ORIGINAL ARTICLE

Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease

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ABSTRACT

BACKGROUND

The comparative efficacy and safety of infliximab and azathioprine therapy alone or in combination for Crohn's disease are unknown.

METHODS

In this randomized, double-blind trial, we evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy, and the two drugs combined in 508 adults with moderate-to-severe Crohn's disease who had not undergone previous immunosuppressive or biologic therapy. Patients were randomly assigned to receive an intravenous infusion of 5 mg of infliximab per kilogram of body weight at weeks 0, 2, and 6 and then every 8 weeks plus daily oral placebo capsules; 2.5 mg of oral azathioprine per kilogram daily plus a placebo infusion on the standard schedule; or combination therapy with the two drugs. Patients received study medication through week 30 and could continue in a blinded study extension through week 50.

RESULTS

Of the 169 patients receiving combination therapy, 96 (56.8%) were in corticosteroid-free clinical remission at week 26 (the primary end point), as compared with 75 of 169 patients (44.4%) receiving infliximab alone ($P=0.02$) and 51 of 170 patients (30.0%) receiving azathioprine alone ($P<0.001$ for the comparison with combination therapy and $P=0.006$ for the comparison with infliximab). Similar numerical trends were found at week 50. At week 26, mucosal healing had occurred in 47 of 107 patients (43.9%) receiving combination therapy, as compared with 28 of 93 patients (30.1%) receiving infliximab ($P=0.06$) and 18 of 109 patients (16.5%) receiving azathioprine ($P<0.001$ for the comparison with combination therapy and $P=0.02$ for the comparison with infliximab). Serious infections developed in 3.9% of patients in the combination-therapy group, 4.9% of those in the infliximab group, and 5.6% of those in the azathioprine group.

CONCLUSIONS

Patients with moderate-to-severe Crohn's disease who were treated with infliximab plus azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free clinical remission than those receiving azathioprine monotherapy. (ClinicalTrials.gov number, NCT00094458.)

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Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract that is defined by relapsing and remitting episodes, with progression over time to complications of stricture, fistulas, or abscesses.[1] Symptoms of mild-to-moderate disease are treated with mesalamine, budesonide, or systemic corticosteroids.[2,3] The therapeutic benefit of corticosteroids is frequently offset by side effects of prolonged exposure.[4] In addition, systemic corticosteroids and budesonide are not effective for maintenance therapy.[5-7] Azathioprine and 6-mercaptopurine are frequently prescribed for patients in whom first-line therapies fail — in particular, those who are dependent on or do not have a response to systemic corticosteroids.[2,3,8] Approximately 40% of patients treated with azathioprine remain in remission at 1 year.[9] Infliximab and other monoclonal antibodies targeting tumor necrosis factor (TNF) have shown efficacy in inducing and maintaining remission in patients with Crohn's disease.[10-12] Treatment guidelines generally recommend initiating treatment with first-line agents, including mesalamine and systemic corticosteroids, followed by azathioprine, with anti-TNF therapies reserved for patients in whom conventional therapies have failed.[2,3,8] In a multicenter trial, we compared the efficacy of infliximab, azathioprine, and the two drugs combined for inducing and maintaining corticosteroid-free clinical remission in patients with active Crohn's disease.

METHODS

STUDY DESIGN AND PATIENTS

The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) was a randomized, double-blind, 30-week trial, with a 20-week extension in which blinding was maintained. The trial was conducted at 92 centers from March 2005 through November 2008. The institutional review board at each center approved the protocol, and all patients provided written informed consent.

Eligible patients were at least 21 years of age and had had Crohn's disease for at least 6 weeks, with a score of 220 to 450 points on the Crohn's Disease Activity Index (CDAI).[13] This index consists of eight factors, with each factor totaled after adjustment with a weighting factor. (Severe disease is defined as a score of more than 450, and remission as a score of less than 150.) Patients were either corticosteroid-dependent (with a CDAI score of at least 220 points after reduction of the corticosteroid dose), were being considered for a second course of systemic corticosteroids within 12 months, or had not had a response to at least 4 weeks of either mesalamine (at a dose of ≥2.4 g per day) or budesonide (at a dose of ≥6 mg per day). None of the patients had undergone previous treatment with azathioprine, 6-mercaptopurine, methotrexate, or an anti-TNF biologic agent.

