Articles

Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial

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Summary

Background We did a randomised controlled trial to assess the benefit of maintenance infliximab therapy in patients with active Crohn's disease who respond to a single infusion of infliximab.

Methods 573 patients with a score of at least 220 on the Crohn's disease activity index (CDAI) received a 5 mg/kg intravenous infusion of infliximab at week 0. After assessment of response at week 2, patients were randomly assigned repeat infusions of placebo at weeks 2 and 6 and then every 8 weeks thereafter until week 46 (group I), repeat infusions of 5 mg/kg infliximab at the same timepoints (group II), or 5 mg/kg infliximab at weeks 2 and 6 followed by 10 mg/kg (group III). The prespecified co-primary endpoints were the proportion of patients who responded at week 2 and were in remission (CDAI <150) at week 30 and the time to loss of response up to week 54 in patients who responded. Analyses of the co-primary endpoints were by intention to treat.

Findings 335 (58%) patients responded to a single infusion of infliximab within 2 weeks. At week 30, 23 of 110 (21%) group I patients were in remission, compared with 44 of 113 (39%) group II (p=0·003) and 50 of 112 (45%) group III (p=0·0002) patients. Thus, patients in groups II and III combined were more likely to sustain clinical remission than patients in group I (odds ratio 2·7, 95% CI 1·6–4·6). Throughout the 54-week trial, the median time to loss of response was 38 weeks (IQR 15 to >54) and more than 54 weeks (21 to >54) for groups II and III, respectively, compared with 19 weeks (10–45) for group I (p=0·002 and p=0·0002, respectively). Infliximab safety was consistent with that seen in other trials of infliximab in Crohn's disease and rheumatoid arthritis. In particular, the incidence of serious infections was similar across treatment groups.

Interpretation Patients with Crohn's disease who respond to an initial dose of infliximab are more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to maintain their response for a longer period of time, if infliximab treatment is maintained every 8 weeks.

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Introduction

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract. Although mild disease can be treated with 5-aminosalicylates, many patients eventually require corticosteroids to control symptoms.[1] Once started, acute and in particular chronic use of corticosteroids is associated with well known adverse effects. Moreover, about 45% of patients are unable to discontinue corticosteroid therapy without disease exacerbation.[2,3] The purine antimetabolites and methotrexate are frequently prescribed for patients who are resistant to or dependent on corticosteroids; however, these drugs have a slow onset of action and clinical remission rates of about 40%. Clinical remission is defined by discontinuation of prednisone and a Crohn's disease activity index (CDAI) score of 150 or less after 16 weeks for methotrexate and as a CDAI of less than 175 at 15 months for azathioprine.[4,5] Thus, there is a need for a long-term treatment that maintains clinical remission and reduces exposure to corticosteroids.

Tumour necrosis factor α (TNFα) is a proinflammatory cytokine that has an important role in the pathogenesis of Crohn's disease.[6–10] Infliximab—a chimeric anti-TNFα monoclonal antibody—binds to TNFα with high affinity, thereby neutralising its biological activity.[11] When given as a 5 mg/kg intravenous infusion, infliximab induces remission in patients with moderately to severely active Crohn's disease and can reduce corticosteroid requirements.[12,13] Clinical experience has shown that patients can relapse after a single infusion of infliximab.[14,15] In a previous assessment of repeated administration of infliximab (four infusions of 10 mg/kg every 8 weeks) in patients with Crohn's disease, retreatment with infliximab maintained the clinical benefit up to 8 weeks after the last infusion in nearly all patients who responded to an initial dose of treatment.[16] However, the results were not statistically significant in that small trial. Further data from a longer study were required to establish the long-term efficacy and safety of repeated doses of infliximab in patients with Crohn's disease who show an initial response to treatment.

In the ACCENT I trial, we aimed to assess the efficacy and safety of repeated infusions of infliximab in patients who improved after an initial infusion. Our hypothesis was that maintenance infliximab treatment is a more effective intervention than a single infusion. Secondary objectives included the assessment of infliximab's corticosteroid-sparing effects and safety in a large number of patients.

Patients and methods

Patients

This multicentre, randomised, double-blind trial was carried out at 55 sites in North America, Europe, and Israel. Recruitment of patients took place from Feb 26, 1999, to Jan 24, 2000. For the prespecified 30-week endpoint analysis, the last completed visit was on Aug 30, 2000. For results up to 54 weeks, the last completed visit was on March 15, 2001. The protocol was approved by the institutional review boards at participating sites. Written informed consent was obtained from all patients.

Eligible patients had Crohn's disease of at least 3 months' duration with a score on the CDAI[17] between 220 and 400. Patients receiving the following treatments were eligible: 5-aminosalicylates or antibiotics (if the dose remained constant for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks). Patients not receiving medical therapy had to have discontinued treatment for at least 4 weeks before screening. Patients were excluded from the study if they had received previous treatment with infliximab or any other agent targeted at TNF.

Procedures

Patients were screened for eligibility 2 weeks before enrolment. At week 0, all eligible patients received a 5 mg/kg intravenous infusion of infliximab. 2 weeks later, patients were assessed for a response to treatment as defined by a decrease in CDAI score of 70 points or more from the baseline value and at least a 25% reduction in the total score. Patients were randomly assigned subsequent infusions, at weeks 2 and 6 and every 8 weeks thereafter until week 46, of placebo (group I), 5 mg/kg infliximab (group II), or 5 mg/kg infliximab at weeks 2 and 6 followed by 10 mg/kg thereafter (group III).

