ORIGINAL ARTICLE

Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis

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ABSTRACT

BACKGROUND

Infliximab, a chimeric monoclonal antibody directed against tumor necrosis factor α, is an established treatment for Crohn's disease but not ulcerative colitis.

METHODS

Two randomized, double-blind, placebo-controlled studies — the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2, respectively) — evaluated the efficacy of infliximab for induction and maintenance therapy in adults with ulcerative colitis. In each study, 364 patients with moderate-to-severe active ulcerative colitis despite treatment with concurrent medications received placebo or infliximab (5 mg or 10 mg per kilogram of body weight) intravenously at weeks 0, 2, and 6 and then every eight weeks through week 46 (in ACT 1) or week 22 (in ACT 2). Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2.

RESULTS

In ACT 1, 69 percent of patients who received 5 mg of infliximab and 61 percent of those who received 10 mg had a clinical response at week 8, as compared with 37 percent of those who received placebo ($P<0.001$ for both comparisons with placebo). A response was defined as a decrease in the Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute rectal-bleeding subscore of 0 or 1. In ACT 2, 64 percent of patients who received 5 mg of infliximab and 69 percent of those who received 10 mg had a clinical response at week 8, as compared with 29 percent of those who received placebo ($P<0.001$ for both comparisons with placebo). In both studies, patients who received infliximab were more likely to have a clinical response at week 30 ($P\leq0.002$ for all comparisons). In ACT 1, more patients who received 5 mg or 10 mg of infliximab had a clinical response at week 54 (45 percent and 44 percent, respectively) than did those who received placebo (20 percent, $P<0.001$ for both comparisons).

CONCLUSIONS

Patients with moderate-to-severe active ulcerative colitis treated with infliximab at weeks 0, 2, and 6 and every eight weeks thereafter were more likely to have a clinical response at weeks 8, 30, and 54 than were those receiving placebo. (ClinicalTrials.gov numbers, NCT00036439 and NCT00096655.)

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Ulcerative colitis is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain. Pharmacologic management of ulcerative colitis has relied mainly on 5-aminosalicylates, corticosteroids, and immunosuppressants, including purine antimetabolites and cyclosporine.[1,2] Corticosteroid dependence is a clinically important problem[3]; furthermore, the probability of colectomy within the first five years after diagnosis ranges from 9 percent in patients with distal colitis to 35 percent in patients with total colitis, most commonly because of failed medical therapy.[4] The cumulative risk of recurrent inflammatory bowel disease in the form of pouchitis ranges from 15.5 percent 1 year after the procedure to 45.5 percent 10 years after the procedure.[5] Accordingly, new treatments for ulcerative colitis are needed.

Tumor necrosis factor α (TNF-α) is a key proinflammatory cytokine in patients with Crohn's disease but is also found in increased concentrations in the blood, colonic tissue, and stools of patients with ulcerative colitis.[6-8] However, the role of TNF-α in the pathogenesis of ulcerative colitis has been debated.[9-13]

Infliximab, a chimeric IgG1 monoclonal antibody, binds with high affinity to TNF-α, neutralizing its biologic activity.[14] Infliximab therapy is effective for the induction and maintenance of clinical remission; closure of enterocutaneous, perianal, and rectovaginal fistulas; maintenance of fistula closure; and corticosteroid sparing in patients with Crohn's disease.[15-18] However, the few small studies of infliximab in patients with active ulcerative colitis have yielded conflicting results.[19-23] We therefore conducted 54-week and 30-week studies of infliximab in patients with moderate-to-severe ulcerative colitis: the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and 2, respectively).

METHODS

PATIENTS

These multicenter, randomized, double-blind, placebo-controlled studies were conducted globally between March 2002 and March 2005 among 364 patients at 62 sites in the ACT 1 trial and 364 patients at 55 sites in the ACT 2 trial. The institutional review board or ethics committee at each site approved the protocols. All patients gave written informed consent.

All eligible patients had an established diagnosis of ulcerative colitis. Patients with positive tuberculin skin tests with the use of purified protein derivative were ineligible. Also, standard chest radiographs were obtained during screening. Endoscopy (flexible sigmoidoscopy unless surveillance colonoscopy was clinically indicated) with biopsy was performed during screening to confirm the diagnosis of ulcerative colitis by both the physician performing the endoscopy and the pathologist reviewing the biopsy specimen. Patients who received a diagnosis of indeterminate colitis, Crohn's disease, or clinical findings suggestive of Crohn's disease (i.e., fistula or granulomas on biopsy) were excluded. Eligible patients had active ulcerative colitis with a Mayo score[24] of 6 to 12 points (scores can range from 0 to 12, with higher scores indicating more severe disease activity) (Table 1) and moderate-to-severe active disease on sigmoidoscopy (Mayo endoscopic subscore of at least 2) despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine in

Table 1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity.*

Stool frequency†
- 0 = Normal no. of stools for this patient
- 1 = 1 to 2 stools more than normal
- 2 = 3 to 4 stools more than normal
- 3 = 5 or more stools more than normal
- Subscore, 0 to 3

Rectal bleeding‡
- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passes
- Subscore, 0 to 3

Findings on endoscopy
- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)
- Subscore, 0 to 3

Physician's global assessment§
- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease
- Subscore, 0 to 3

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al.[24]

† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

‡ The daily bleeding score represents the most severe bleeding of the day.

§ The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

ACT 1 or despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine and medications containing 5-aminosalicylates in ACT 2. Concurrent therapy was not required at enrollment for patients in ACT 1 and ACT 2 who had had no response to corticosteroids within the preceding 18 months or who could not tolerate corticosteroids, patients in either study who had had no response to azathioprine or mercaptopurine within the preceding 5 years or who could not tolerate these drugs, and patients in ACT 2 who had had no response to medications containing 5-aminosalicylates within the preceding 18 months or who could not tolerate such drugs. Rectally administered corticosteroids or medications containing 5-aminosalicylates were not permitted within two weeks before screening. Patients previously exposed to infliximab or any other anti-TNF agent were excluded.

STUDY DESIGN

Eligible patients were randomly assigned in a 1:1:1 ratio to receive intravenous infusions of infliximab (Remicade, Centocor) at a dose of 5 mg or 10 mg per kilogram of body weight or placebo at weeks 0, 2, and 6 and then every eight weeks through week 22 in ACT 2 or week 46 in ACT 1. Patients were followed through week 30 in ACT 2 and week 54 in ACT 1.