Patients with the short bowel syndrome, an ostomy, a symptomatic stricture, an abscess, a recent history of abdominal surgery (within the previous 6 months), a history of tuberculosis or other granulomatous infection, a positive chest radiograph or tuberculin skin test with purified protein derivative, a recent history of an opportunistic infection (within the previous 6 months), active infection with hepatitis B or C, infection with the human immunodeficiency virus, multiple sclerosis, cancer, or a homozygous mutant or heterozygous thiopurine methyltransferase phenotype were not eligible (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

STUDY TREATMENTS AND RANDOMIZATION

Patients were randomly assigned to receive intravenous infusions of infliximab (Remicade, Centocor Ortho Biotech) at a dose of 5 mg per kilogram of body weight plus daily oral placebo capsules, oral azathioprine capsules at a daily dose of 2.5 mg per kilogram plus placebo infusions, or combination therapy with infliximab and azathioprine. Infusions were administered at weeks 0, 2, and 6, and then every 8 weeks. Patients were followed through week 30, when they were given the option of continuing to receive their assigned therapy, with blinding maintained, in a 20-week extension trial, with follow-up through week 50. A follow-up telephone interview was conducted to collect reports of serious adverse events and related concomitant use of medications 4 weeks after a patient completed the study at week 30 or week 50 or withdrew from the trial.

Randomization was performed centrally with the use of an adaptive randomization procedure stratified according to center, the duration of Crohn's disease (<3 years or ≥3 years), and status with respect to the systemic corticosteroid dose

(the equivalent of <20 mg or ≥20 mg of prednisone daily).

Oral mesalamine was continued at a stable dose. Systemic corticosteroids could be initiated (for patients not receiving them at baseline) with the dose maintained, increased, or decreased until week 14 (maximum allowed dose, 40 mg per day). After week 14, the dose was tapered at a rate of at least 5 mg per week. Budesonide could be maintained or decreased until week 14 (maximum dose, 9 mg per day). After week 14, budesonide was tapered at a rate of 3 mg every 2 weeks to a dose of 6 mg per day or less.

EVALUATION OF EFFICACY AND SAFETY

Scores on the CDAI and the Inflammatory Bowel Disease Questionnaire (IBDQ)[14] were determined at weeks 0, 2, 6, 10, 18, 26, 34, 42, and 50. Ileocolonoscopy was performed at baseline and again at week 26 in patients who had mucosal ulcers at the baseline examination. All colonoscopies were videotaped with the use of a standard protocol and interpreted by a single reviewer, who was unaware of study-group assignments and the timing of the procedure (i.e., at baseline or week 26). Clinical remission was defined as an absolute CDAI score of less than 150 points.[13,15] Corticosteroid-free clinical remission was defined as clinical remission in patients who had not received budesonide at a daily dose of more than 6 mg or systemic corticosteroids for at least 3 weeks. Response-70 and response-100 were defined as reductions from baseline in the CDAI score of at least 70 and 100 points, respectively.[13,15] Mucosal healing was defined as the absence of mucosal ulceration at week 26 in patients who had confirmed mucosal ulceration at baseline.

Monitoring for adverse events and use of concomitant medications was performed through week 54. Blood samples were collected for testing at weeks 0 and 26 for levels of C-reactive protein (CRP) and at weeks 0, 30, and 46 for the presence of antibodies to infliximab.[16]

PRIMARY AND SECONDARY END POINTS

The primary efficacy end point was the rate of corticosteroid-free clinical remission at week 26; the rates of corticosteroid-free clinical remission at other time points were secondary efficacy end points. Additional secondary efficacy end points included the proportion of patients with mucosal healing at week 26 among those who had ulcerations at baseline, the rate of any remission, response-70, response-100, the IBDQ score, the corticosteroid dose at each data-collection time point (weeks 0, 2, 6, 10, 18, 26, 34, 42, and 50), and the change in the CRP level from baseline to week 26.

STUDY OVERSIGHT

The study was jointly designed by members of the SONIC executive committee of academic investigators and researchers employed by Centocor Ortho Biotech, one of the trial sponsors. Data were collected and analyzed by Quintiles. The two lead academic authors wrote the first draft of the manuscript. The academic authors and representatives of the sponsor made the decision to submit the manuscript for publication. The academic authors vouch for the veracity and completeness of the data and data analyses.

STATISTICAL ANALYSIS

For the primary end point, the rate of corticosteroid-free clinical remission at week 26, it was estimated that 500 patients would be needed to provide a power of 94% in order to detect a difference in remission rates of 20% between the combination-therapy group and the azathioprine group, on the assumption that the rate of remission would be 60% in the combination-therapy group and 40% in the azathioprine group.

To control for a type I error of 0.05 or less, the primary end-point analyses were conducted in a prespecified, sequential manner, in which the azathioprine group was compared with the combination-therapy group first at a 0.05 (two-sided) significance level. The azathioprine and infliximab groups were then compared at a 0.05 (two-sided) significance level only if the first comparison was significant. If the first comparison was not significant, then the second comparison was to be considered not significant. Given the large number of prespecified secondary efficacy variables that were evaluated at multiple time points during the study, the P values for all secondary efficacy variables should be considered nominal, since no adjustments were made for multiple comparisons.