The prespecified co-primary efficacy endpoints were the proportion of week-2 responders in clinical remission at week 30, and the time to loss of response up to week 54 among week-2 responders. The findings presented here address the primary objective of this study, which was to assess the benefit of infliximab maintenance treatment in patients with an initial early (within 2 weeks) response to a single infliximab infusion.

Taking variability between sites and effects of concomitant medications into account, allocation of patients to a treatment group was done with an adaptive stratified design with investigational site and duration of continuous exposure to corticosteroids (<1 year; >1 year; no corticosteroids and no other Crohn's disease medications; no corticosteroids but other Crohn's disease medications) as the strata. Since there were 55 investigative sites from North America, Europe, and Israel involved in the study, an adaptive randomisation procedure was used to allocate patients centrally to treatment based on the current balance of treatment groups within each stratum. An interactive voice-response system was used. A pharmacist prepared the infusion (infliximab [Remicade] or an identically appearing placebo, both from Centocor, Malvern, PA, USA). Neither the patients nor study investigators were aware of the treatment assignment.

Patients were assessed at weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, and 54. At each visit, adverse events were prospectively collected by direct questioning of patients by primary investigators or site coordinators, and samples for clinical laboratory assessments and the patient's CDAI scores were obtained. Health-related quality of life was mainly assessed by the inflammatory-bowel-disease questionnaire (IBDQ).[18] Blood samples for measurement of infliximab concentrations were collected immediately before each infusion and at the end of the infusion at weeks 0, 22, and 46.

At week 14 or later, patients who initially responded but then worsened were eligible to cross over to active episodic retreatment. This regimen comprised 5, 10, or 15 mg/kg infliximab from that point forward on an as-needed basis, for patients originally assigned to groups I, II, and III, respectively. Worsening was defined by: (1) an increase in CDAI of at least 70 points from the qualifying score with a total score of at least 175, (2) an increase in CDAI of 35% or more from the baseline value, or (3) the introduction of a new treatment for active Crohn's disease. Patients and physicians remained unaware of the treatment assignment. All data obtained after episodic retreatment were included in the safety analyses but not in the efficacy analyses.

Patients receiving corticosteroids were to maintain a stable dose until week 6, after which a defined tapering schedule was started if the patient's condition had improved. Patients who entered the trial receiving corticosteroid doses of more than 20 mg per day prednisone equivalent had their treatment tapered at a maximum rate of 5 mg per week; the maximum rate for patients receiving 20 mg per day prednisone equivalent or less was 2·5 mg per week. Aminosalicylates and immunomodulators were maintained at a constant dose.

All study participants were included in the safety analysis. Blood samples were collected to determine the presence of antinuclear antibodies (ANA) at weeks 0, 10, 30, and 54. Samples positive for ANA were tested for anti-double-stranded-DNA antibodies (anti-dsDNA). The criterion for a positive anti-dsDNA result was the presence of an ANA titre of 1:40 or more and a positive result on Crithidia assay. The Crithidia assay provides ready access to non-nuclear dsDNA. Samples for determination of antibodies to infliximab were obtained at weeks 0, 14, 22, and 54. During episodic retreatment, samples were drawn specifically to test for antibodies to infliximab before each episodic retreatment infusion. Patients were also tested at study termination.

Statistical analysis

The main objective of the study was to assess the efficacy and safety of infliximab maintenance treatment in patients responding to a single infliximab infusion. Efficacy was assessed as the continued benefit provided by the maintenance treatment. For this purpose, the primary endpoint of this study was designed as the time to loss of response up to and including week 54 among week-2 responders, as defined by a CDAI of at least 175, a CDAI increase of at least 35%, and a CDAI at least 70 points more than the week-2 CDAI for at least two consecutive visits (21 days or longer). Later, in an amendment made to the original protocol, the proportion of week-2 responders who were in remission at week 30, as defined by a CDAI score of less than 150 points, was added as a co-primary efficacy endpoint to provide an earlier assessment of the efficacy of maintenance infliximab infusions.

Patients who crossed over to episodic infliximab retreatment, who received a drug not allowed by the protocol, who had surgery for Crohn's disease, or who discontinued follow-up due to lack of efficacy or loss of response were judged to have failed treatment, irrespective of the CDAI score. Patients who discontinued the study for reasons other than lack of efficacy or loss of response