Each study used central randomization with a dynamic treatment allocation stratified according to the investigational site and whether patients had ulcerative colitis that was refractory to corticosteroid therapy. Patients were considered to have ulcerative colitis that was refractory to corticosteroids if their symptoms of ulcerative colitis had not improved after they received the equivalent of at least 40 mg of prednisone daily, administered orally for at least two weeks or intravenously for at least one week.

Doses of concomitant medications remained constant except for corticosteroids, which were tapered by 5 mg weekly after week 8 until a dose of 20 mg per day was reached. Thereafter, the dose was reduced by 2.5 mg weekly until discontinuation.

FOLLOW-UP AND SAFETY AND EFFICACY EVALUATIONS

Patients in both studies were evaluated at weeks 0, 2, 6, 8, 14, 22, and 30. Patients in ACT 1 were also evaluated at weeks 38, 46, and 54. The Mayo score (Table 1) was determined at weeks 0, 8, and 30 for patients in both studies and at week 54 for patients in ACT 1. A partial Mayo score (Mayo score without endoscopy) was determined at all visits.

Clinical response was defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing was defined as an absolute subscore for endoscopy of 0 or 1.

Clinical response, clinical remission, and mucosal healing were assessed at weeks 8 and 30 in both studies and at week 54 in ACT 1. Patients who had a clinical response or who were in clinical remission at each time were considered to have a sustained clinical response or to be in sustained clinical remission, respectively.

In both studies, adverse events and concomitant medications were recorded at each visit. Serum specimens for the identification of antibodies against infliximab and antinuclear antibodies were collected at weeks 0 and 30 in both studies and at week 54 in ACT 1, with the use of previously described methods.[25] Samples positive for antinuclear antibodies were tested for antibodies against double-stranded DNA.

STATISTICAL ANALYSIS

The primary end point was a clinical response at week 8. Secondary end points were a clinical response or clinical remission with discontinuation of corticosteroids at week 30 in both studies and at week 54 in ACT 1, a clinical remission and mucosal healing at weeks 8 and 30 in both studies and at week 54 in ACT 1, and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids. Patients who took prohibited medication because of lack of efficacy or loss of response to the study medication, who discontinued the study medication because of lack of efficacy, or who underwent a colectomy or ostomy were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing from the time of the event onward, regardless of their Mayo score. In addition, patients with insufficient data for the assessment of a response were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing at that visit.

Demographic and baseline characteristics were compared with the use of the chi-square test or Fisher's exact test for categorical variables and with the use of analysis of variance for van der Waerden normal scores for continuous variables. A two-sided Cochran–Mantel–Haenszel chi-square test, at a significance level of 0.05, stratified according to corticosteroid-refractory status and the location of the study center, was used to compare dichotomous end points (i.e., clinical response, clinical remission, mucosal healing, and clinical remission with discontinuation of corticosteroids) among treatment groups. All efficacy analyses used intention-to-treat methods. Safety comparisons were performed with the use of Fisher's exact test and were based on the combination of the two groups receiving infliximab as compared with the placebo group. Assuming a response rate of 30 percent in the pla-

Table 2. Baseline Characteristics of the Patients in ACT 1 and ACT 2.*

Characteristic	ACT 1				ACT 2			
	Placebo (N=121)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=122)	P Value†	Placebo (N=123)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=120)	P Value†
Male sex — no. (%)	72 (59.5)	78 (64.5)	72 (59.0)	0.63	71 (57.7)	76 (62.8)	68 (56.7)	0.58
White race — no. (%)	111 (91.7)	116 (95.9)	113 (92.6)	0.62	117 (95.1)	116 (95.9)	111 (92.5)	0.03
Age — yr	41.4±13.7	42.4±14.3	41.8±14.9	0.86	39.3±13.5	40.5±13.1	40.3±13.3	0.68
Weight — kg	76.8±16.2	80.0±17.8	76.9±17.1	0.25	76.1±17.4	78.4±17.8	79.6±20.6	0.34
Duration of disease — yr	6.2±5.9	5.9±5.4	8.4±8.1	0.03	6.5±6.7	6.7±5.3	6.5±5.8	0.18
Colonic area involved								
Total no. of patients	120	119	121		120	118	120	
Left side — no. (%)	66 (55.0)	63 (52.9)	67 (55.4)	0.92	70 (58.3)	70 (59.3)	75 (62.5)	0.79
Extensive — no. (%)	54 (45.0)	56 (47.1)	54 (44.6)		50 (41.7)	48 (40.7)	45 (37.5)	
Mayo score‡	8.4±1.8	8.5±1.7	8.4±1.4	0.86	8.5±1.5	8.3±1.5	8.3±1.6	0.58
C-reactive protein§								
Total no. of patients	119	120	121		121	120	119	
Mean — mg/dl	1.7±2.7	1.4±1.9	1.6±2.3	0.82	1.6±2.9	1.3±2.3	1.4±2.2	0.86
Median — mg/dl	0.8	0.9	1.0		0.6	0.8	0.6	
Elevated — no. (%)	74 (62.2)	78 (65.0)	81 (66.9)	0.74	72 (59.5)	76 (63.3)	64 (53.8)	0.32
Concomitant medication — no. (%)								
Corticosteroids	79 (65.3)	70 (57.9)	73 (59.8)	0.47	60 (48.8)	60 (49.6)	66 (55.0)	0.58
≥20 mg/day	54 (44.6)	45 (37.2)	46 (37.7)		43 (35.0)	40 (33.1)	47 (39.2)	
5-Aminosalicylates	85 (70.2)	82 (67.8)	86 (70.5)	0.88	89 (72.4)	92 (76.0)	91 (75.8)	0.76
Immunosuppressants	53 (43.8)	66 (54.5)	59 (48.4)	0.25	54 (43.9)	52 (43.0)	50 (41.7)	0.94
Azathioprine	36 (29.8)	45 (37.2)	44 (36.1)		35 (28.5)	41 (33.9)	37 (30.8)	
Mercaptopurine	17 (14.0)	21 (17.4)	15 (12.3)		19 (15.4)	11 (9.1)	13 (10.8)	
Corticosteroid-refractory disease — no. (%)	38 (31.4)	36 (29.8)	38 (31.1)	0.96	36 (29.3)	35 (28.9)	34 (28.3)	0.99
Smoking status — no. (%)				0.50				0.95
Current smoker	7 (5.8)	2 (1.7)	3 (2.5)		6 (4.9)	8 (6.6)	6 (5.0)	
Nonsmoker	60 (49.6)	65 (53.7)	66 (54.1)		63 (51.2)	65 (53.7)	63 (52.5)	
Former smoker	54 (44.6)	54 (44.6)	53 (43.4)		54 (43.9)	48 (39.7)	51 (42.5)	

* Plus–minus values are means ±SD.
† P values for all categorical variables except race and smoking status are based on a two-sided chi-square test. P values for race and smoking status are based on Fisher's exact test. P values for continuous variables are based on analysis of variance for the van der Waerden normal scores. Race was assigned by the local investigator.
‡ The Mayo scores range from 0 to 12, with higher scores indicating more severe disease.
§ Elevated baseline C-reactive protein values were those of 0.6 mg per deciliter or more.

