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


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 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.

Lancet 2002; 359: 1541–49

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.6–8 Infliximab—a chimeric anti-TNFα monoclonal antibody—binds to TNFα with high affinity, thereby neutralising its biological activity.9 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.10,11 Clinical experience has shown that patients can relapse after a single infusion of infliximab.12,13 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.14 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 between 220 and 400. Patients receiving the following treatments were eligible: 5-aminosulicylates 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). 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.

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 between 220 and 400. Patients receiving the following treatments were eligible: 5-aminosulicylates 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.

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). 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.

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 between 220 and 400. Patients receiving the following treatments were eligible: 5-aminosulicylates 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.

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). 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.

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 between 220 and 400. Patients receiving the following treatments were eligible: 5-aminosulicylates 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.

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). 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.
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 χ² 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 χ² 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.

Incidentsof 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 χ² 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
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%], 40 [26%], and 38 [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 (1·2, 0·74–2·20). 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 9 [5%]; 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 infliximab were 0.0 (0.0–0.0) 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).

### Table 1: Baseline characteristics

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

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.
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 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.

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).
For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.

For personal use. Only reproduce with permission from The Lancet publishing Group.
For patients with 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 both groups. However, the 14% incidence of antibody to infliximab is only 16% of infusions were associated with an infusion reaction in the positive patients compared with 8% of infusions in the negative patients. This ambiguity results from the ongoing presence of infliximab in the serum, which competes with antibodies to infliximab in the ELISA used. Thus, despite the absence of controlled data, there might be an association between infliximab treatment and reactivation of tuberculosis. This potential 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. 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). Thus, the risk-benefit ratio for patients with Crohn’s disease require some steroids to control their disease.

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. 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. 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-idsDNA, 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.

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, population-based assessments show an increased risk of cancer in patients with Crohn’s disease compared with the general population. 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.

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 responded 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, I 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.

ACCENT I Investigators
B Sands (Massachusetts General Hospital, Boston, MA); S R Targan (Cedars Sinai Medical Center, Los Angeles, CA); S B Hanauer (University of Chicago Medical Center, Chicago, IL); M S Harris (Sinaí Samaritan Medical Center, Milwaukee, WI); D Present, L Mayer (Mount Sinai Medical Center, New York, NY); J Onlein (Duke University Medical Center, Durham, NC); J P Bunker (University of Kentucky Medical Center, Lexington, KY); D G Feagan (London Health Sciences Center, London, Ontario); S J H van Deventer (Academisch Medisch Centrum, Amsterdam, Netherlands); R Mas (University of Kentucky Medical Center, St Paul, MN); K Mamm (St Marios Hospital, Middlesex, UK); P B Miner (Oklahoma Foundation for Digestive Research, Oklahoma City, OK); J Faubion (Academisch Ziekenhuis, Leuven, Belgium); B Lasher (Cleveland Clinic Foundation, Cleveland, OH); J R Korzenik (Washington University School of Medicine, St Louis, MO); J F Collins (Portland VA Medical Center and Oregon Health Science University, Portland, OR); S Katz (Long Island Clinical Research Associates, Great Neck, NY); F Saibl (Sunnybrook and Women’s College Health Science Center, Toronto, Ontario); M J Goldstein (North Shore University Hospital, Manhasset, NY); M H Vatt (Medison Gastro, Oslo, Norway); R Löfberg (Huddinge University Hospital Department of Gastroenterology, Hudding, Sweden); S Schreiber (Christian Albrechts University, Keil, Germany); M Campi (Università di Bologna, Bologna, Italy); D P Jewell (John Radcliffe Hospital, Oxford, UK); H Malchow (Klinikum Leverkusen, Leverkusen, Germany); J Scholmerich (Klinikum der Universität, Regensburg, Germany); J F Colombel (Hôpital Claude Huriez, Cedes, France); J Rutgeerts (Universitätsklinikum Charité, Berlin, Germany); D Rachmilewitz (Tel Aviv Sourasky, Tel Aviv, Israel); S Bar-Meir (Chaim Sheba Medical Center, Ramat-Gan, Israel); M A Gassull (University Hospital, Badalona, Spain); R N Fedorak (University of Alberta, Edmonton, Alberta); M Safdi (Consultants for Clinical Research, Cincinnati, OH); J Valente, C Snydsky (Gainesville VA Medical Center, Gainesville, FL); C N Williams (Queen Elizabeth 2 Health Science Centre, Halifax, Nova Scotia); G Wild (Montreal General Hospital, Montreal, Quebec); F Anderson (Vancouver Hospital, Vancouver, BC); W Chay (Chester Institute for Digestive Diseases and Sciences, Rochester, NY); B Winston (Houston Methodist Research Associates, Houston, TX); J Lutterland (University of Calgary Research Services, Calgary, Alberta); C Bernstein (Health Science Centre Hospital, Winnipeg, Manitoba); M Gaspari (Carolina Digestive Health Associates, Charlotte, NC); W DePew (Hotel Dieu Hospital, Kingston, Ontario); H Schwartz (Miami Research Associates, Miami, FL); L Wruble (Mid-South Clinical Research Institute, Memphis, TN); K Das (Crohn’s and Colitis Center of New Jersey, New Brunswick, NJ); C W Antenson (Gastroenterology Specialties, PC, Lincoln, NE).

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.

Acknowledgments
We thank G Keenan for clinical input and M Perate for editorial support. The study was supported by Centocor.

References

For personal use. Only reproduce with permission from The Lancet publishing Group.


23 Schaible TF. Long term safety of infliximab. Can J Gastroenterol Update Low Inflammatory Bowel Dis (ULIBD) 2000; 14: 29–32C.