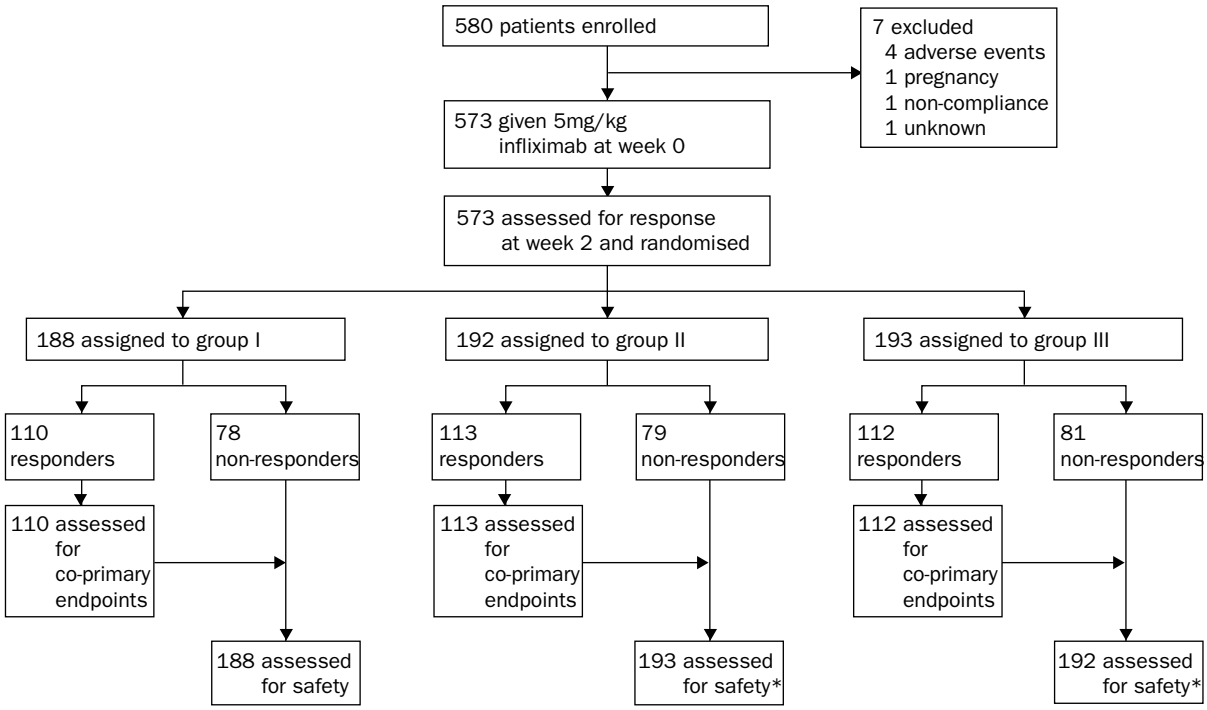

Figure 1: **Trial profile**
*One patient assigned to group III (10 mg/kg maintenance dose) actually received 5 mg/kg and was analysed for safety as group II.

and those with missing CDAI scores were censored in the analysis of time to loss of response up to week 54. These patients were treated as not in clinical response or clinical remission for other analyses.

In the primary analysis at week 30, a χ^2 test compared the proportion of patients in remission at week 30 among the treatment groups. A p value of 0·01 was set to define significance. The analysis of the time to loss of response up to week 54 was done with the log-rank test for grouped data. Time to loss of response was defined as the week of assessment corresponding to the earliest occurrence of loss of response, as defined above. The median time to loss of response was obtained by interpolation between the two visits between which 50% of patients had a loss of response. The α level of 0·04 was used for the week 54 co-primary endpoint analysis. Nominal two-sided p values with an α of 0·05 were reported for secondary analyses.

A χ^2 test was also used to calculate the proportion of patients who were in remission and not receiving corticosteroid therapy and the proportion of patients who responded according to the previously described criterion. The consistency of treatment benefit was examined for the primary endpoint (the proportions of patients in remission) in subgroups by odds ratios, with 95% CIs calculated from a logistic regression. Subgroups were defined by demographic features, geographic location, baseline disease characteristics, and concomitant medications at baseline. Analysis of variance based on ranks was used to compare the median CDAI, IBDQ, and C-reactive protein values at predefined study visits. To be conservative about patients' status in this comparison, the closest previous value was carried forward for patients treated with a protocol-prohibited medication or dose because of lack of efficacy or loss of response, for those who had Crohn's-disease-related surgery, for those who crossed over to episodic retreatment, and for those who discontinued regularly scheduled follow-up.

Incidences of adverse events were tabulated by treatment groups. Incidences of serious adverse events and infections requiring antimicrobial treatment were determined for patients who received only a single infusion of infliximab and compared against respective incidences among patients who received several infliximab infusions.

Assuming that 60% of patients responded at week 2 and were therefore included in the primary efficacy analysis, a sample size of 170 per treatment group provided approximately 95% power to detect a significant treatment effect in remission rate at week 30, with a two-sided χ^2 test at an α level of 0·01. This sample size also provided approximately 90% power to detect a significant treatment effect in the time to loss of response up to week 54, with a two-sided log-rank test for grouped data at an α level of 0·04.

Role of the funding source

This study was designed by a committee composed of Centocor staff members and the ACCENT Steering Committee members. Centocor staff collected data from all clinical sites to create the clinical database. Centocor staff members and members of the ACCENT Steering Committee analysed and interpreted the data, wrote the paper, and agreed to submit it for publication. The principal investigators approved the content of the paper before submission.

Results

Patients' disposition, baseline characteristics, and previous or concomitant medication

Of 580 patients enrolled, 573 patients at 55 study centres (40 North America, 13 Europe, and two Israel) were started on infliximab 5 mg/kg; 335 (58%) were responders at week 2. These 335 responders were randomly assigned placebo (group I, 110 patients), the 5 mg/kg maintenance regimen (group II, 113 patients), or the 10 mg/kg maintenance regimen (group III, 112 patients) and were assessed in the predefined primary efficacy analyses (figure 1). The 573 patients comprised 239 (42%) men and 334 (58%) women with a median age of 35 years (range