Demographic and baseline characteristics were compared with the use of the chi-square test or Fisher's exact test for categorical variables and with analysis of variance on a van der Waerden normal-scores test for continuous variables. A

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Azathioprine (N=170)	Infliximab (N=169)	Combination Therapy (N=169)	All Patients (N=508)	P Value†
Male sex — no. (%)	90 (52.9)	84 (49.7)	88 (52.1)	262 (51.6)	0.83
White race — no. (%)‡	147 (91.3)	146 (93.0)	142 (94.0)	435 (92.8)	0.22
Median age — yr§	35.0	35.0	34.0	34.0	0.95
Median body weight — kg	69.6	68.9	72.0	70.2	0.45
Median disease duration — yr	2.4	2.2	2.2	2.3	0.60
Median C-reactive protein — mg/dl¶	1.0	1.1	1.0	1.1	0.40
Crohn's Disease Activity Index score‖	287.2±52.9	284.8±62.1	289.9±55.0	287.3±56.7	0.59
Gastrointestinal area involved — no./total no. (%)					
Ileum or colon	170/170 (100.0)	163/169 (96.4)	167/169 (98.8)	500/508 (98.4)	
Ileum only	68/170 (40.0)	54/163 (33.1)	54/167 (32.3)	176/500 (35.2)	0.34
Colon only	33/170 (19.4)	45/163 (27.6)	40/167 (24.0)	118/500 (23.6)	
Ileum and colon	69/170 (40.6)	64/163 (39.3)	73/167 (43.7)	206/500 (41.2)	
Proximal gastrointestinal tract	7/170 (4.1)	12/169 (7.1)	16/169 (9.5)	35/508 (6.9)	0.15
Systemic corticosteroids — no. (%)					
Any type, according to daily dose**					
0	130 (76.5)	117 (69.2)	122 (72.2)	369 (72.6)	0.59
<20 mg	14 (8.2)	19 (11.2)	14 (8.3)	47 (9.3)	
≥20 mg	26 (15.3)	33 (19.5)	33 (19.5)	92 (18.1)	
Budesonide — no. (%)	25 (14.7)	28 (16.6)	19 (11.2)	72 (14.2)	0.36
5-Aminosalicylic compounds — no. (%)	104 (61.2)	87 (51.5)	85 (50.3)	276 (54.3)	0.09

* Plus–minus values are means ±SD.
† P values are for all comparisons among the three groups. P values for all categorical variables are based on a two-sided chi-square test. P values for continuous variables are based on analysis of variance on the van der Waerden normal scores.
‡ Race was self-reported. Data regarding race were not collected for 39 patients in France: 9 in the azathioprine group, 12 in the infliximab group, and 18 in the combination-therapy group.
§ The age range was 18 to 79 years in the azathioprine group, 18 to 80 in the infliximab group, and 19 to 68 in the combination-therapy group. On March 27, 2007, after hepatosplenic T-cell lymphoma had been reported in adolescents and very young adults receiving combination therapy with azathioprine and infliximab, the protocol was amended to increase the minimum eligible age from 18 to 21 years.
¶ Data for C-reactive protein were missing for one patient each in the azathioprine and infliximab groups and for four patients in the combination-therapy group.
‖ This index consists of eight factors, with each factor totaled after adjustment with a weighting factor ranging from 1 to 30, for a total possible score of approximately 600. Severe disease is defined as a total score of more than 450, and remission as a score of less than 150.
** Patients were stratified according to whether they were receiving a daily prednisone-equivalent dose of less than 20 mg (including those not taking corticosteroids at baseline) or 20 mg or more.

two-sided Cochran–Mantel–Haenszel chi-square test, stratified according to the duration of Crohn's disease and status with respect to corticosteroid dose at baseline, was used to compare remission, response, and mucosal healing. Changes in IBDQ scores were compared with the use of analysis of variance on van der Waerden normal scores, with adjustment for the duration of Crohn's disease and status with respect to the corticosteroid dose at baseline. Descriptive statistics summarize systemic corticosteroid use.

To evaluate the consistency of the treatment effect on corticosteroid-free clinical remission among the azathioprine, infliximab, and combi-

