Adalimumab Induction Therapy for Crohn Disease Previously Treated with Infliximab
A Randomized Trial

Background: Adalimumab, a fully human tumor necrosis factor (TNF) antagonist, is an effective treatment for patients with Crohn disease who are naive to the chimeric TNF antagonist, infliximab. No anti-TNF agent has been evaluated prospectively in patients with Crohn disease who had responded to another anti-TNF agent and then lost that response or were intolerant of the agent.

Objective: To determine whether adalimumab induces remissions more frequently than placebo in adult patients with Crohn disease who have symptoms despite infliximab therapy or who cannot take infliximab because of adverse events.

Design: 4-week, randomized, double-blind, placebo-controlled trial (November 2004 to December 2005).

Setting: 52 sites in the United States, Canada, and Europe.

Patients: 325 adults 18 to 75 years of age who had a history of Crohn disease for 4 months or more that was moderate to severe at baseline (Crohn’s Disease Activity Index [CDAI] score, 220 to 450 points).

Intervention: Patients were randomly assigned to receive induction doses of adalimumab, 160 mg and 80 mg, at weeks 0 and 2, respectively, or placebo at the same time points.

Measurements: The primary end point was induction of remission at week 4. Decreases in CDAI score by 70 or more and 100 or more points (secondary end points) were also measured.

Results: A total of 301 patients completed the trial. Twenty-one percent (34 of 159) of patients in the adalimumab group versus 7% (12 of 166) of those in the placebo group achieved remission at week 4 ($P < 0.001$). The absolute difference in clinical remission rates was 14.2 percentage points (95% CI, 6.7 to 21.6 percentage points). A 70-point response occurred at week 4 in 52% (82 of 159) of patients in the adalimumab group versus 34% (56 of 166) of patients in the placebo group ($P = 0.001$). The absolute difference in 70-point response rates was 17.8 percentage points (CI, 7.3 to 28.4 percentage points). Two of 159 patients in the adalimumab group and 4 of 166 patients in the placebo group discontinued treatment because of adverse events. No patients in the adalimumab group and 4 of 166 patients in the placebo group had a serious infection.

Limitations: The trial did not directly compare alternative active treatments and did not evaluate maintenance of response or long-term immunogenicity of adalimumab.

Conclusion: Adalimumab induces remissions more frequently than placebo in adult patients with Crohn disease who cannot tolerate infliximab or have symptoms despite receiving infliximab therapy.


For author affiliations, see end of text.

ClinicalTrials.gov registration number: NCT00105300.

Tumor necrosis factor (TNF) is an important proinflammatory cytokine in treating Crohn disease (1). Infliximab is a chimeric, anti-TNF monoclonal antibody effective in inducing and maintaining response and remission in patients with moderate to severe Crohn disease (2, 3). Some patients treated with infliximab experience a loss of efficacy over time or become intolerant of infliximab (4–7). Adalimumab, a human anti-TNF monoclonal antibody, is effective for inducing and maintaining remission in patients with Crohn disease who are naive to infliximab (8–10). Both adalimumab and certolizumab pegol (a pegylated humanized antibody fragment [Fab’] to TNF) are effective for maintaining remission in a broad population of patients with Crohn disease who are naive to infliximab or who have responded to infliximab and then electively discontinued treatment despite continued response or because of lost response, intolerance, or both (10, 11). To our knowledge, no controlled trials have been conducted with these agents in a sample restricted to patients with lost response or intolerance to infliximab. We conducted a 4-week, placebo-controlled trial (GAIN [Gauging Adalimumab Efficacy in Infliximab Nonresponders]), in which adult patients with moderate to severe Crohn disease who had symptoms despite infliximab therapy or who could not take infliximab because of adverse events received adalimumab induction therapy. The Appendix (available at www.annals.org) shows the list of investigators for the GAIN trial group.
Adalimumab Induction Therapy for Crohn Disease

Context
Can adalimumab, an anti–tumor necrosis factor (anti-TNF) agent, induce remission in patients with Crohn disease who do not respond to or cannot tolerate another anti-TNF agent?