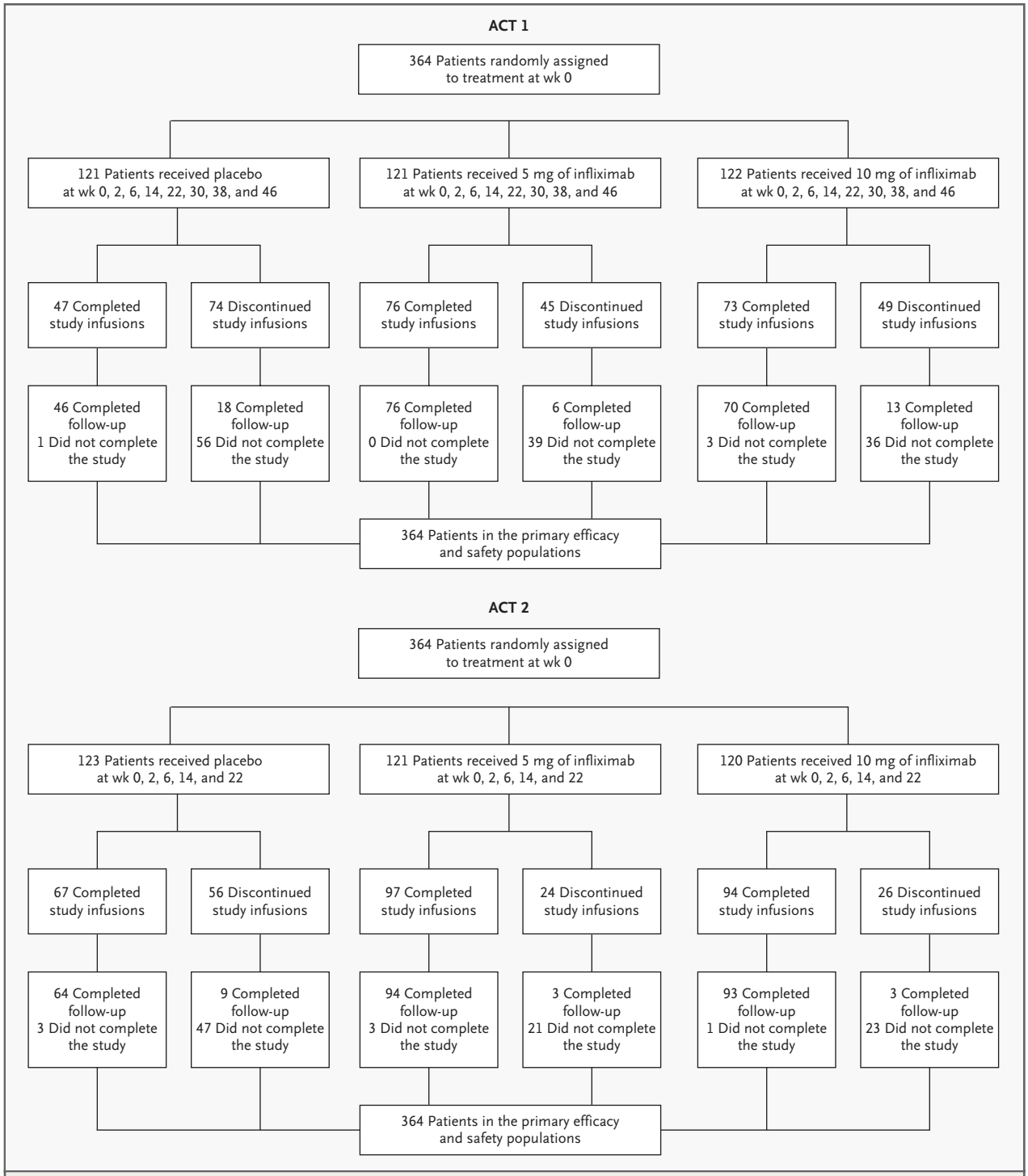

Figure 1. Enrollment and Treatment.

In ACT 1, 121 patients with moderate-to-severe ulcerative colitis were randomly assigned to receive intravenous placebo, 121 to receive 5 mg of infliximab per kilogram, and 122 to receive 10 mg of infliximab per kilogram at weeks 0, 2, 6, 14, 22, 30, 38, and 46. The efficacy and safety populations through week 54 consist of all 364 patients who underwent randomization, all of whom received at least one dose of study medication. In ACT 2, 123 patients with moderate-to-severe ulcerative colitis were randomly assigned to receive intravenous placebo, 121 to receive 5 mg of infliximab per kilogram, and 120 to receive 10 mg of infliximab per kilogram at weeks 0, 2, 6, 14, and 22. The efficacy and safety populations consist of all 364 patients who underwent randomization, all of whom received at least one dose of study medication.

cebo group and a two-sided probability of 0.05, we estimated that 120 patients would be needed in each group to give the study a statistical power of 95 percent to detect an improvement in the response rate to 50 percent.

These studies were designed and conducted by the steering committees for ACT 1 and ACT 2 and by Centocor. The members of the steering committee and Centocor jointly analyzed and interpreted the data and contributed to the manuscript. The academic authors had full access to the data and vouch for the veracity and completeness of the data and the data analyses.

RESULTS

CHARACTERISTICS OF THE PATIENTS

In ACT 1, 364 patients underwent randomization: 121 were assigned to receive placebo, 121 to receive 5 mg of infliximab, and 122 to receive 10 mg of infliximab. The baseline characteristics of the patients were similar (Table 2), although the mean duration of disease among patients who received 10 mg of infliximab was longer than among those who received 5 mg or placebo. Treatment was discontinued prematurely by 74 patients in the placebo group (61.2 percent), 45 patients in the group receiving 5 mg of infliximab (37.2 percent), and 49 patients in the group receiving 10 mg of infliximab (40.2 percent) (Fig. 1).

In ACT 2, 364 patients underwent randomization: 123 were assigned to receive placebo, 121 to receive 5 mg of infliximab, and 120 to receive 10 mg of infliximab. The baseline characteristics of the patients were similar (Table 2). More than twice as many patients in the placebo group as in the other two groups prematurely discontinued the study infusions (Fig. 1).