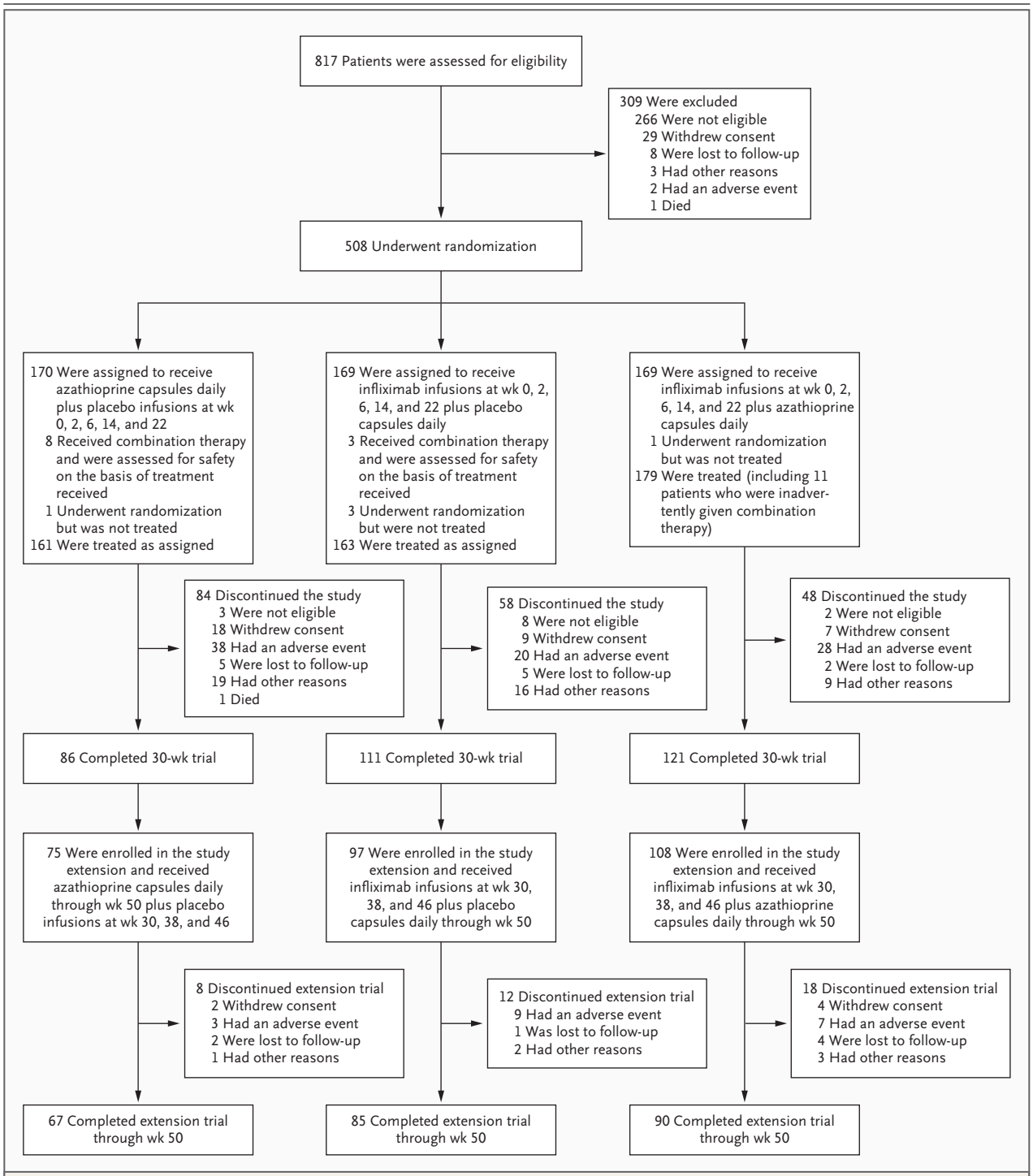

Figure 1. Enrollment and Outcomes through Week 50.

nation-therapy groups, we performed 11 prespecified subgroup analyses of demographic and baseline disease characteristics (Fig. 1 in the Supplementary Appendix). The odds ratios were calculated on the basis of logistic regression. We also performed post hoc subgroup analyses of the rates of corticosteroid-free clinical remission according to baseline mucosal lesion status and

Table 2. Efficacy Results.*

Variable	Azathioprine (N=170)	Infliximab (N=169)	P Value for Infliximab vs. Azathioprine†	Combination Therapy (N=169)	P Value for Combination Therapy vs. Infliximab†	P Value for Combination Therapy vs. Azathioprine†
Patients with corticosteroid-free clinical remission — no. (%)						
Week 6	24 (14.1)	50 (29.6)	<0.001	55 (32.5)	0.55	<0.001
Week 10	41 (24.1)	63 (37.3)	0.006	79 (46.7)	0.07	<0.001
Week 18	44 (25.9)	72 (42.6)	<0.001	89 (52.7)	0.06	<0.001
Week 26	51 (30.0)	75 (44.4)	0.006	96 (56.8)	0.02	<0.001
Week 34						
All patients‡	45 (26.5)	62 (36.7)	0.04	73 (43.2)	0.22	0.001
Patients with week 26 status carried forward through week 50§	52 (30.6)	70 (41.4)	0.03	89 (52.7)	0.03	<0.001
Patients entering trial extension¶	45 (60.0)	62 (63.9)	0.41	73 (67.6)	0.56	0.20
Week 42						
All patients‡	44 (25.9)	67 (39.6)	0.007	77 (45.6)	0.27	<0.001
Patients with week 26 status carried forward through week 50§	51 (30.0)	75 (44.4)	0.006	93 (55.0)	0.04	<0.001
Patients entering trial extension¶	44 (58.7)	67 (69.1)	0.13	77 (71.3)	0.67	0.06
Week 50						
All patients‡	41 (24.1)	59 (34.9)	0.03	78 (46.2)	0.04	<0.001
Patients with week 26 status carried forward through week 50§	48 (28.2)	67 (39.6)	0.03	94 (55.6)	0.002	<0.001
Patients entering trial extension¶	41 (54.7)	59 (60.8)	0.32	78 (72.2)	0.07	0.01
Patients who received systemic corticosteroid during the main study‖						
No. of patients (%)	60 (35.3)	60 (35.5)		58 (34.3)		
Baseline						
No. of patients	40	52		47		
Mean dose (mg/day)	23.8±12.6	24.8±16.2	ND	24.9±12.8	ND	ND
Week 2						
No. of patients	48	50		49		
Mean dose (mg/day)	22.9±12.5	21.2±11.9	ND	22.8±11.9	ND	ND
Week 6						
No. of patients	53	52		51		
Mean dose (mg/day)	18.6±11.6	17.7±11.0	ND	18.3±11.6	ND	ND
Week 10						
No. of patients	56	56		52		
Mean dose (mg/day)	16.2±11.2	15.7±14.9	ND	15.0±11.1	ND	ND
Week 18						
No. of patients	59	57		56		
Mean dose (mg/day)	13.5±10.9	13.2±17.2	ND	11.6±10.9	ND	ND
Week 26						
No. of patients	60	60		58		
Mean dose (mg/day)	11.6±10.3	11.0±16.0	ND	9.4±10.1	ND	ND