Contribution
This double-blind, placebo-controlled trial included 325 adults with Crohn disease who had symptoms despite treatment with infliximab or who could not tolerate infliximab because of adverse events. At 4 weeks, more patients randomly assigned to the adalimumab group achieved remission than did those in the placebo group (21% vs. 7%).

Cautions
The trial did not directly compare efficacy of different anti-TNF agents and did not assess maintenance of response or the long-term immunogenicity of adalimumab.

—The Editors

Methods
Design Overview
This randomized, double-blind, placebo-controlled trial was conducted at 52 centers from November 2004 to December 2005 (last patient contact was on 26 June 2006). The protocol was approved by the institutional review board at each center. All patients provided written informed consent.

Setting and Participants
Fifty-two sites in the United States, Canada, Belgium, and France enrolled patients, with 1 to 29 patients at each site. We recruited patients from tertiary care centers, academic medical institutions, and independent research organizations.

Eligible patients included men and women 18 to 75 years of age with Crohn disease for at least 4 months that was moderately to severely active at baseline, defined by a Crohn’s Disease Activity Index (CDAI) (12) score of 220 to 450 points (range, 0 to 600 points; greater scores indicate more severe disease activity). We required radiologic or endoscopic evidence to confirm the presence of Crohn disease. To be included, patients must have been intolerant of infliximab or must have previously responded to infliximab and then lost response. We excluded patients who had a primary nonresponse to infliximab as defined by the investigator, received infliximab or another TNF antagonist within the past 8 weeks, previously received adalimumab (Humira, Abbott Laboratories, Abbott Park, Illinois), or participated in an adalimumab clinical trial.

Concurrent therapies, including stable dosages of 5-aminosalicylates, prednisone (≤40 mg/d), budesonide (≤9 mg/d), azathioprine, 6-mercaptopurine, methotrexate, and antibiotics, were permitted. We excluded patients who changed dosages or discontinued azathioprine, 6-mercaptopurine, or methotrexate treatment within 12 weeks of screening. Similarly, we excluded patients who changed dosages or discontinued 5-aminosalicylates, mesalamine, or sulfasalazine treatment within 4 weeks of screening. Prednisone (≤40 mg/d) and budesonide (≤9 mg/d) dosages must have been stable for 2 weeks or more before screening. Dosages of all these medications were required to remain stable during the study.

We excluded patients with the short bowel syndrome, a symptomatic stricture, or bowel resection within the past 6 months; those who had undergone ostomy or ileal pouch; and those receiving total parenteral nutrition. We also excluded patients who had received antibiotic treatment for infections not related to Crohn disease within 3 weeks of the study and those with untreated tuberculosis or demyelinating disorders. We excluded female patients who were pregnant or were breast-feeding. We also excluded patients with a history of clinically significant drug or alcohol abuse in the past year; abnormal results on electrocardiography; or elevated concentrations of aspartate or alanine aminotransferase (>1.75 times the upper limit of the reference range), total bilirubin (>51.3 μmol/L [=3 mg/dL]), or serum creatinine (>141.4 μmol/L [=1.6 mg/dL]).

Randomization and Intervention
We randomly assigned eligible patients to receive subcutaneous injections of adalimumab, 160 mg at week 0 and 80 mg at week 2, or placebo at weeks 0 and 2 and followed patients through week 4. Patients, investigators, study site personnel, and Abbott Laboratories were unaware of treatment assignments. Randomization was completed through a central computer-generated scheme stratified by site, with block sizes of 4. Patient numbers were centrally assigned by an interactive voice-response system in consecutive order. The system provided access to blinded patient treatment information for medical emergencies only. Patients who successfully completed week 4 were eligible to enter an open-label extension study of the long-term safety of repeated administration of adalimumab.

Outcomes and Measurements
We classified patients as having a loss of response if they had a history of an initial response to infliximab, as defined by the investigator; had received at least 2 doses of infliximab of 5 mg/kg of body weight or more every 8 weeks; and had lacked improvement or had worsening in at least 1 of the following signs or symptoms related to Crohn disease at least 2 weeks after receiving the last dose of infliximab: stool frequency, daily abdominal pain, fever, recurring drainage from a previously nondraining fistula or development of a new draining fistula, rectal bleeding, or change in use of antidiarrheal medication.