	All patients (n=573)	Week-2 responders (n=335)	Week-2 non-responders (n=238)
Sex			
Male	239 (42%)	130 (39%)	109 (46%)
Female	334 (58%)	205 (61%)	129 (54%)
Race			
White	549 (96%)	315 (94%)	234 (98%)
Black	12 (2%)	10 (3%)	2 (1%)
Asian	5 (1%)	4 (1%)	1
Other	7 (1%)	6 (2%)	1
Age (years), median (IQR)	35 (28–46)	35 (27–46)	37 (30–46)
Disease duration (years), median (range)	7·9 (3·9–14·7)	7·5 (3·7–14·2)	9·3 (4·6–15·3)
Involved intestinal area			
Ileum	137/568 (24%)	74/331 (22%)	63/237 (27%)
Colon	109/568 (19%)	74/331 (22%)	35/237 (15%)
Ileum and colon	322/568 (57%)	183/331 (55%)	139/237 (59%)
Gastroduodenum	43/573 (8%)	24/335 (7%)	19/238 (7%)
Previous segmental resection(s)	291/573 (51%)	148/335 (44%)	143/238 (60%)
CDAI*, median (IQR)	297 (260–342)	299 (264–342)	291 (249–340)
IBDQ, median (IQR)	127 (110–147)	129 (114–147)	125 (106–145)
C-reactive protein concentration (mg/dL), median (IQR)	0·8 (0·4–2·3)	1·1 (0·4–2·8)	0·6 (0·4–1·5)
Patients with concomitant medication			
5-aminosalicylates	288 (50%)	159 (47%)	129 (54%)
6-mercaptopurine and azathioprine	144 (25%)	81 (24%)	63 (27%)
Methotrexate	23 (4%)	10 (3%)	13 (6%)
Patients with concomitant corticosteroids			
Any	293 (51%)	175 (52%)	118 (50%)
>20 mg per day	93 (16%)	61 (18%)	32 (13%)

IBDQ=inflammatory bowel disease questionnaire (values can range from 32 to 224). *On final clinical data review, 13 enrolled patients had baseline Crohn's disease activity index (CDAI) <220. For nine of these patients, CDAI as calculated by investigator was ⩾220. Remaining four patients were protocol violators.

Table 1: **Baseline characteristics**

18–76). Baseline characteristics of the week-2 responders compared with non-responders were similar with the exception of Crohn's disease duration, previous segmental resections, and C-reactive protein concentration (table 1).

124 (22%) patients had discontinued maintenance study treatment by week 54. Among all patients, the proportions of patients who discontinued study treatment (and did not cross over) were similar across groups I, II, and III (38 [20%], 49 [26%], and 37 [19%], respectively). Within group I, the most common reason for discontinuing study treatment was lack of efficacy (23 [12%]); in groups II and III, the most common reasons for discontinuation were adverse event (38 [10%]) and lack of efficacy (31 [8%]), respectively. Further details of adverse events leading to discontinuation of study treatment among all patients are provided under safety results.

Efficacy

Throughout follow-up, patients assigned continued active treatment showed a greater therapeutic benefit than patients retreated with placebo. At week 30 (figure 2), the proportion of week-2 responders in remission was higher in both group II and group III (44 [39%] and 50 [45%], respectively) than in group I (23 [21%]). Thus, patients in groups II and III combined were more likely to be in clinical remission at 30 weeks than patients in group I (odds ratio 2·7, 95% CI 1·6–4·6). The difference in remission rates between groups II or III and group I was seen as early as week 10 (2·0, 1·3–3·2) and was sustained thereafter. Similar results were seen at week 54 (figure 2). No difference in the rate of remission was present between groups II and III at week 30 (1·3, 0·74–2·20) or week 54 (1·58, 0·90–2·80). A similar pattern of clinical response was observed at weeks 30 and 54 (figure 2).

Patients in groups II and III had a significantly longer time to loss of response than patients in group I (p=0·0002). The median time to loss of response was 46 weeks (IQR 17 to >54) in groups II and III combined compared with 19 weeks (10–45) in group I. When compared separately, patients in both groups II and III had a significantly longer time to loss of response than patients in group I (median 38 weeks [15 to >54], p=0·002, and >54 weeks [21 to >54], p=0·0002, respectively).

At week 54, about three times as many patients (32 [29%] *vs* 5 [9%]; odds ratio 4·2, 95% CI 1·5–11·5) in groups II and III combined had discontinued corticosteroids while in clinical remission compared with patients in group I (p=0·004). The median corticosteroid doses over time up to week 54 are shown in figure 3. The median corticosteroid dose was reduced more rapidly in groups II and III (0 mg per day by week 22) than in group I (10 mg per day at week 22).

Median CDAI scores (figure 4) were at or near remission levels for all three treatment groups at week 2. The proportions of patients who maintained a clinical remission at every visit from week 14 to week 54 were 11% (12/110), 25% (28/113), and 33% (37/112) for group I, group II, and group III, respectively. An analogous pattern of improvement was seen for IBDQ (figure 4).

Pharmacokinetics

In group I patients who received only a single dose of 5 mg/kg infliximab, concentrations of infliximab in serum were undetectable in more than 50% of patients by week 14. In patients who received maintenance infliximab infusions (groups II and III), the trough concentrations of drug remained relatively constant up to week 54. From week 22 onwards, higher trough concentrations were seen in group III than in group II, as would be expected. Median trough infliximab concentrations in patients positive for antibody to