Table 2. (Continued.)

Variable	Azathioprine (N=170)	Infliximab (N=169)	P Value for Infliximab vs. Azathioprine†	Combination Therapy (N=169)	P Value for Combination Therapy vs. Infliximab†	P Value for Combination Therapy vs. Azathioprine†
Extension-study patients who received systemic corticosteroid during the main study or study extension‖						
No. of patients (%)	22 (29.3)	41 (42.3)		36 (33.3)		
Week 34						
No. of patients	22	37		36		
Mean dose (mg/day)	7.4±6.3	5.8±5.5	ND	6.4±5.7	ND	ND
Week 42						
No. of patients	22	38		36		
Mean dose (mg/day)	6.3±5.3	4.7±4.6	ND	5.7±5.8	ND	ND
Week 50						
No. of patients	22	41		36		
Mean dose (mg/day)	5.7±5.0	3.9±3.9	ND	5.0±5.4	ND	ND
Mucosal healing						
Baseline lesions — no. (%)**	115 (67.6)	99 (58.6)	0.08	111 (65.7)	0.18	0.70
Patients included in week 26 analysis — no. (%)††	109 (64.1)	93 (55.0)	0.09	107 (63.3)	0.12	0.88
Mucosal healing — no. (%)	18 (16.5)	28 (30.1)	0.02	47 (43.9)	0.06	<0.001

* Plus–minus values are means ±SD.
† P values were calculated by means of the Cochran–Mantel–Haenszel test, stratified according to the duration of Crohn's disease and the dose of systemic corticosteroid at baseline (the equivalent of 0 to <20 mg or ≥20 mg of prednisone daily). ND denotes not done; descriptive statistics were preplanned, and no post hoc statistical tests were performed because mean doses were similar among the three study groups.
‡ This category includes all patients who underwent randomization, with the assumption that patients who did not enter the trial extension did not reach the end point through week 50.
§ This category includes all patients who underwent randomization, with week 26 status carried forward through week 50 for patients who did not enter the trial extension.
¶ Results for weeks 34, 42, and 50 are based on 75 patients in the azathioprine group, 97 in the infliximab group, and 108 in the combination-therapy group who entered the trial extension.
‖ The systemic corticosteroid dose for a study week was calculated as the cumulative dose that a patient received up to a given study week divided by the number of days that the patient participated in the study up to that study week.
** Sixteen patients (four in the combination-therapy group, six in the infliximab group, and six in the azathioprine group) were excluded from the analysis of mucosal healing at week 26 because they underwent endoscopy before or after week 26.
†† Patients with lesions at baseline who did not undergo endoscopy at week 26 or who had results that could not be evaluated were assumed to have a lesion. These patients included 50 of 109 (45.9%) in the azathioprine group, 29 of 93 (31.2%) in the infliximab group, and 31 of 107 (29.0%) in the combination-therapy group.

CRP level and the presence or absence of antibodies to infliximab.

Efficacy analyses were performed according to the intention-to-treat principle and included all patients who had undergone randomization, with analyses performed according to the randomized study-group assignments, except for mucosal healing, which was analyzed according to prespecified per-protocol methods. Patients who required surgery for Crohn's disease or withdrew from the study were not considered to be in remission. After week 30, prespecified analyses were based on data only for patients who entered the extension trial. To perform exploratory analyses of outcomes for all patients through week 50, we assumed that the clinical end point at week 50 was not reached by patients who did not enter the trial extension, and we used the week 26 clinical end-point status carried forward through week 50 for those who did not enter the trial extension.