EFFICACY

In ACT 1 at week 8, 69.4 percent of patients in the group receiving 5 mg of infliximab (84 of 121) and 61.5 percent of patients in the group receiving 10 mg of infliximab (75 of 122) had had a clinical response, as compared with 37.2 percent of patients in the placebo group (45 of 121, P<0.001 for both comparisons) (Fig. 2A). In ACT 2 at week 8, 64.5 percent of patients in the group receiving 5 mg of infliximab (78 of 121) and 69.2 percent of patients in the group receiving 10 mg of infliximab (83 of

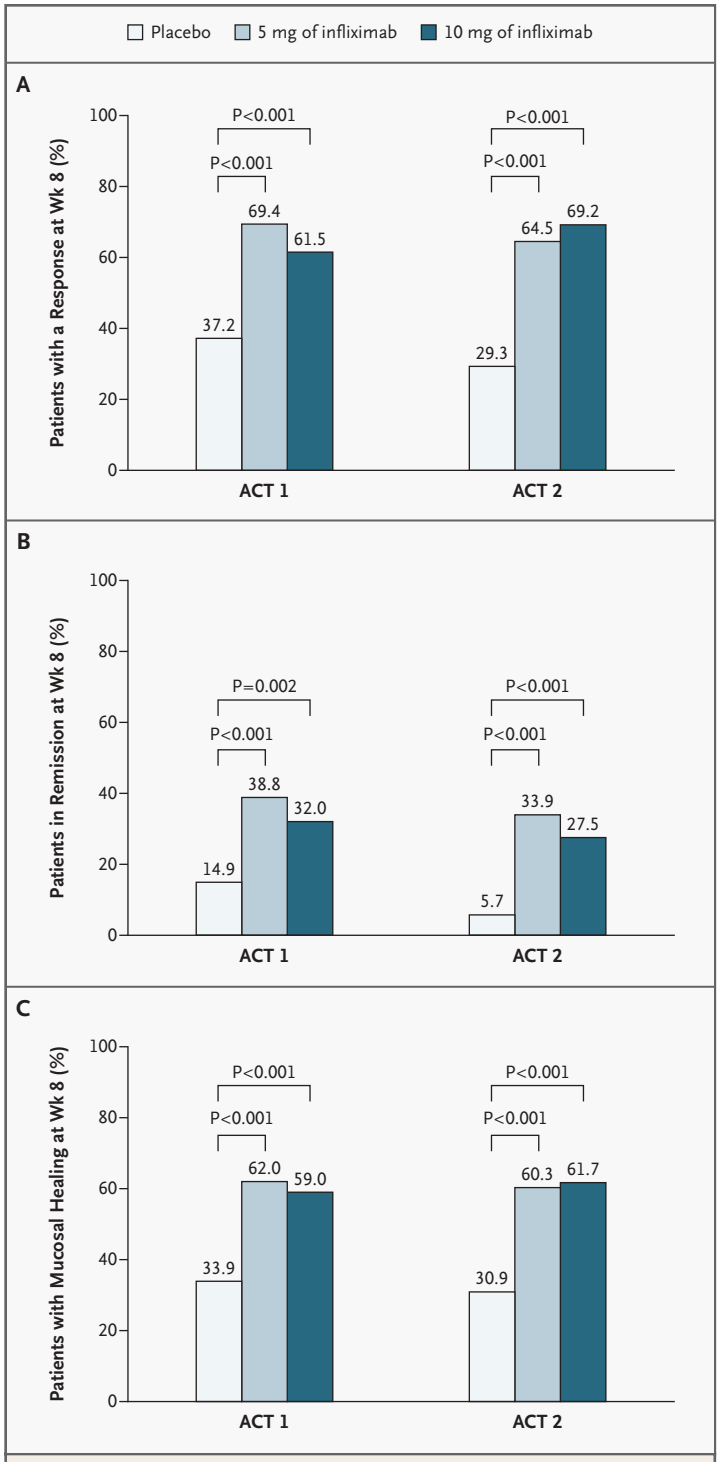

Figure 2. Proportion of Patients with a Clinical Response (Panel A), in Clinical Remission (Panel B), and with Mucosal Healing (Panel C) at Week 8 in ACT 1 and ACT 2.

Table 3. Summary of Primary and Secondary Efficacy Results from ACT 1 and ACT 2.*

Variable	ACT 1			ACT 2		
	Placebo (N=121)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=122)	Placebo (N=123)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=120)
Clinical response						
Week 8 — no. (%)	45 (37.2)	84 (69.4)	75 (61.5)	36 (29.3)	78 (64.5)	83 (69.2)
P value		<0.001	<0.001		<0.001	<0.001
Week 30 — no. (%)	36 (29.8)	63 (52.1)	62 (50.8)	32 (26.0)	57 (47.1)	72 (60.0)
P value		<0.001	0.002		<0.001	<0.001
Week 54 — no. (%)	24 (19.8)	55 (45.5)	54 (44.3)	—	—	—
P value		<0.001	<0.001			
Refractory to corticosteroid therapy at week 8 — no./total no. (%)	12/34 (35.3)	24/31 (77.4)	21/31 (67.7)	12/32 (37.5)	19/30 (63.3)	19/29 (65.5)
P value		<0.001	0.010		0.053	0.011
Not refractory to corticosteroid therapy at week 8 — no./total no. (%)	33/87 (37.9)	60/90 (66.7)	54/91 (59.3)	24/91 (26.4)	59/91 (64.8)	64/91 (70.3)
P value		<0.001	0.005		<0.001	<0.001
Clinical remission — no. (%)						
Week 8	18 (14.9)	47 (38.8)	39 (32.0)	7 (5.7)	41 (33.9)	33 (27.5)
P value		<0.001	0.002		<0.001	<0.001
Week 30	19 (15.7)	41 (33.9)	45 (36.9)	13 (10.6)	31 (25.6)	43 (35.8)
P value		0.001	<0.001		0.003	<0.001
Week 54	20 (16.5)	42 (34.7)	42 (34.4)	—	—	—
P value		0.001	0.001			
Partial Mayo score — median (interquartile range)†						
Baseline	6.0 (5.0–7.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)
Week 2	5.0 (4.0–6.0)	3.0 (2.0–5.0)	4.0 (2.0–5.0)	5.0 (4.0–7.0)	4.0 (2.0–5.0)	4.0 (3.0–5.0)
Week 6	5.0 (3.0–6.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	5.0 (4.0–7.0)	3.0 (1.0–5.0)	3.0 (2.0–5.0)
Week 8	5.0 (3.0–6.0)	2.0 (1.0–4.0)	3.0 (1.0–5.0)	5.0 (3.0–7.0)	2.0 (1.0–4.0)	3.0 (2.0–5.0)
Week 30	5.0 (3.0–6.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	6.0 (3.0–7.0)	4.0 (1.0–6.0)	3.0 (1.0–5.0)
Week 54	5.0 (4.0–7.0)	3.0 (1.0–6.0)	4.0 (1.0–6.0)	—	—	—

120) had had a clinical response, as compared with 29.3 percent of patients in the placebo group (36 of 123, P<0.001 for both comparisons) (Fig. 2A).