We classified patients as having intolerance of infliximab if they had a history of discontinuing infliximab treatment because of a clinically significant acute or de-
Adalimumab Induction Therapy for Crohn Disease

Follow-up Procedures

Patients were assessed 2 weeks before randomly assigned treatment began; on day 0; and at 1, 2, and 4 weeks. At each visit, the CDAI score was determined, adverse events and concomitant medications were recorded, and samples were collected for laboratory evaluations. The Inflammatory Bowel Disease Questionnaire (IBDQ) was administered to assess patient-reported outcomes at weeks 0 and 4 (total score range, 32 to 224; greater scores indicate better quality of life) (13). Safety evaluations included physical examinations. Laboratory evaluations included hematologic analysis; serum biochemical analysis; urinalysis; and determination of concentrations of C-reactive protein, adalimumab and antibodies to adalimumab, and infliximab and antibodies to infliximab.

Adverse events were recorded through queries, observations by site personnel, and spontaneous patient reports. Investigators assessed and recorded any adverse event, including date of onset, description, severity, time course, duration, outcome, relationship of event to the study drug, alternate causes for events not considered to be probably related to the study drug, final diagnosis (if known), and any actions taken. Investigators rated the severity of each event (mild, moderate, or severe) and the relationship to study drug (probably related, possibly related, probably not related, or not related) on the basis of standard definitions.

Serious adverse events were recorded through scheduled telephone contacts, study visits, and spontaneous patient reports from the time informed consent was signed until 70 days after withdrawal of study drug treatment. A data monitoring committee met every 4 to 6 months to discuss unblinded data and recommend either continuing or amending the study. A sponsor steering committee of senior executives who were not directly participating in the study and who remained blinded to the data made final decisions based on those recommendations. If the rate of serious adverse events exceeded 0.45 event per patient-year or serious infections exceeded 0.09 infection per patient-year, an ad hoc data monitoring committee meeting was required.

Statistical Analysis

We estimated that at least 300 patients would be needed to achieve 80% power to detect an absolute difference in remission rates of 15% between the adalimumab and placebo groups, assuming a 35% rate of remission with adalimumab, a 20% rate of remission with placebo, a 5% rate of patients who could not be evaluated, and a 2-sided α level of 5%.

The primary efficacy end point was remission at week 4 in the intention-to-treat sample. Prespecified secondary analyses included the proportions of patients attaining clinical response (70-point and 100-point responses) at week 4 in the adalimumab and placebo groups; changes from baseline in CDAI total score, IBDQ total score, and C-reactive protein concentration; improvement in the number of draining fistulas at week 4 (decrease ≥50% in the number of draining fistulas at weeks 2 and 4 vs. baseline); and fistula remission at week 4 (closure of all fistulas at weeks 2 and 4 that were draining at screening and at baseline).

We performed a 2-sided Pearson chi-square test to compare the proportions of patients achieving remission, 70-point response, 100-point response, fistula improvement, and fistula remission between treatment groups. We compared continuous response parameters, including CDAI total score, IBDQ total score, and C-reactive protein concentration, by using analysis of covariance. Dependent variables were CDAI total score, IBDQ score, and C-reactive protein concentration. Independent variables were their respective baseline values and treatment groups for each analysis of covariance model. We used the Fisher exact test for the analysis of adverse events. For clinical remission and response measures, we considered patients with missing CDAI scores to be nonresponders. For all continuous variables, we included only patients with complete data in the analyses. In addition, we performed analyses to explore the effect of adalimumab in subpopulations of patients who had an elevated C-reactive protein concentration (>10 mg/L) at baseline, who lost response to infliximab, who had positive results for antibodies to infliximab, and who were intolerant of infliximab or were receiving immunosuppressive agents.

We conducted statistical analyses through logistic regression, with terms for treatment, subgroup, and treatment-by-subgroup interactions, to assess the effects of baseline characteristics on clinical remission at week 4.
We used SAS, version 8.1 (SAS Institute, Cary, North Carolina), for analyses.

