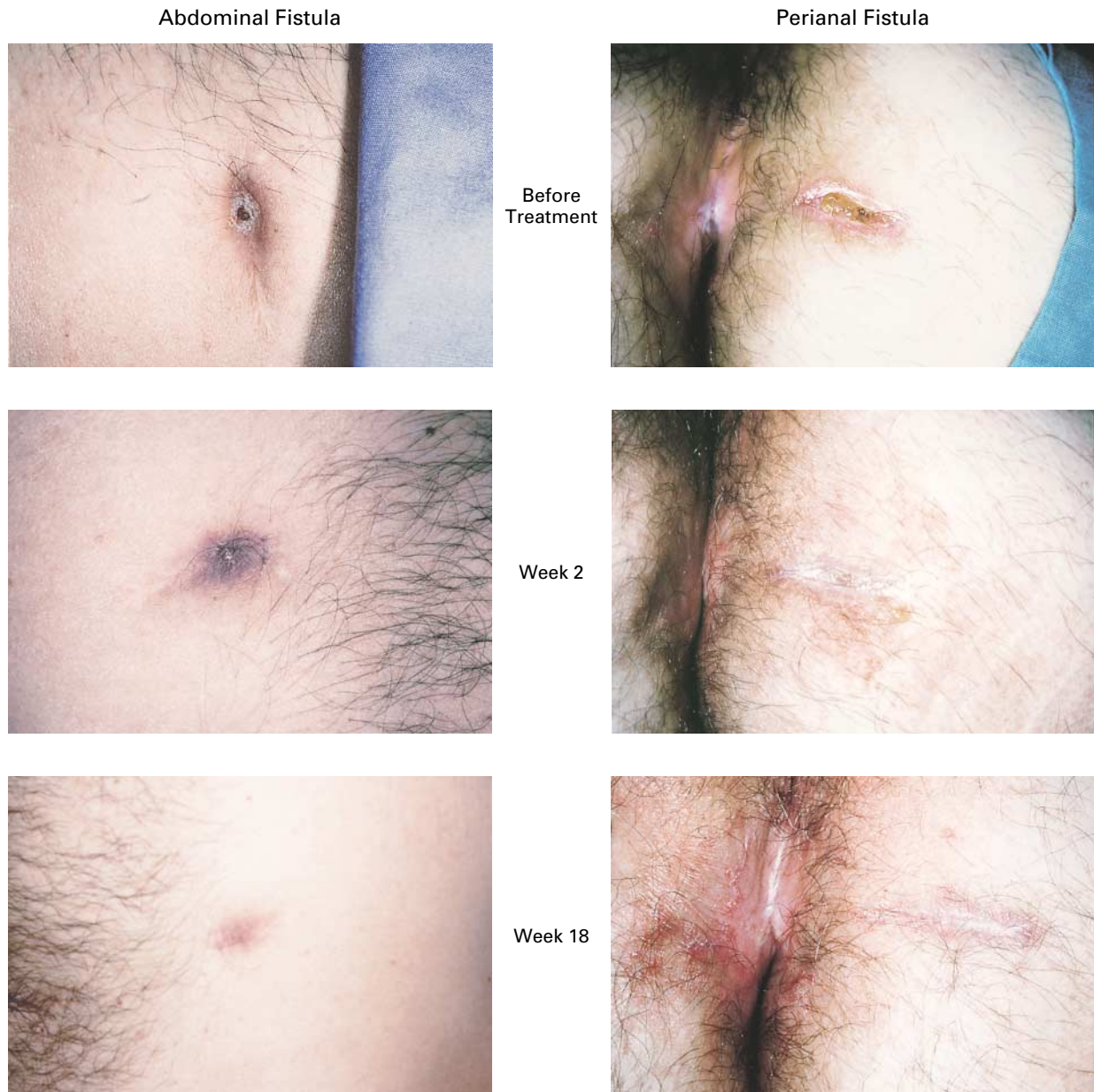
§The Crohn's Disease Activity Index is based on eight variables (described in the Methods section). Scores range approximately from 0 to 600; scores below 150 indicate remission, and scores above 450 indicate severe illness. Values shown are based on 79 of the 94 patients; patients with a stoma were excluded because the number of stools could not be assessed.

¶The Perianal Disease Activity Index is based on five variables. Scores range from 0 to 20, with higher scores indicating more severe disease.

visits at which this end point was observed. The median time to the onset of a response (Table 2) was shorter among patients treated with infliximab (two weeks) than among those given placebo (six weeks). The duration of the response was defined as the maximal period during which the patient had a reduction of 50 percent or more in the number of draining fistulas at consecutive visits. The median duration of response was approximately three months in patients who reached the primary end point (Table 2). Changes over time in the scores on the Crohn's Disease

Activity Index and the Perianal Disease Activity Index are shown in Table 2, according to treatment group.