In both studies, the proportions of patients who had a clinical response or remission at weeks 8 and 30, and at week 54 in the ACT 1 trial, were higher by a factor of 1.7 to more than 2 in the infliximab groups than in the placebo groups (Fig. 2A and 2B). The rates of clinical response were similar between the subpopulations of patients who were corticosteroid-refractory and those who were not corticosteroid-refractory (Table 3).

The proportions of patients with a sustained clinical response or remission were significantly higher in the infliximab groups than in the placebo groups (Fig. 3). The partial Mayo scores in both studies provide evidence of clinical improvement as early as week 2 (Table 3).

Mucosal healing at weeks 8 and 30 in each study and at week 54 in ACT 1 occurred in significantly more patients in the infliximab groups than in the placebo groups (P≤0.009 for all comparisons) (Table 3 and Fig. 2C).

At baseline, 61.0 percent of patients (222 of 364) were receiving corticosteroids in ACT 1, as were 51.1 percent in ACT 2 (186 of 364). The baseline

Table 3. (Continued.)

Variable	ACT 1			ACT 2		
	Placebo (N=121)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=122)	Placebo (N=123)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=120)
Mucosal healing — no. (%)						
Week 8	41 (33.9)	75 (62.0)	72 (59.0)	38 (30.9)	73 (60.3)	74 (61.7)
P value		<0.001	<0.001		<0.001	<0.001
Week 30	30 (24.8)	61 (50.4)	60 (49.2)	37 (30.1)	56 (46.3)	68 (56.7)
P value		<0.001	<0.001		0.009	<0.001
Week 54	22 (18.2)	55 (45.5)	57 (46.7)	—	—	—
P value		<0.001	<0.001			
Daily corticosteroid dose in mg — median (interquartile range)						
Baseline	20.0 (10.0–30.0)	20.0 (10.0–25.0)	20.0 (10.0–25.0)	20.0 (15.0–30.0)	20.0 (10.0–30.0)	20.0 (15.0–26.7)
Week 8	20.0 (10.0–30.0)	20.0 (10.0–25.0)	20.0 (10.0–25.0)	20.0 (15.0–30.0)	20.0 (10.0–30.0)	20.0 (10.0–25.0)
Week 30	10.0 (0.8–30.0)	5.6 (0.0–20.0)	10.0 (0.0–20.0)	20.0 (5.6–30.0)	7.5 (0.0–20.0)	5.0 (0.0–20.0)
Week 54	20.0 (5.0–30.0)	5.0 (0.0–20.0)	10.0 (0.0–20.0)	—	—	—
Clinical remission and discontinued use of corticosteroids — no./total no. (%)						
Week 30	8/79 (10.1)	17/70 (24.3)	14/73 (19.2)	2/60 (3.3)	11/60 (18.3)	18/66 (27.3)
P value		0.030	0.125		0.010	<0.001
Week 54	7/79 (8.9)	18/70 (25.7)	12/73 (16.4)	—	—	—
P value		0.006	0.149			

* Dashes denote not applicable.
† Mayo scores range from 0 to 12, with higher scores indicating more severe disease. A partial Mayo score is the Mayo score without the endoscopic subscore.

median daily corticosteroid dose was 20 mg per day in both studies. The proportions of patients who were in clinical remission and had discontinued corticosteroids at week 30 in both studies and at week 54 in ACT 1 were higher in the infliximab groups than in the placebo groups. Similarly, the decreases in the median daily corticosteroid doses were greater among patients in the infliximab groups than among those in the placebo group (Table 3).

ANTIBODIES AGAINST INFLIXIMAB

At week 54, among 229 patients in ACT 1 who had serum samples available for the assessment of antibodies against infliximab, 14 (6.1 percent) had positive tests for antibodies at some point after the first infusion of infliximab (Table 4), 36 (15.7 percent) had negative tests (undetectable serum infliximab concentrations), and 179 (78.2 percent) had inconclusive tests (negative for antibodies in the presence of detectable serum infliximab concentrations). Among 188 patients in ACT 2 who had serum samples available for the assessment of antibodies against infliximab, 12 (6.4 percent) had positive tests for antibodies, 34 (18.1 percent) had negative tests, and 142 (75.5 percent) had inconclusive tests.

In ACT 1, a clinical response at week 54 occurred in 3 of 14 patients with positive tests for antibodies (21.4 percent), as compared with 3 of 36 patients with negative tests (8.3 percent) and 103 of 179 patients with inconclusive tests (57.5 percent). In ACT 2, a clinical response at week 30 occurred in 11 of 19 patients with positive tests for antibodies (57.9 percent), as compared with 45 of 79 patients with negative tests (57.0 percent) and 71 of 92 patients with inconclusive tests (77.2 percent).

SAFETY

In the 54-week ACT 1, patients were treated for a mean of 24.2 weeks in the placebo group, 34.8