Role of the Funding Source

Three investigators and members of Abbott Laboratories staff designed the study. The authors had access to all data, participated in the analysis and interpretation of the data, and helped write the manuscript or reviewed it critically for intellectual content. The statistician who analyzed the data is an Abbott Laboratories employee who was blinded to the treatment assignments during and after the study until the full database was locked and the blinding was broken. The lead author, an investigator, was primarily responsible for writing the manuscript, including developing the first draft, and either writing or approving all subsequent revisions requested by co-authors. Medical writing and editing support were provided by an Abbott Laboratories employee and a contract medical writer provided by Abbott Laboratories. The Abbott authors reviewed and approved the manuscript and, with the other authors, consented to its publication.

RESULTS

Study Patients

A total of 325 patients were randomly assigned, and 301 patients completed the study. Fifteen patients did not enroll in the ongoing, open-label extension study, including 14 patients who discontinued treatment prematurely (10 in the placebo group and 4 in the adalimumab group) and 1 patient who completed the study. Of the 14 patients who discontinued treatment, 6 withdrawals were the result of protocol violations. Protocol violations included entry criteria violations, wrong or incorrect dosage of study medication, and use of prohibited concomitant medications. No patient who met withdrawal criteria remained in the study. No patients crossed over to the other study group. Figure 1 summarizes the flow of patients through the study. Baseline characteristics were similar in the 2 groups (Table 1).

Fifty-two sites were involved in the study, with 1 to 29 patients at each site. One-hundred fourteen patients receiving adalimumab and 111 receiving placebo were from the United States; 18 and 18, respectively, were from Belgium; 28 and 25, respectively, were from Canada; and 6 and 5, respectively, were from France.

Efficacy

At week 4, 21% (34 of 159) of patients in the adalimumab group compared with 7% (12 of 166) of patients in the placebo group achieved remission ($P < 0.001$) (Table 2). The absolute difference in the rates of clinical remission between the 2 groups was 14.2 percentage points (95% CI, 6.7 to 21.6 percentage points). The difference between the adalimumab and placebo groups was evident at week 1 for a decrease of 70 points or more in the CDAI score, the more sensitive measure of response. The rates of 70-point response were greater in the adalimumab group than in the placebo group at weeks 1, 2, and 4: 35% (55 of
versus 21% (34 of 166) of patients, 52% (83 of 159) versus 33% (54 of 166) of patients, and 52% (82 of 159) versus 34% (56 of 166) of patients, respectively. The differences in 70-point response between the groups at weeks 1, 2, and 4 were 14.1 percentage points (CI, 4.5 to 23.7 percentage points), 19.7 percentage points (CI, 9.1 to 30.2 percentage points), and 17.8 percentage points (CI, 7.3 to 28.4 percentage points), respectively. The rates of 100-point response were also greater in the adalimumab group than in the placebo group at weeks 1, 2, and 4: 20% (31 of 159) versus 12% (20 of 166) of patients, 37% (58 of 159) versus 18% (30 of 166) of patients, and 38% (61 of 159) versus 25% (41 of 166) of patients, respectively. The differences in 100-point response rates between the adalimumab and placebo groups at weeks 1, 2, and 4 were 7.4 percentage points (CI, −0.5 to 15.4 percentage points), 18.4 percentage points (CI, 8.9 to 27.9 percentage points), and 13.7 percentage points (CI, 3.7 to 23.7 percentage points), respectively. A Breslow–Day test for homogeneity that compared the rates of clinical remission in North America versus Europe did not show statistical significance ($P = 0.15$).