All patients receiving at least one dose of a study drug (administered orally or by infusion) were included in the safety analysis, according to the study drug that was actually received, with safety comparisons performed with the use of

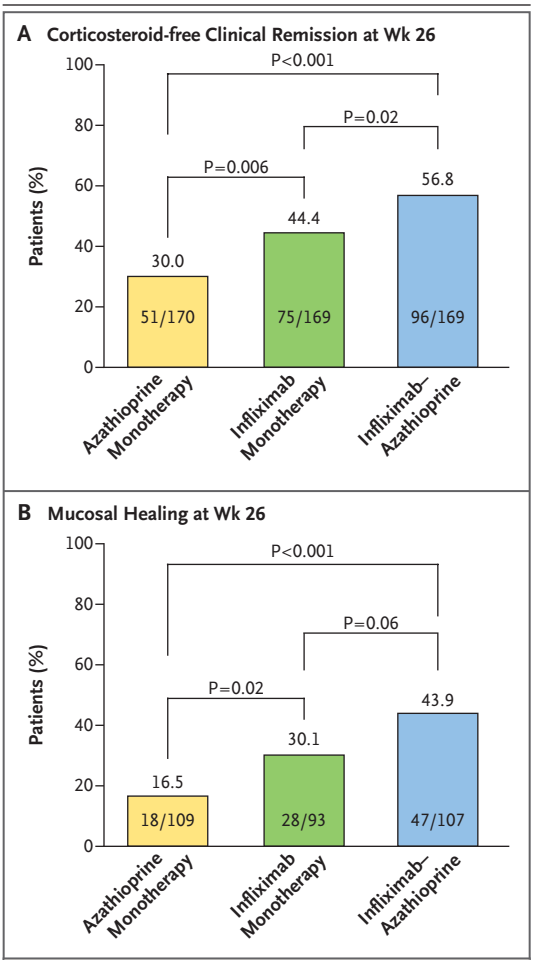

Figure 2. Patients with Corticosteroid-free Clinical Remission (Panel A) and Mucosal Healing (Panel B) at Week 26.

Fisher's exact test. Patients with at least one serum sample that was collected after the first infliximab infusion were included in the analysis of trough levels. Infliximab levels were compared by means of analysis of variance on van der Waerden normal scores, with adjustment for the duration of Crohn's disease and status with respect to corticosteroid dose at baseline.

RESULTS

PATIENTS

Of the 508 patients who underwent randomization, 170 were assigned to receive azathioprine monotherapy, 169 to receive infliximab monotherapy, and 169 to receive combination therapy with the two drugs. The baseline disease characteristics were similar in the three groups (Table 1, and Table 2 in the Supplementary Appendix). A total of 318 patients completed the 30-week trial, of whom 280 entered the extension trial (Fig. 1).

PRIMARY END POINT

At week 26, a total of 96 of the 169 patients (56.8%) receiving combination therapy, 75 of the 169 patients (44.4%) receiving infliximab, and 51 of the 170 patients (30.0%) receiving azathioprine were in corticosteroid-free clinical remission ($P=0.006$ for the comparison of infliximab vs. azathioprine, $P<0.001$ for the comparison of combination therapy vs. azathioprine, and $P=0.02$ for the comparison of combination therapy vs. infliximab) (Table 2 and Fig. 2A). The efficacy of combination therapy and infliximab was generally consistent among subgroups defined according to demographic and baseline disease characteristics (Fig. 1A, 1B, and 1C in the Supplementary Appendix).

SECONDARY END POINTS AND EXPLORATORY ANALYSES

At baseline, mucosal ulcerations were detected in 325 patients: 111 of 169 patients (65.7%) in the combination therapy group, 99 of 169 patients (58.6%) in the infliximab group, and 115 of 170 patients (67.6%) in the azathioprine group. In 93 patients, no ulcerations were found on ileocolonoscopy, and in 90 patients, either the findings were judged to be inconclusive by the central reader because of poor colon preparation or poor videotape technique or the procedure was not performed. At week 26, mucosal healing had occurred in 47 of 107 patients (43.9%) receiving combination therapy, in 28 of 93 patients (30.1%) receiving infliximab, and in 18 of 109 patients (16.5%) receiving azathioprine ($P=0.02$ for infliximab vs. azathioprine, $P<0.001$ for combination therapy vs. azathioprine, and $P=0.06$ for combination therapy vs. infliximab) (Table 2 and Fig. 2B).

For secondary end points at weeks 34, 42, and 50, the between-group differences also favored combination therapy and infliximab monotherapy over azathioprine (Table 2, and Table 3 in the Supplementary Appendix). Results of exploratory analyses that included all randomized patients at week 50 were consistent with those at week 26, with combination therapy and infliximab monotherapy providing a significantly greater benefit than azathioprine monotherapy,

and combination therapy providing a significantly greater benefit than infliximab monotherapy (Table 2, and Tables 4 and 5 and Fig. 2A and 2B in the Supplementary Appendix).