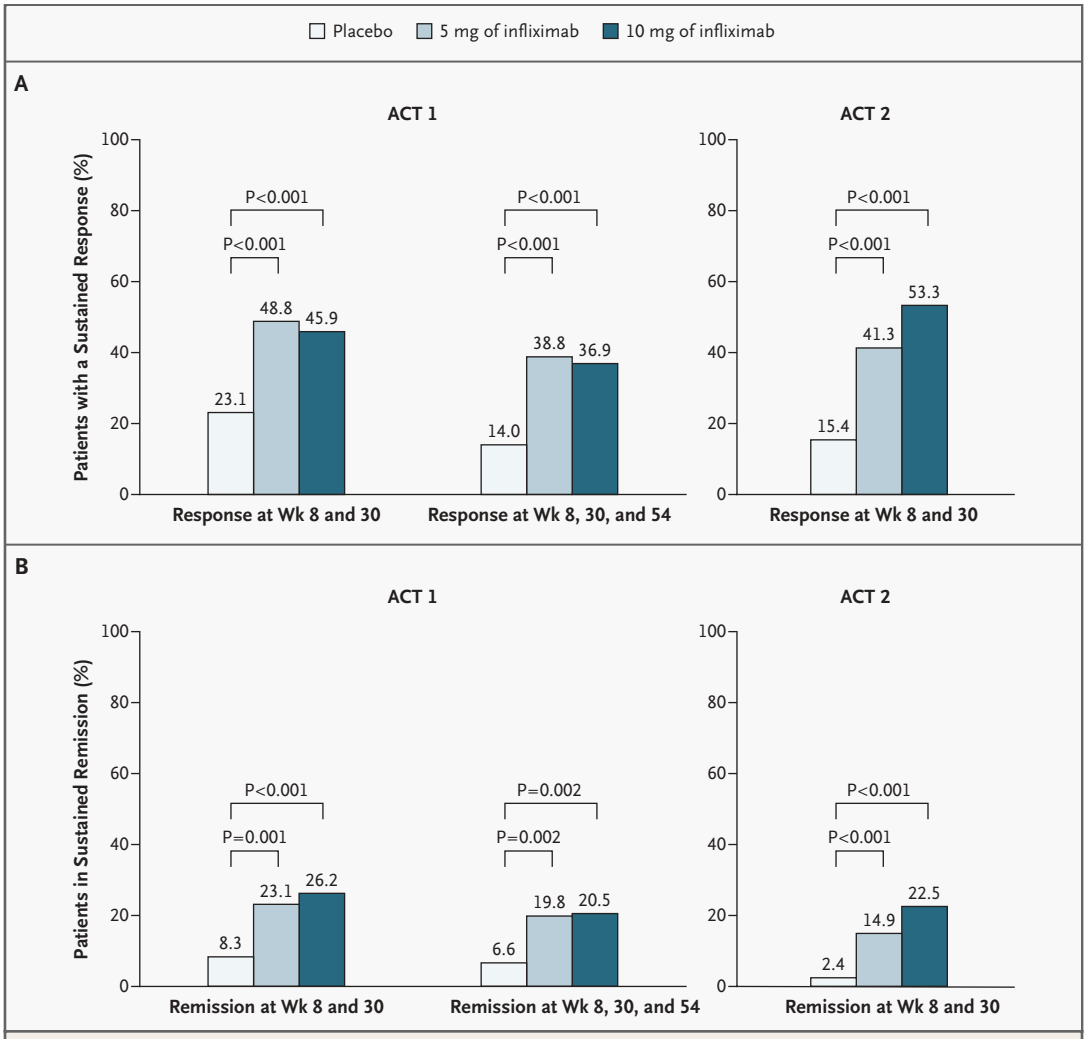

Figure 3. **Proportion of Patients with a Sustained Clinical Response (Panel A) and in Sustained Clinical Remission (Panel B) in ACT 1 and ACT 2.**

weeks in the group receiving 5 mg of infliximab, and 33.3 weeks in the group receiving 10 mg of infliximab. In the 30-week ACT 2, patients received treatment for 14.4 weeks in the placebo group, 19.3 weeks in the group receiving 5 mg of infliximab, and 18.6 weeks in the group receiving 10 mg of infliximab (Table 4).

In both studies, the proportions of patients with adverse events were similar in the placebo group and the two infliximab groups (Table 4). In ACT 1, serious adverse events occurred in 25.6 percent of patients in the placebo group, 21.5 percent of patients receiving 5 mg of infliximab, and 23.8 percent of patients receiving 10 mg of infliximab. In ACT 2, the respective rates of serious adverse events were 19.5 percent, 10.7 percent, and 9.2 percent. In both studies, serious adverse events were most commonly related to the gastrointestinal system.

In ACT 1, similar numbers of patients in each group discontinued treatment because of an adverse event; in ACT 2, more patients in the placebo group than in the two infliximab groups discontinued treatment because of an adverse event (Table 4). Among adverse events in ACT 1, prostatic adenocarcinoma developed in one patient with a two-year history of an elevated prostate-specific antigen concentration, and colonic dysplasia developed in one patient; both had received 5 mg of infliximab. Basal-cell carcinoma developed in one patient treated with 10 mg of infliximab. In ACT 2,

basal-cell carcinoma developed in one patient who received placebo, and rectal adenocarcinoma developed in one patient treated with 5 mg of infliximab.

Only three neurologic events occurred, all in patients treated with infliximab. In ACT 1, optic neuritis developed in one patient who received 5 mg of infliximab. After the completion of ACT 2, a multifocal motor neuropathy with conduction block syndrome developed in one patient who received 10 mg of infliximab and optic neuritis developed in one patient who received 5 mg of infliximab.

In both studies, the development of antinuclear antibodies and anti–double-stranded DNA antibodies was more common among patients in the infliximab groups than among those in the placebo group (Table 4). Only one patient had a lupus-like reaction. This patient was enrolled in ACT 2 and received 5 mg of infliximab.

The incidence of infections was similar among the groups in both studies (Table 4). In ACT 1, serious infections occurred in five patients (4.1 percent) in the placebo group, three patients (2.5 percent) in the group receiving 5 mg of infliximab, and eight patients (6.6 percent) in the group receiving 10 mg of infliximab. In ACT 2, serious infections occurred in one patient (0.8 percent) in the placebo group, two patients (1.7 percent) in the group receiving 5 mg of infliximab, and three patients (2.5 percent) in the group receiving 10 mg of infliximab. In ACT 1, tuberculosis developed in one patient treated with 10 mg of infliximab. Histoplasma pneumonia developed in one patient in the group receiving 5 mg of infliximab during the ACT 2 extension, a study phase in which patients who completed the 30-week, double-blind phase — and in the opinion of the investigators would benefit from continued treatment — were enrolled and continued to receive the study medication to which they had been randomly assigned. The disease progressed to acute respiratory distress syndrome, resulting in the patient's death.

In ACT 1, infusion reactions occurred in 13 patients (10.7 percent) in the placebo group, 12 patients (9.9 percent) in the group receiving 5 mg of infliximab, and 15 patients (12.3 percent) in the group receiving 10 mg of infliximab (Table 4). A possible delayed hypersensitivity reaction developed in two patients (1.7 percent) in the placebo group and two patients (1.7 percent) in the group receiving 5 mg of infliximab. In ACT 2, infusion reactions occurred in 10 patients (8.1 percent) in the placebo group, 14 patients (11.6 percent) in the group receiving 5 mg of infliximab, and 14 patients (11.7 percent) in the group receiving 10 mg of infliximab. A possible delayed hypersensitivity reaction occurred in one patient (0.8 percent) in the group receiving 10 mg of infliximab.