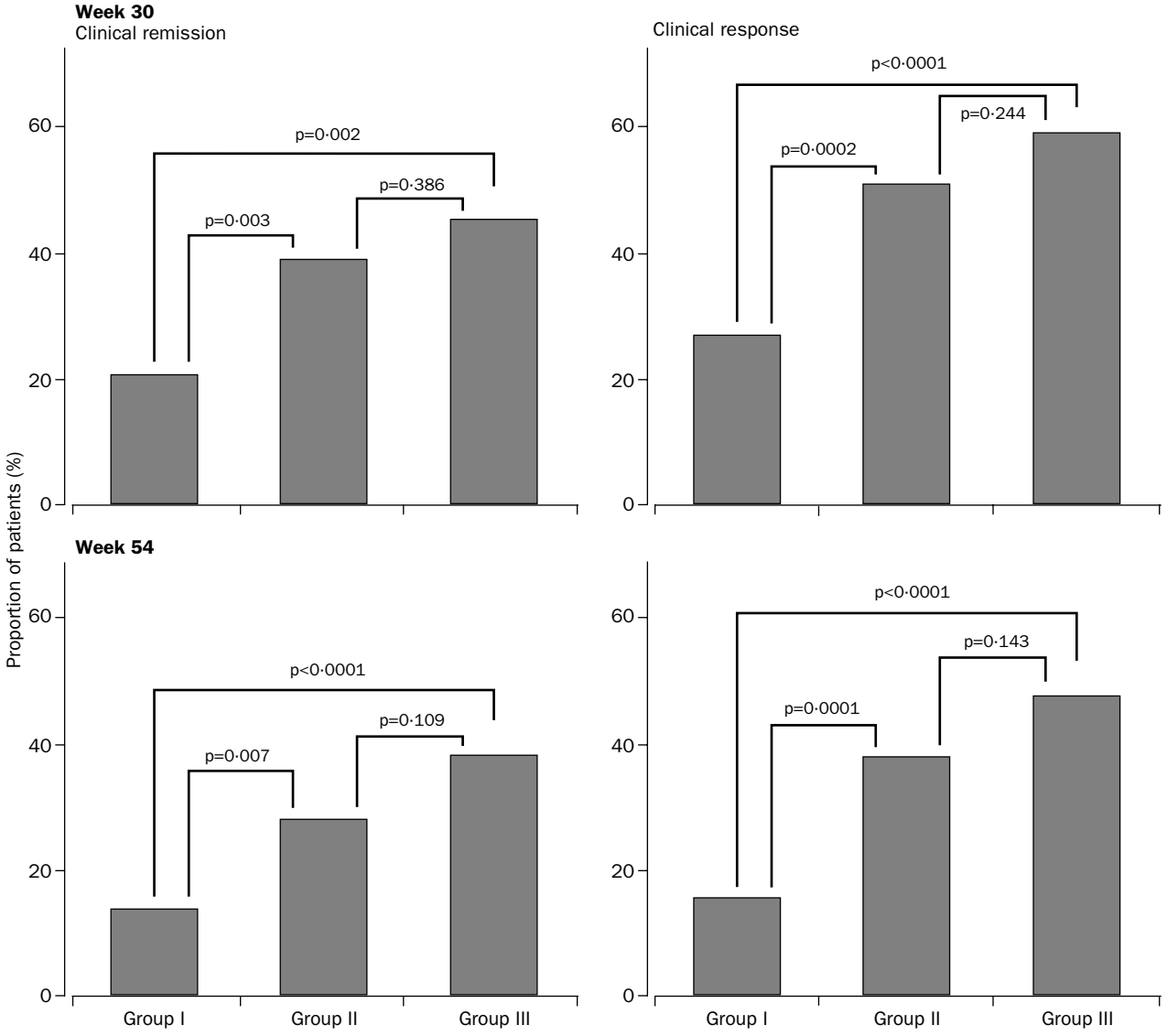

Figure 2: **Clinical response and clinical remission for week-2 responders**
Clinical response=reduction in CDAI to ⩾70 points and ⩾25% from baseline. Clinical remission=CDAI <150 points.

infliximab were lower than in patients who had negative or inconclusive test results.

Antibodies to infliximab

Up to week 54, 442 patients were assessed for the presence of antibodies to infliximab (table 2). The presence of infliximab in the serum is known to interfere with the interpretation of the analyses for antibodies to infliximab. Results for patients who were not positive for antibodies to infliximab but who had detectable concentrations of infliximab after their last infusion were classified as inconclusive. In this assessment, 64 of 442 (14%) patients developed antibodies to infliximab: 41 (28%) in group I, 14 (9%) in group II, and nine (6%) group III. Close to half the patients (46%) had inconclusive test results for antibodies to infliximab due to the detection of infliximab in the serum, which could compete for the detection of antibodies to infliximab in the immunoassay used. Antibody titres were similar across all treatment groups, and only three patients had a titre greater than 1:40.

Four (6%) of the 64 patients receiving steroids at baseline in combination with immunomodulators

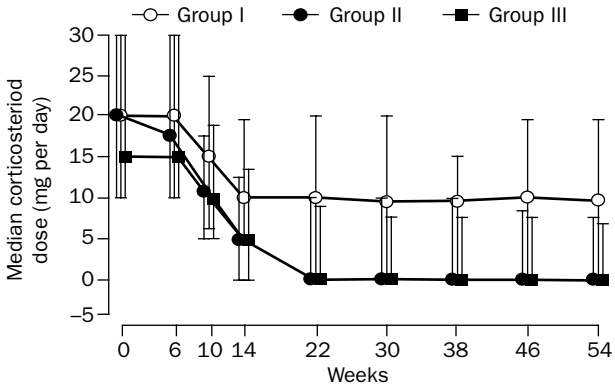

Figure 3: **Median daily corticosteroid dose to week 54**
Bars=IQR. Includes all week-2 responders who were receiving corticosteroids at baseline (last observation carried forward for patients who crossed over or discontinued regularly scheduled follow-up).