At baseline (6 days before the first dose of study medication was administered), budesonide or a systemic corticosteroid was being administered in 66 of 169 patients (39.1%) receiving combination therapy, 80 of 169 patients (47.3%) receiving infliximab, and 65 of 170 patients (38.2%) receiving azathioprine (Table 1). During the main study, systemic corticosteroid therapy was initiated in 11 patients receiving combination therapy, 8 patients receiving infliximab, and 20 patients receiving azathioprine. Mean doses of systemic corticosteroids through week 50 are summarized in Table 2.

The rates of corticosteroid-free clinical remission at week 26 in both the combination-therapy group and the infliximab group, as compared with the azathioprine group, were greater among subgroups of patients with higher baseline CRP levels (0.8 mg per deciliter or more), baseline mucosal lesions, and both higher baseline CRP levels and mucosal lesions (Fig. 3A, 3B, and 3C in the Supplementary Appendix).

SAFETY

Through week 50, the incidence of adverse events was generally similar among the three groups (Table 3). Infusion reactions occurred in 9 of 179 patients (5.0%) in the combination-therapy group, in 27 of 163 patients (16.6%) in the infliximab group, and in 9 of 161 patients (5.6%) in the azathioprine group.

In one patient receiving combination therapy, tuberculosis developed approximately 3 months after a negative tuberculin skin test and chest radiograph. The patient recovered after receiving antituberculosis treatment. Colon cancer developed in two patients receiving azathioprine. Another patient receiving azathioprine died from sepsis after colectomy.

ANTIBODIES TO INFLIXIMAB AND INFLIXIMAB LEVELS

Antibodies to infliximab were detected at week 30 in 1 of 116 patients (0.9%) receiving combination therapy and 15 of 103 patients (14.6%) receiving infliximab. The rates of corticosteroid-free clinical remission at weeks 26 and 50 were higher among patients with inconclusive results of antibody tests (indicating the presence of infliximab in the serum) than among patients with negative or positive results (Fig. 4A and 4B in the Supplementary Appendix). Median trough levels of serum infliximab at week 30 were 1.6 μg per milliliter for patients in the infliximab group and 3.5 μg per milliliter for those in the combination-therapy group (P<0.001) (Fig. 5A in the Supplementary Appendix). Rates of corticosteroid-free clinical remission were greater among patients with increased trough levels of serum infliximab but were still high among patients with lower trough levels (Fig. 5B in the Supplementary Appendix). The findings were similar for serum infliximab trough levels and rates of corticosteroid-free clinical remission at week 46 (Fig. 6A and 6B in the Supplementary Appendix).

DISCUSSION

In this study, treatment with infliximab-based strategies, as compared with azathioprine, resulted in significantly higher rates of corticosteroid-free clinical remission and mucosal healing at week 26 among patients with active Crohn's disease who did not have a response to first-line therapy. The greatest efficacy was observed with combination therapy.

The absolute rate of corticosteroid-free clinical remission among patients treated with azathioprine (30% at week 26) was generally similar to such rates that have been reported in previous studies that used the CDAI to measure efficacy: 36% at week 17,[5] 27% at week 16,[17] 29% at week 24,[18] and 38% at month 7.[19] In contrast, several other studies that either had very small samples[20,21] or used other, nonvalidated instruments to measure efficacy[22] have reported higher rates of treatment success with azathioprine. The time to the onset of action for azathioprine is estimated at 8 to 12 weeks.[17,22] For this reason, we permitted the initiation or continuation of systemic corticosteroid use until week 14. The proportion of patients receiving corticosteroids during the trial was similar among the three study groups, and the magnitude of the difference in the end points among the groups was relatively greater among patients who had received corticosteroids at baseline. It is possible that by excluding patients who had a heterozygous thiopurine methyltransferase phenotype we excluded patients who were more likely to have a response to azathioprine.[23] However, such pa-