Patients in the adalimumab group had statistically significantly lower mean CDAI total scores at weeks 1, 2, and 4 (Figure 2) than did patients in the placebo group. The mean IBDQ total scores at week 4 were 150 in the adalimumab group and 139 in the placebo group ($P = 0.001$). The mean changes from baseline in IBDQ score for adalimumab and placebo groups were 30 and 15, respectively, and the rate difference between the groups at week 4 was

### Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (n = 166)</th>
<th>Adalimumab Group (n = 159)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>65 (39)</td>
<td>50 (31)</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>37 (12)</td>
<td>39 (12)</td>
</tr>
<tr>
<td>Mean weight (SD), kg</td>
<td>72 (19)</td>
<td>72 (19)</td>
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<tr>
<td>Intestinal area involved, n (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>113 (68)</td>
<td>105 (66)</td>
</tr>
<tr>
<td>Ileum</td>
<td>124 (75)</td>
<td>112 (70)</td>
</tr>
<tr>
<td>Rectum</td>
<td>37 (22)</td>
<td>36 (23)</td>
</tr>
<tr>
<td>Perianal or anus</td>
<td>31 (19)</td>
<td>27 (17)</td>
</tr>
<tr>
<td>Gastroduodenal</td>
<td>16 (10)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Jejunum</td>
<td>4 (2)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Abdominal or perianal fistula at baseline, n (%)</td>
<td>25 (15)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>Mean CDAI score (SD)</td>
<td>313 (66)</td>
<td>313 (58)</td>
</tr>
<tr>
<td>Mean baseline IBDQ score (SD)§</td>
<td>124 (28)</td>
<td>120 (27)</td>
</tr>
<tr>
<td>CRP concentration, mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20 (37)</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>7 (0–235)</td>
<td>9 (0–115)</td>
</tr>
<tr>
<td>CRP concentration ≥10 mg/L, n (%)§§</td>
<td>68 (41)</td>
<td>77 (48)</td>
</tr>
<tr>
<td>Previous loss of response to infliximab, n (%)‡</td>
<td>87 (52)</td>
<td>77 (48)</td>
</tr>
<tr>
<td>Previous intolerance of infliximab, n (%)‡†</td>
<td>95 (57)</td>
<td>95 (60)</td>
</tr>
<tr>
<td>Acute reaction</td>
<td>63 (38)</td>
<td>68 (43)</td>
</tr>
<tr>
<td>Delayed reaction</td>
<td>52 (31)</td>
<td>43 (27)</td>
</tr>
<tr>
<td>Acute and delayed reaction</td>
<td>20 (12)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Previous loss of response to and intolerance of infliximab, n (%)‡†</td>
<td>21 (13)</td>
<td>19 (12)</td>
</tr>
<tr>
<td>Antibodies to infliximab, n (%)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>91 (57)</td>
<td>88 (59)</td>
</tr>
<tr>
<td>Indeterminate††</td>
<td>8 (6)</td>
<td>12 (8)</td>
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<tr>
<td>Present</td>
<td>60 (38)‡‡</td>
<td>50 (33)</td>
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<tr>
<td>Concomitant medication, n (%)</td>
<td></td>
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<tr>
<td>Steroids§§</td>
<td>73 (44)</td>
<td>55 (35)</td>
</tr>
<tr>
<td>Any immunosuppressive agent</td>
<td>85 (51)</td>
<td>73 (46)</td>
</tr>
<tr>
<td>5-aminosalicylates</td>
<td>60 (36)</td>
<td>45 (28)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>56 (34)</td>
<td>55 (35)</td>
</tr>
</tbody>
</table>

* CDAI = Crohn’s Disease Activity Index; CRP = C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire.† Patients received adalimumab, 80 mg or 160 mg.‡ Percentages total more than 100% because a patient could have been counted in more than 1 category.§ Scores for the IBDQ can range from 32 to 224. Greater scores indicate a better quality of life.
| High-sensitivity cardiology assay for CRP. Normal range is <2.83 mg/L.¶ Missing data for 1 patient in the placebo group.** Missing data for 7 patients in the placebo group and 6 patients in the adalimumab group.†† Results are indeterminate because of the presence of infliximab in 8 patients in the placebo group and 12 patients in the adalimumab group.‡‡ One patient in the placebo group had a measurable infliximab concentration and antibody to infliximab.§§ Budesonide, betamethasone, cortisone, clobrednol, corticosteroids, dexamethasone, deflazacort, fluorocortolone, glucocorticoids, glucocorticosteroids, hydrocortisone, methylprednisolone, paramethasone, prednisolone, prednisone, or prednylidene.|| Balsalazide, mesalamine, olsalazine, or sulfasalazine.
Adalimumab Induction Therapy for Crohn Disease