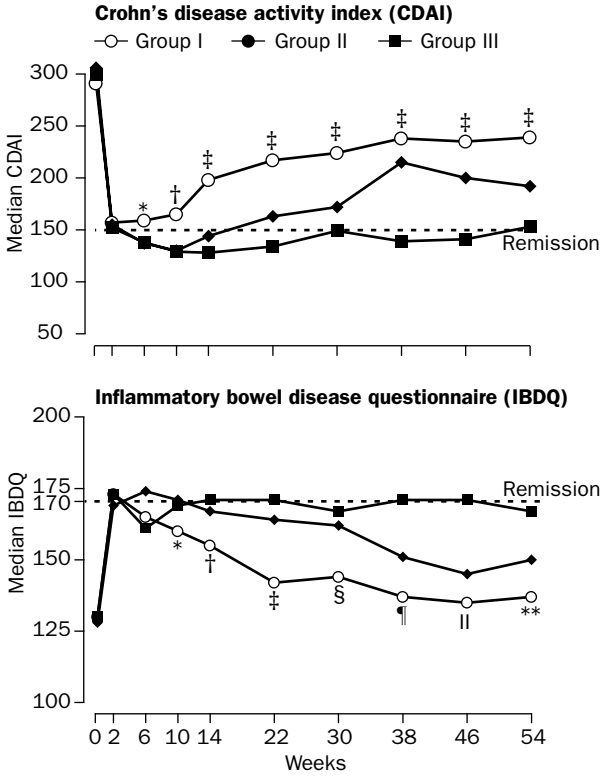

Figure 4: **Median CDAI and IBDQ scores to week 54 among week-2 responders**

Top panel: *p=0·010 (group II *vs* group I), p=0·040 (group III *vs* group I). †p<0·0001 (group II *vs* group I), p=0·0002 (group III *vs* group I). ‡p<0·0001 (group II *vs* group I and group III *vs* group I). Lower panel: *p=NS (group II *vs* group I), p=NS (group III *vs* group I). †p=0·050 (group II *vs* group I), p=0·0076 (group III *vs* group I). ‡p=0·013 (group II *vs* group I), p<0·0001 (group III *vs* group I). §p=0·015 (group II *vs* group I), p=0·001 (group III *vs* group I). ¶p=0·015 (group II *vs* group I), p<0·0001 (group III *vs* group I). ||p=0·060 (group II *vs* group I), p<0·0001 (group III *vs* group I). **p=0·015 (group II *vs* group I), p<0·0001 (group III *vs* group I).

developed antibodies to infliximab. By contrast, 17% (26/154) of patients receiving steroids alone (at baseline), 10% (7/70) of patients receiving immunomodulators alone, and 18% (27/154) of patients receiving neither corticosteroids nor immunomodulators developed antibodies to infliximab.

Safety

Safety data for all 573 treated patients are reported according to the actual treatment received. Since some patients in each group received episodic treatment, a number of patients in group I received several infusions of infliximab. Total exposure to infliximab for each group is presented in table 3. Headache, abdominal pain, and upper respiratory tract infection (URTI) were reported most frequently. The incidences of URTI and influenza-like symptoms were similar among treatment groups.

Infusion reactions generally characterised by headache, dizziness, nausea, injection-site irritation, flushing, chest pain, dyspnoea, and pruritus occurred in 61 of 993 (6%) and 45 of 1033 (4%) group II and III infliximab infusions, respectively, compared with 23 of 837 (3%) of group I infusions. Infusion reactions led to discontinuation of study agent in 12 patients (nine in group II, three in group III). Among the 442 patients with evaluable samples, 42 of 254 (16%) infusions resulted in infusion reactions among patients positive for antibodies to infliximab, compared with 55 of 656 (8%) and 47 of 1470 (3%) in patients negative for antibodies to infliximab and with inconclusive status, respectively (table 2). Over the course of the trial, the lowest incidence of infusion reactions occurred among patients receiving both steroids and immunosuppressives (7/85 [8%]) compared with 17/84 (20%) of patients receiving only immunosuppressives, 47/207 (23%) of patients receiving steroids alone, and 62/197 (32%) of patients without corticosteroids or immunosuppressives. Serum-sickness-like reactions were seen in three (2%) patients in group I, five (3%) patients in group II, and six (3%) patients in group III (table 3). Reactions were generally seen after one to five maintenance infusions.

The proportion of patients who had serious adverse events is reported in table 3. To compare the safety of infliximab between single and multiple infusions, we analysed data at week 14. There was no difference in the incidence of serious adverse events between patients who received a single infliximab infusion (22 of 88 [12%] patients) and those who received multiple infusions (38 of 385 [10%]; p=0·561) up to week 14. By week 54, infusion syndrome (5 patients), allergic reaction (4 patients), arthralgia (4 patients), serum sickness (4 patients), and rash (3 patients) were the most common adverse events leading to discontinuation of the study drug.

Serious infections occurred in 22 (4%) of 573 patients (table 3). By week 14, there was no difference in the incidence of infections requiring treatment between patients receiving a single infliximab infusion (25 of 188 [13%] patients) and those receiving multiple infusions (51 of 385 [13%]; p=1·00). At week 54, 186 (32%) patients had an infection requiring treatment. A 35-year-old woman died of sepsis secondary to a small bowel obstruction 2 months after the week-6 infliximab infusion (group II). Two additional patients died before the end of the study: a patient in group II died of myocardial infarction 25 days after the last infusion, and a patient in group II died of sepsis 144 days after the last study infusion. For both these patients, the events leading to death were judged to be probably not related to study agent. A 64-year-old woman developed tuberculosis 4 weeks after her week 14 infusion and was successfully treated. This patient received infliximab 5 mg/kg at weeks 0, 2, and 6, followed by crossover to episodic retreatment due to disease flare, and infliximab 15 mg/kg at week 14.