At week 54 in ACT 1, 35.7 percent of patients with positive tests for antibodies against infliximab (5 of 14) had infusion reactions, as compared with 9.8 percent of patients with negative or inconclusive tests (21 of 215). In ACT 2, at week 30, 50.0 percent of patients with positive tests for antibodies against infliximab (6 of 12) had infusion reactions, as compared with 9.7 percent of patients with negative or inconclusive tests (17 of 176). No patient in either study who had a positive test for antibodies had a serious infusion reaction or an anaphylactic reaction. Only one patient in the group receiving 5 mg of infliximab in ACT 1 who had a positive test for antibodies had a serious delayed hypersensitivity reaction.

DISCUSSION

Inducing and maintaining a clinical response and clinical remission and minimizing the use of corticosteroids are unmet goals in the treatment of patients with ulcerative colitis, particularly those who have not had a response to corticosteroids, azathioprine, or mercaptopurine.[26] Our results show that infliximab is effective in patients who have moderate-to-severe disease despite the use of conventional therapy, in terms of a clinical response and remission. As compared with patients who received placebo, patients who received infliximab were significantly more likely to have a clinical response and be in clinical remission at weeks 8 and 30 in both trials and in week 54 in ACT 1. Similarly, patients who received infliximab were significantly more likely to have mucosal healing at weeks 8 and 30 in both trials and in week 54 in ACT 1. These findings are of particular importance in light of the recent suggestion that mucosal healing is the strongest predictor of a reduced risk of cancer among patients with ulcerative colitis.[27,28]

It is noteworthy that these studies were conducted in patients who had active disease despite treatment with conventional therapy. At baseline, among all 728 patients, 72 percent were receiving 5-aminosalicylates, 56 percent were receiving corticosteroids, and 46 percent were receiving immunosuppressants. Of the patients who were receiv-

Table 4. Summary of Safety and Immunogenicity Analyses for All Patients Who Underwent Randomization.*

Variable	ACT 1 (through Week 54)				ACT 2 (through Week 30)			
	Placebo (N=121)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=122)	P Value†	Placebo (N=123)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=120)	P Value†
Mean duration of treatment — wk	24.2	34.8	33.3	ND	14.4	19.3	18.6	ND
Mean duration of follow-up — wk	36.2	44.9	44.2	ND	21.9	27.5	26.6	ND
Any adverse event — no. of patients (%)	103 (85.1)	106 (87.6)	111 (91.0)	0.31	90 (73.2)	99 (81.8)	96 (80.0)	0.11
Adverse events occurring in ≥10% of any treatment group — no. of patients (%)								
Worsening ulcerative colitis	40 (33.1)	23 (19.0)	26 (21.3)		20 (16.3)	11 (9.1)	12 (10.0)	
Abdominal pain	16 (13.2)	11 (9.1)	21 (17.2)		14 (11.4)	10 (8.3)	13 (10.8)	
Nausea	14 (11.6)	14 (11.6)	17 (13.9)		9 (7.3)	6 (5.0)	10 (8.3)	
Upper respiratory tract infection	28 (23.1)	20 (16.5)	29 (23.8)		14 (11.4)	16 (13.2)	14 (11.7)	
Pharyngitis	10 (8.3)	12 (9.9)	14 (11.5)		3 (2.4)	7 (5.8)	9 (7.5)	
Sinusitis	4 (3.3)	8 (6.6)	16 (13.1)		7 (5.7)	11 (9.1)	7 (5.8)	
Pain	19 (15.7)	14 (11.6)	14 (11.5)		11 (8.9)	9 (7.4)	12 (10.0)	
Rash	16 (13.2)	14 (11.6)	7 (5.7)		3 (2.4)	2 (1.7)	5 (4.2)	
Arthralgia	18 (14.9)	21 (17.4)	21 (17.2)		6 (4.9)	16 (13.2)	10 (8.3)	
Headache	27 (22.3)	22 (18.2)	18 (14.8)		18 (14.6)	19 (15.7)	26 (21.7)	
Fever	10 (8.3)	14 (11.6)	12 (9.8)		12 (9.8)	13 (10.7)	9 (7.5)	
Anemia	12 (9.9)	4 (3.3)	9 (7.4)		13 (10.6)	6 (5.0)	2 (1.7)	
Fatigue	11 (9.1)	14 (11.6)	14 (11.5)		6 (4.9)	6 (5.0)	14 (11.7)	
Adverse events of particular interest — no. of patients (%)								
Fungal dermatitis	8 (6.6)	1 (0.8)	3 (2.5)		0	0	1 (0.8)	
Pneumonia	0	2 (1.7)	4 (3.3)		0	0	2 (1.7)	
Varicella–zoster virus infection	1 (0.8)	1 (0.8)	0		0	1 (0.8)	0	
Herpes zoster	0	1 (0.8)	0		1 (0.8)	2 (1.7)	1 (0.8)	
Adverse events leading to discontinuation of study drug — no. of patients (%)	11 (9.1)	10 (8.3)	11 (9.0)	1.00	12 (9.8)	2 (1.7)	5 (4.2)	0.01
Serious adverse events — no. of patients (%)	31 (25.6)	26 (21.5)	29 (23.8)	0.60	24 (19.5)	13 (10.7)	11 (9.2)	0.01
Infections — no. of patients (%)	47 (38.8)	53 (43.8)	60 (49.2)	0.18	29 (23.6)	33 (27.3)	34 (28.3)	0.45
Infections requiring antimicrobial treatment — no. of patients (%)	25 (20.7)	39 (32.2)	43 (35.2)	0.01	15 (12.2)	18 (14.9)	17 (14.2)	0.63
Serious infections — no. of patients (%)	5 (4.1)	3 (2.5)	8 (6.6)	1.00	1 (0.8)	2 (1.7)	3 (2.5)	0.67
Bacterial infection	1 (0.8)	0	0		0	0	0	
Upper respiratory tract infection	1 (0.8)	0	0		0	0	0	
Pneumonia	0	0	3 (2.5)		0	0	0	
Tuberculosis	0	0	1 (0.8)		0	0	0	
Abscess	1 (0.8)	0	2 (1.6)		1 (0.8)	0	1 (0.8)	