Table 3. Safety Data at Week 54.*

Variable	Azathioprine (N=161)	Infliximab (N=163)	P Value for Infliximab vs. Azathioprine†	Combination Therapy (N=179)	P Value for Combination Therapy vs. Infliximab†	P Value for Combination Therapy vs. Azathioprine†
Mean duration of treatment in main study — wk	21.1	24.1		24.9		
Mean duration of treatment in study extension — wk‡	18.9	18.8		18.7		
Mean duration of post-treatment follow-up — wk	5.1	5.4		5.3		
Total patient-years of follow-up — no.	108.1	126.9		142.2		
Patients with any adverse event — no. (%)	144 (89.4)	145 (89.0)	1.00	161 (89.9)	0.86	1.00
Adverse events occurring in >10% of any study group — no. (%)						
Nausea	52 (32.3)	36 (22.1)		45 (25.1)		
Abdominal pain	26 (16.1)	41 (25.2)		31 (17.3)		
Worsening of Crohn's disease	27 (16.8)	30 (18.4)		19 (10.6)		
Vomiting	28 (17.4)	23 (14.1)		15 (8.4)		
Diarrhea	13 (8.1)	20 (12.3)		14 (7.8)		
Fatigue	25 (15.5)	24 (14.7)		26 (14.5)		
Pyrexia	18 (11.2)	16 (9.8)		16 (8.9)		
Arthralgia	18 (11.2)	32 (19.6)		21 (11.7)		
Headache	20 (12.4)	27 (16.6)		23 (12.8)		
Nasopharyngitis	20 (12.4)	15 (9.2)		21 (11.7)		
Adverse events leading to discontinuation of a study drug — no. (%)	42 (26.1)	29 (17.8)	0.08	37 (20.7)	0.58	0.25
Any serious adverse event — no. (%)	43 (26.7)	39 (23.9)	0.61	27 (15.1)	0.04	0.01
Infection — no. (%)						
Any	73 (45.3)	75 (46.0)	0.91	75 (41.9)	0.45	0.58
Serious	9 (5.6)	8 (4.9)	0.81	7 (3.9)	0.79	0.61
Adverse event of interest — no. (%)						
Colon carcinoma§	2 (1.2)	0		0		
Sepsis	1 (0.6)	0		0		
Tuberculosis	0	0		1 (0.6)		
Infusions						
No. of patients with infusion reaction — no. (%)¶	9 (5.6)	27 (16.6)	0.002	9 (5.0)	<0.001	1.00
No. of infusions						
Mean no. per patient	5.4	6.1		6.1		
Total no.	862	990		1097		
With infusion reaction	10	45		11		

* Excluded from the safety analyses were five patients who underwent randomization but did not receive a study drug (one patient in the azathioprine group, three in the infliximab group, and one in the combination-therapy group). The safety population for the combination-therapy group included 11 patients who were assigned to one of the monotherapy groups but inadvertently were given at least one dose of both active oral and intravenous therapy (8 patients in the azathioprine group and 3 in the infliximab group).

† P values were calculated with the use of Fisher's exact test.

‡ Analyses of results for the trial extension included 75 patients in the azathioprine group, 97 in the infliximab group, and 108 in the combination-therapy group.

§ The two patients underwent colectomy. Although colonoscopy was performed at baseline, the protocol did not require that biopsy samples be obtained.

¶ Infusion reactions were defined as any adverse event that occurred during or within 1 hour after the infusion of a study drug.

tients are also more likely to be intolerant to azathioprine,[24,25] and we believe it is unlikely that the net effect of these competing forces had an important effect on the outcome of the study.

Subgroup analyses of earlier clinical trials of infliximab that included patients who did not have a response to azathioprine have not shown greater efficacy during a period of 6 to 12 months among patients receiving combination therapy with infliximab and azathioprine, as compared with patients receiving infliximab monotherapy.[26] In addition, a randomized trial of azathioprine withdrawal in this patient population did not show a clinical benefit from continued use of azathioprine,[27] and toxic effects of azathioprine combined with anti-TNF biologic agents have recently been reported.[28,29] Our trial did not address the question of whether combination therapy was superior to infliximab monotherapy after failure of azathioprine. The benefits that we found for combination therapy may not extend to patients in whom azathioprine has already failed.

Previously, no single variable has consistently predicted a response to infliximab. In post hoc analyses, we found that patients with objective evidence of inflammation (i.e., a high CRP level or observed mucosal lesions) had the best clinical results with infliximab. In patients with a normal CRP level or no endoscopic lesions, no significant differences were observed among the three study groups. It is possible that prospective studies will show that measurement of CRP and endoscopy can identify patients who are most likely to have a greater response to infliximab monotherapy or combination therapy than to azathioprine monotherapy.

The overall incidence of adverse events was similar among the three groups. However, infusion reactions occurred less frequently among patients receiving combination therapy than among those receiving infliximab monotherapy. Serious infections (including tuberculosis) developed in 3.9% of patients in the combination-therapy group, 4.9% of those in the infliximab group, and 5.6% of those in the azathioprine group. Evidence suggests that the combination of azathioprine and anti-TNF biologic agents increases the relative risk of serious and opportunistic infections and hepatosplenic T-cell lymphoma.[28,29] Our data showed that for patients who had not received previous therapy with azathioprine, combination therapy was superior to infliximab monotherapy. However, the increased risks of rare but serious toxic effects associated with combination therapy must also be considered. The concomitant use of corticosteroids as a third immunosuppressive agent may further increase the relative risk of serious and opportunistic infections.[30] Ultimately, the choice of infliximab monotherapy or combination therapy in patients who have not received such therapy previously is an individualized benefit–risk decision. Although the greater efficacy of combination therapy in our study may have been due in part to suppression of immunogenicity, it is likely that the enhanced benefit was primarily due to the additive effects of two effective drugs. The two drugs have also been shown to share mechanisms of action, such as apoptosis.[31,32]

In conclusion, infliximab monotherapy and combination therapy with infliximab plus azathioprine, as compared with azathioprine alone, resulted in significantly higher rates of corticosteroid-free clinical remission among patients with moderate-to-severe Crohn's disease. Combination therapy was the most effective treatment.

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