Six (1%) patients had a malignant disorder: an epithelial-cell skin neoplasm was diagnosed about 6·5 months after infliximab infusion (group I); a natural-killer-cell lymphoma was diagnosed about 10 months after the week-14 infusion (group I, patient discontinued treatment 50 days after the week 14 infusion); a basal-cell carcinoma was identified 2 weeks after receipt of the week-6 infusion (group II); a hypernephroma for which the patient

	Positive*	Negative†	Inconclusive‡	All patients
Evaluable patients with appropriate samples§	64 (14%)	173 (40%)	205 (46%)	442 (100%)
Patients with infusion reactions	24 (38%)	42 (24%)	34 (17%)	100 (23%)
Infusions with infusion reactions	42/254 (17%)	55/656 (8%)	47/1470 (3%)	144/2380 (6%)

*Includes all patients with appropriate samples who had at least one positive sample at any time. †Includes all patients with appropriate samples who had a negative sample after last assessment, excluding patients who were positive. ‡Includes all patients with appropriate samples who had an inconclusive sample (sample with detectable infliximab concentration) after last assessment, excluding those who were positive. §Patients with appropriate samples either had antibodies to infliximab at some time after first infusion or had one or more samples obtained after last infusion.

Table 2: **Incidence of infusion reactions during infliximab infusions by antibodies to infliximab status up to week 54**

	Group I (n=188)*	Group II (n=193)	Group III (n=192)	Total (n=573)
Infliximab exposure over 54 weeks, mean (SD)				
Number of infusions	2·2 (1·5)	6·7 (1·9)	6·8 (2·1)	5·3 (2·9)
Total dose (mg/kg)	10·7 (7·6)	36·0 (11·1)	55·5 (21·1)	34·3 (23·3)
Adverse events leading to discontinuation of study agent	5 (3%)	29 (15%)	16 (8%)	50 (9%)
Serious adverse events				
All events	55 (29%)	54 (28%)	43 (22%)	152 (27%)
Reasonably related	13 (7%)	15 (8%)	11 (6%)	39 (7%)
Infections				
Infection requiring antimicrobial treatment	70 (37%)	64 (33%)	52 (27%)	186 (32%)
Serious infection	8 (4%)	8 (4%)	6 (3%)	22 (4%)
Intestinal stenosis	6 (3%)	3 (2%)	5 (3%)	14 (2%)
Infusion reactions†	17 (9%)	44 (23%)	36 (19%)	97 (17%)
Serum-sickness-like reactions‡	3 (2%)	5 (3%)	6 (3%)	14 (2%)

*92 (49%) of 188 patients crossed over to episodic retreatment and received two or more infliximab infusions. †Defined as any adverse experience that occurred during or within 1 h after infusion. Reported infusion reactions occurred during maintenance infusions (initial infusion excluded). ‡Defined as features occurring 1–14 days after reinfusion of infliximab, including delayed hypersensitivity reactions, myalgia, arthralgia, fever, and/or rash.

Table 3: **Summary of safety findings for all patients (n=573) up to week 54**

underwent surgery was diagnosed 9 weeks after the week-6 infusion (group II); a malignant breast neoplasm was recognised 51 days after the week-30 infusion (group II); and a bladder carcinoma was seen 49 days after the week-42 infusion (group III).

More group II and III patients developed anti-dsDNA and ANA (123 [34%] and 363 [56%], respectively) than group I patients (19 [11%] and 63 [35%], respectively). One patient (group III) developed arthralgia in conjunction with positivity for ANA and anti-dsDNA, which was judged by the investigator to be a lupus-like syndrome. There was no evidence of renal or other organ involvement. This patient responded to discontinuation of infliximab and administration of prednisone. Another patient (group III) was judged to have a lupus-like syndrome due to positivity for antihistone antibodies. This patient discontinued the trial at week 30 due to non-compliance.

Discussion

Since previous studies have established that single-dose infliximab is safe and effective for the management of acute Crohn's disease, the primary purpose of ACCENT I was to determine whether maintenance infliximab therapy would provide better long-term efficacy than no further treatment for patients with Crohn's disease who respond to a single infusion of infliximab. The results of this trial indicate that maintenance treatment with infliximab every 8 weeks is better than subsequent placebo treatment among patients who responded to a single infliximab infusion. Patients assigned to maintenance infliximab infusions were more likely to maintain clinical responses and clinical remissions, and to discontinue corticosteroids. More than twice as many patients who received maintenance infliximab therapy maintained a clinical remission continuously from week 14 to week 54 compared with patients who received placebo maintenance.

These beneficial outcomes have clinically important implications. Infliximab has previously been shown to provide a rapid onset of benefit. Here we established that a durable benefit over 1 year of treatment is possible. Many of the patients who participated in ACCENT I had failed other treatments. Infliximab with or without immunomodulators in this setting provided important benefits. Hence, patients thought previously to be refractory to therapy have an additional therapeutic option. Steroid-associated complications are well known, yet many patients with Crohn's disease require some steroids to control their disease. More than half the study patients were receiving corticosteroids at study entry. Patients on steroids who received maintenance infliximab were able to reduce steroid use, and a third of these patients were able to stop steroids with maintenance of clinical benefit. This steroid-sparing effect of infliximab is an important treatment advance in the management of Crohn's disease.