A consistent benefit of infliximab treatment was observed for all demographic subgroups we evaluated (Table 3). A significant benefit of treatment was still evident when the analyses were adjusted for sex or prior bowel resection with logistic regression ( $P=0.001$ , data not shown). Significantly more of the patients with single fistulas who were treated with infliximab reached the primary end point than patients assigned to placebo (52 percent vs. 8 percent,  $P=0.02$ ); the



**Figure 1.** Closure of an Abdominal Fistula in a 60-Year-Old Man and a Perianal Fistula in a 42-Year-Old Man. Both patients received 5 mg of infliximab per kilogram.

same was true for patients with multiple fistulas (71 percent vs. 39 percent,  $P=0.03$ ). In addition, infliximab was consistently beneficial regardless of concomitant therapy (e.g., corticosteroids, mercaptopurine or azathioprine, or antibiotics).

#### Safety

All 94 patients were evaluated for safety. The percentage of patients with adverse events was the same for the group assigned to receive 5 mg of infliximab per kilogram and that assigned to placebo (65 per-

cent); there was a trend toward more adverse events among the patients assigned to receive 10 mg of infliximab per kilogram (84 percent,  $P=0.09$ ). The most frequently reported adverse events among patients treated with infliximab were headache, abscess, upper respiratory tract infection, and fatigue (Table 4). One patient in the group receiving 10 mg of infliximab per kilogram discontinued treatment because of pneumonia, which developed 22 days after the second infusion. The symptoms resolved within a week with antibiotic treatment. Altogether, five patients had

**TABLE 3.** RESULTS OF TREATMENT ACCORDING TO SELECTED VARIABLES.

| VARIABLE                              | PLACEBO         |                          | INFLIXIMAB      |                          | ODDS RATIO* | P VALUE |
|---------------------------------------|-----------------|--------------------------|-----------------|--------------------------|-------------|---------|
|                                       | NO. IN SUBGROUP | % WITH PRIMARY END POINT | NO. IN SUBGROUP | % WITH PRIMARY END POINT |             |         |
|                                       |                 | All patients             |                 | 31                       |             |         |
| Sex                                   |                 |                          |                 |                          |             |         |
| Male                                  | 17              | 18                       | 27              | 74                       | 13.3        | <0.001  |
| Female                                | 14              | 36                       | 36              | 53                       | 2.0         | 0.28    |
| Area of involvement                   |                 |                          |                 |                          |             |         |
| Ileum                                 | 3               | 0                        | 11              | 73                       | —           | —       |
| Colon                                 | 9               | 33                       | 17              | 53                       | 2.3         | 0.35    |
| Ileum and colon                       | 19              | 26                       | 35              | 65                       | 5.1         | 0.01    |
| No. of enterocutaneous fistulas       |                 |                          |                 |                          |             |         |
| 1                                     | 13              | 8                        | 29              | 52                       | 12.9        | 0.02    |
| >1                                    | 18              | 39                       | 34              | 71                       | 3.8         | 0.03    |
| Dose of oral corticosteroids          |                 |                          |                 |                          |             |         |
| 20 mg/day                             | 5               | 20                       | 6               | 67                       | 8.0         | 0.14    |
| <20 mg/day                            | 6               | 17                       | 15              | 53                       | 5.7         | 0.15    |
| None                                  | 20              | 30                       | 42              | 64                       | 4.2         | 0.01    |
| Use of mercaptopurine or azathioprine |                 |                          |                 |                          |             |         |
| Yes                                   | 9               | 44                       | 29              | 59                       | 1.8         | 0.46    |
| No                                    | 22              | 18                       | 34              | 65                       | 8.3         | 0.001   |
| Use of antibiotics                    |                 |                          |                 |                          |             |         |
| Yes                                   | 11              | 27                       | 17              | 65                       | 4.9         | 0.06    |
| No                                    | 20              | 25                       | 46              | 61                       | 4.7         | 0.01    |

\*The odds ratio is for the odds of reaching the primary end point in the infliximab group as compared with the placebo group.

serious adverse events: four assigned to receive 10 mg of infliximab per kilogram and one assigned to receive 5 mg per kilogram. In the 10-mg group, these events were chest pain and pneumonia (in the patient who discontinued treatment), intestinal obstruction, abscess of the arm and leg (furunculosis), and anal abscess. In the patient in the 5-mg infliximab group, ureteral obstruction developed after the third infusion. In four of the patients receiving infliximab (6 percent), adverse events occurred during an infusion or within two hours after the end of the infusion, with some patients having multiple adverse reactions; these adverse events were mild dizziness in two patients, subfebrile temperature elevation in two, headache in one, and chest pain with flushing in two. There were no consistent differences in routine laboratory values between the infliximab and placebo groups. No deaths occurred during the study period.