Pharyngitis	1 (0.8)	0	1 (0.8)		0	0	0	
Gastroenteritis	0	1 (0.8)	1 (0.8)		0	1 (0.8)	0	
Earache	0	0	0		0	1 (0.8)	0	
Fever	0	0	1 (0.8)		0	1 (0.8)	0	
Vaginitis	0	0	0		0	0	1 (0.8)	
Appendicitis	0	1 (0.8)	0		0	0	0	
Colitis	0	0	1 (0.8)		0	0	0	
Surgical-wound infection	1 (0.8)	0	1 (0.8)		0	0	1 (0.8)	
Pancreatitis	0	1 (0.8)	0		0	0	0	
Pleurisy	0	0	1 (0.8)		0	0	0	
Sinusitis	1 (0.8)	0	0		0	0	0	
Acute infusion reaction (any adverse event occurring ≤2 hr after start of infusion) — no. of patients (%)	13 (10.7)	12 (9.9)	15 (12.3)	1.00	10 (8.1)	14 (11.6)	14 (11.7)	0.37
Possible delayed hypersensitivity reactions — no. of patients (%)	2 (1.7)	2 (1.7)	0	0.60	0	0	1 (0.8)	1.00
Antinuclear antibodies — no. of patients/total no. (%)‡	7/95 (7.4)	32/101 (31.7)	33/95 (34.7)	<0.001	6/82 (7.3)	23/88 (26.1)	22/78 (28.2)	<0.001
Antibodies against double-stranded DNA — no. of patients/total no. (%)‡	0/104	12/112 (10.7)	7/108 (6.5)	<0.001	0/93	5/102 (4.9)	6/100 (60.0)	0.02
Antibodies against infliximab during the study — no. of patients/total no. (%)§	—	9/116 (7.8)	5/113 (4.4)	—	—	9/95 (9.5)	3/93 (3.2)	—
Pharmacologic management at baseline — no. of patients/total no. (%)¶								
Corticosteroids or immunosuppressants	—	6/96 (6.2)	2/94 (2.1)		—	3/65 (4.6)	2/64 (3.1)	
Corticosteroids and immunosuppressants	—	0/34	1/30 (3.3)		—	0/24	0/48	
Corticosteroids without immunosuppressants	—	5/34 (14.7)	1/38 (2.6)		—	3/22 (13.6)	2/27 (7.4)	
Immunosuppressants without corticosteroids	—	1/28 (3.6)	0/26		—	0/19	0/13	
Neither corticosteroids nor immunosuppressants	—	3/20 (15.0)	3/19 (15.8)		—	6/30 (20.0)	1/29 (3.4)	

* ND denotes not done, and dashes not applicable.
† P values are based on Fisher's exact test for the comparison of the combined infliximab groups with the placebo group.
‡ Denominators represent patients with negative findings at baseline. Test results for antinuclear antibodies were considered positive if the titer was at least 1:40. Samples positive for antinuclear antibodies were tested for antibodies against double-stranded DNA . Test results for anti–double-stranded DNA were positive if the titer was at least 1:10 (according to a crithidia assay) and at least 5.4 IU (according to Farr radioimmunoassay).
§ Denominators represent patients with appropriate serum samples (i.e., patients with either antibodies against infliximab at some time after their first infusion or at least one sample obtained after their last infusion).
¶ Immunosuppressants include mercaptopurine and azathioprine.

ing corticosteroids at baseline, approximately 22 percent of patients treated with infliximab had discontinued corticosteroids by week 30 among 269 patients in both studies or by week 54 among 143 patients in ACT 1 while maintaining clinical remission. Since corticosteroid therapy is associated with considerable morbidity,[29] this corticosteroid-sparing effect is likely to be clinically meaningful.

Our data do not show any major differences in efficacy between the two doses of infliximab that were studied. Thus, the preferred initial dose of infliximab in patients with ulcerative colitis is 5 mg per kilogram on the basis of a combination of safety, efficacy, and pharmacoeconomic issues.

In both studies, the proportions of patients reporting any adverse event were similar among the three groups. The numbers of serious infections, lupus-like reactions, and neurologic diseases were slightly higher among patients treated with infliximab than among patients who received placebo. The case of tuberculosis and the fatal case of histoplasmosis in patients receiving infliximab underscore the need for physicians and patients to remain vigilant for signs and symptoms of infection. Studies such as ACT 1 and ACT 2 were designed to evaluate efficacy and lack sufficient statistical power to detect differences among treatment groups in the occurrence of rare side effects. The safety findings in these studies were similar to the data reported in clinical studies of infliximab in patients with Crohn's disease,[15,16,30-32] in cohort studies,[33,34] and in post-marketing surveillance.[35]

The risks of infliximab use must be weighed against the risks of colectomy with the creation of an ileoanal pouch, which include pouchitis in approximately 50 percent of patients,[5] pouch failure in approximately 10 percent of patients,[36] an 80 percent reduction in female fecundity,[37] and the inconvenience of nocturnal fecal incontinence in approximately 24 percent of patients.[38]

The rate of development of antibodies against infliximab after the three-dose induction regimen and after the maintenance dose every eight weeks in the patients with ulcerative colitis in our studies is similar to that reported for patients with Crohn's disease.[15,16,25,31] As was true of patients with Crohn's disease who were treated with infliximab, patients with ulcerative colitis who had positive tests for antibodies were more likely than those without antibodies to have infusion reactions; however, most of these infusion reactions were mild. In contrast to previous experience, patients with positive or inconclusive tests for antibodies were more likely to have a clinical response at week 30 or 54[25] than were patients with negative antibody tests. Patients with negative tests had a lower rate of clinical response at those times, perhaps owing to undetectable serum infliximab concentrations. This effect was most prominent at week 54. Concomitant use of mercaptopurine or azathioprine may have protected against the development of antibodies against infliximab; however, these findings should be interpreted with caution because of the small number of patients with positive tests for antibodies.

Our results also provide insight into the pathogenesis of ulcerative colitis. Ulcerative colitis is believed to result from an immune response of type 2 helper T cells in the colonic mucosa, whereas Crohn's disease is considered an immune disease of type 1 helper T cells, which would suggest that TNF-α is not an important mediator in ulcerative colitis. Our findings show that TNF-α plays a role in the disease process and that targeting this cytokine is an effective therapy for ulcerative colitis. Whether the mechanism of action of infliximab in ulcerative colitis also includes the induction of apoptosis of inflammatory cells expressing membrane-bound TNF-α, as in Crohn's disease,[39] requires further investigation.

In conclusion, an induction regimen of three doses of infliximab followed by maintenance infusions every eight weeks in patients with moderate-to-severe active ulcerative colitis was superior to placebo in achieving clinical response and remission, mucosal healing, and corticosteroid-sparing effects during 30 to 54 weeks of therapy.

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APPENDIX

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