Maintenance infliximab therapy was well tolerated. Although more patients who were assigned to maintenance infliximab discontinued treatment due to adverse events than those who received placebo maintenance, the rates of serious adverse events and infections were similar between patients who received only a single infliximab infusion and those who received several infliximab infusions. Two patients died of sepsis—one in association with an exacerbation of Crohn's disease with bowel obstruction and treated with partial bowel resection of the inflamed bowel.

The risk-benefit ratio for patients at high risk of infection should be considered before starting infliximab therapy. In particular, the development of a case of tuberculosis is a cause for concern.[19] Since becoming widely available in 1998, infliximab has been given to about 175 000 patients, and 101 cases of tuberculosis have been reported (62 patients with rheumatoid arthritis, 21 with Crohn's disease, four with other diagnoses, and 14 with unknown diagnoses).[20] Thus, despite the absence of controlled data, there might be an association between infliximab treatment and reactivation of tuberculosis.[19] This potential is consistent with the putative biological activity of TNF in controlling intracellular pathogens. Accordingly, physicians who prescribe infliximab should carefully screen patients for exposure to tuberculosis and treat patients who are positive for latent tuberculosis accordingly. By contrast with data cited in a single-site non-randomised experience,[21] 1-year data from our randomised controlled trial indicate there was no increased risk of intestinal stenosis associated with infliximab therapy.

Close to half the patients had inconclusive test results for antibodies to infliximab. This ambiguity results from the ongoing presence of infliximab in the serum, which competes with antibodies to infliximab in the ELISA used. However, the 14% incidence of antibody to infliximab is consistent with results of other infliximab clinical trials. Although 38% of patients positive for antibodies to infliximab had one or more infusion reactions, compared with 24% of patients negative for antibodies to infliximab, only 16% of infusions were associated with an infusion reaction in the positive patients compared with 8% of infusions in the negative patients. Most infusion reactions

were mild to moderate in nature, and only 2% of patients assigned maintenance infliximab discontinued study agent as a result of these reactions. In a previous trial of patients with rheumatoid arthritis, coadministration of 7·5 mg methotrexate decreased the development of antibodies to infliximab.[22] In the current trial, there was a trend for a lower incidence of development of antibodies to infliximab with concurrent corticosteroid plus immunosuppressive therapy. In previous infliximab trials, the development of antibodies to infliximab was lower in individuals receiving concurrent immunosuppressive therapy than in patients not receiving this treatment.[22] Serum-sickness-like reactions were relatively uncommon and responded promptly to discontinuation of infliximab or administration of corticosteroids.

Although 34% of patients assigned maintenance treatment developed anti-dsDNA, only two patients developed a lupus-like syndrome. Organ involvement was not present in either case. This finding is in keeping with previous reports that suggest that infliximab rarely causes drug-induced lupus.[23]

Six cancers were seen. Although an association between infliximab therapy and malignancy cannot be ruled out, the consistency of the incidence and type of cancers observed in the present trial with those expected for the general population, along with the interval between infliximab treatment and diagnosis, makes a causal association unlikely. The lack of a group of patients who did not receive infliximab limits further examination. Although there have been anecdotal reports of malignancy in patients with Crohn's disease treated with infliximab,[24] population-based assessments show an increased risk of cancer in patients with Crohn's disease compared with the general population.[25] The incidence of malignancies was not unexpectedly high given that many patients receiving infliximab have long histories of immunosuppressive therapies, and that Crohn's disease is associated with a higher risk of developing lymphomas independent of receiving immunosuppressant therapy.[25–27]

Azathioprine and methotrexate are the only drugs that have demonstrated efficacy for steroid sparing. However, these agents are associated with various important adverse effects and have a relatively slow onset of action. Future randomised controlled trials should assess which of these treatments is preferred in patients who fail to respond to or become dependent on corticosteroids. Furthermore, combination therapy with infliximab and either methotrexate or azathioprine should be assessed. Since the use of immunomodulators at study entry was non-random, firm conclusions cannot be made. However, our data support the concept that combination therapy might have additive or synergistic efficacy. 50% of patients who received a concomitant baseline immunosuppressive maintained clinical response at week 54 compared with 41% of those who were not receiving these drugs.

In summary, the results of ACCENT I showed that patients with Crohn's disease who respond to an initial dose of infliximab are more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to maintain their response for a longer period of time if infliximab therapy is maintained every 8 weeks. Maintenance infliximab treatment was safe and well tolerated.

Contributors

P Rutgeerts, S B Hanauer, and B G Feagan collaborated to write the paper, with statistical support from W Bao and clinical input from A Olson. G R Lichtenstein, L F Mayer, S Schreiber, J F Colombel, D Rachmilewitz, and D C Wolf, who participated in the conduct of the trial, provided review and approval of the paper.

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Conflict of interest statement

S B Hanauer has acted as a consultant for, received honoraria from, provided paid expert testimony for, and received travel grants from Centocor. B G Feagan has received honoraria from Centocor. G R Lichtenstein has acted as a consultant for, received honoraria from, and received travel grants from Centocor. L F Mayer has acted as a consultant for, and received honoraria from Centocor. D C Wolf has acted as a consultant for, received honoraria from, and received travel grants from Centocor. A Olson and W Bao are employees of Centocor. P Rutgeerts has provided paid expert testimony for Centocor.

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