**Immunologic Results**

Antibodies against double-stranded DNA were detected in eight patients treated with infliximab (13 percent); one patient remained positive for these antibodies at the last evaluation. None had symptoms suggestive of lupus erythematosus. Serum samples were collected both before and after treatment from 92 patients and assayed for human antichimeric antibodies. Three tested positive for human antichimeric antibodies, all at a titer of 1:10. Thirteen patients

**TABLE 4.** ADVERSE EVENTS THAT OCCURRED IN AT LEAST 10 PERCENT OF PATIENTS IN ANY TREATMENT GROUP.

| EVENT                             | PLACEBO (N=31) | INFLIXIMAB       |                 |                      |
|-----------------------------------|----------------|------------------|-----------------|----------------------|
|                                   |                | 5 mg/kg (N=31)   | 10 mg/kg (N=32) | 5 OR 10 mg/kg (N=63) |
|                                   |                | number (percent) |                 |                      |
| Headache                          | 7 (23)         | 5 (16)           | 6 (19)          | 11 (17)              |
| Abscess                           | 1 (3)          | 2 (6)            | 5 (16)          | 7 (11)               |
| Upper respiratory tract infection | 2 (6)          | 1 (3)            | 5 (16)          | 6 (10)               |
| Fatigue                           | 2 (6)          | 2 (6)            | 4 (12)          | 6 (10)               |

had measurable concentrations of infliximab in all post-treatment samples and therefore could not be evaluated. None of the adverse events in the patients who were positive for human antichimeric antibodies were suggestive of a sensitivity reaction.

**DISCUSSION**

Closure of fistulas is rare in patients with Crohn's disease who are receiving standard therapy, such as 5-aminosalicylates or corticosteroids. Several antibiotics have shown promise for the healing of fistulas

in Crohn's disease,<sup>21-23</sup> but their efficacy has not been established in controlled clinical trials. Immunomodulatory agents have been used to treat fistulas, with some success. In one uncontrolled study, fistulas closed in about one third of patients treated with methotrexate.<sup>24</sup> Small, uncontrolled studies have demonstrated that intravenous cyclosporine induces the closure of fistulas; however, patients relapsed when switched to oral cyclosporine.<sup>4,25</sup> A double-blind, placebo-controlled study<sup>3</sup> suggested that mercaptopurine was more effective than placebo in the treatment of fistulas in patients with Crohn's disease; however, the study had too few patients for the statistical significance of this finding to be assessed. In addition, approximately three months was required for a response to appear in patients treated with mercaptopurine.

In our study, we found a significant reduction in the number of draining fistulas in patients with Crohn's disease, as compared with the number at base line, after two or three infusions of infliximab at doses of 5 or 10 mg per kilogram. The effect of treatment with infliximab became evident rapidly — in about two weeks — and lasted for a median of three months; a complete response (defined as the absence of draining fistulas) occurred in 46 percent of patients treated with infliximab, as compared with 13 percent of the placebo group ( $P=0.001$ ). The beneficial effect of infliximab did not appear to be dose-related; patients treated with 5 mg of infliximab per kilogram had a higher rate of response than those treated with 10 mg per kilogram (68 percent vs. 56 percent).

The frequency of adverse events was the same in the placebo group and the group assigned to 5 mg of infliximab per kilogram; there was a trend toward more adverse events in the group assigned to 10 mg of infliximab per kilogram. Eight patients treated with infliximab (13 percent) had low levels of antibodies against double-stranded DNA. In all but one, these antibodies disappeared by the end of the study. The clinical significance of these serologic findings is uncertain; none of the patients had symptoms suggestive of lupus erythematosus. In an earlier trial,<sup>17</sup> a duodenal lymphoma developed in one patient with a 30-year history of Crohn's disease. The association of this event with infliximab is uncertain, since the incidence of lymphoma is increased in chronic Crohn's disease.<sup>26</sup>

Some issues remain to be addressed regarding the use of infliximab in patients with Crohn's disease that is complicated by fistulas. These include the use of infliximab as an effective corticosteroid-sparing agent, the long-term toxicity of the regular or intermittent use of infliximab, and the best timing for the administration of infliximab. The majority of patients in this study had chronically active disease and had previously received several therapies, including immunosuppressive agents. The efficacy of a regimen based on infliximab as a first-line therapy to induce

early closure of fistulas, with mercaptopurine or azathioprine reserved for long-term maintenance after fistulas have healed, needs further investigation.

In conclusion, we found that infliximab was efficacious in the treatment of enterocutaneous fistulas complicating Crohn's disease. Our results support the use of an initial dose of 5 mg per kilogram, with subsequent identical doses given two and six weeks later.

Dr. Hanauer, Dr. Podolsky, and Dr. Sands have served as paid consultants to Centocor. Dr. Present and Dr. Hanauer have received honorariums from Centocor for lectures. Dr. Mayer owns stock in Centocor.

## APPENDIX

In addition to the authors, the following participated in the study: *Duke University Medical Center, Durham, N.C.* — J. Onken; *Methodist Hospital, Houston* — A.L. Buchman; *Thomas Jefferson University Hospital, Philadelphia* — A.J. DiMarino; *Saint Mark's Hospital, London* — M. Kamm; and *Leeds General Infirmary, Leeds, United Kingdom* — D.M. Chalmers.

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