Table 2. Patients Achieving Remission at Each Visit*

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo Group (n = 166), n (%)</th>
<th>Adalimumab Group (n = 159), n (%)</th>
<th>Rate Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (4)</td>
<td>10 (6)</td>
<td>2.7 (-2.0 to 7.4)</td>
</tr>
<tr>
<td>2</td>
<td>10 (6)</td>
<td>34 (21)</td>
<td>14.7 (7.2 to 22.0)</td>
</tr>
<tr>
<td>4</td>
<td>12 (7)</td>
<td>34 (21)</td>
<td>14.2 (6.7 to 21.6)</td>
</tr>
</tbody>
</table>

* Patients with missing values were treated as nonresponders. At weeks 1, 2, and 4, there were 5, 3, and 8 patients in the placebo group, respectively, and 4, 3, and 6 patients in the adalimumab group, respectively, who were missing Crohn’s Disease Activity Index scores.

14.1 percentage points (CI, 7.92 to 20.41 percentage points). Three patients in the adalimumab group and 5 in the placebo group had missing IBDQ total scores. Despite having a greater mean C-reactive protein concentration at baseline (9.0 mg/L vs. 7.0 mg/L), patients in the adalimumab group also had a statistically significantly lower median C-reactive protein concentration at week 4 than did patients in the placebo group (5.0 mg/L vs. 7.0 mg/L). Fourteen percent (45 of 325) of randomly assigned patients had draining enterocutaneous or perianal fistulas at baseline. The rates of fistula improvement and remission at week 4 were similar for both groups: 20% (5 of 25) of patients in the placebo group versus 15% (3 of 20) of patients in the adalimumab group for improvement and 8% (2 of 25) versus 5% (1 of 20), respectively, for remission.

The efficacy of adalimumab was demonstrated in subgroups of patients stratified for concomitant immunosuppressive therapy (azathioprine, 6-mercaptopurine, and methotrexate), concomitant corticosteroid therapy, previous loss of response to infliximab, previous intolerance of infliximab, previous loss of response to and intolerance of infliximab, presence of antibodies to infliximab at screening, and C-reactive protein concentration of 10 mg/L or more at week 0 (Figure 3).

Adverse Events

Patients receiving placebo reported adverse events and exacerbations of Crohn disease more frequently than those receiving adalimumab (Table 3). The groups did not differ greatly in the numbers of patients who discontinued treatment because of an adverse event (1% in the adalimumab group vs. 2% in the placebo group). Treatment-emergent adverse events were predominantly mild to moderate. Thirty-two percent of patients in the placebo group and 27% of those in the adalimumab group reported a treatment-emergent adverse event. Three patients (1.8%) in the placebo group and no patients in the adalimumab group reported a treatment-emergent serious adverse event that investigators considered to be possibly related or probably related to the study drug. Serious adverse events occurred in 1% of patients in the adalimumab group (2 cases of dehydration) compared with 5% of patients in the placebo group (3 abscesses, 1 staphylococcal sepsis, 2 Crohn disease flares, and 2 cases of severe abdominal pain). The rate difference of serious adverse events between the 2 groups was −3.5 percentage points (CI, −5.7 to 0.8 percentage points). No solid tumors or cases of hematologic cancer occurred. No patients developed clinical symptoms consistent with lupus or lupus-like disease, and no patient died.

Laboratory values for patients in either group did not clinically significantly change. The incidences of infectious adverse events in the adalimumab group (16% [26 of 159 patients]) and the placebo group (24% [39 of 166 patients]) were similar (rate difference, −7.1 percentage points [CI, −15.9 to 2.2 percentage points]). Serious infectious adverse events did not occur in any of the 159 patients in the adalimumab group but occurred in 2% of patients in the placebo group (rate difference, −2.4 percentage points [CI, −4.7 to −0.1 percentage points]). No patient in either group developed tuberculosis or opportunistic infections. Other nonserious infections, including nasopharyngitis, upper respiratory tract infection, and urinary tract infection, occurred at similar rates between groups. Injection-site reactions occurred in 11% and 10% of patients in the adalimumab and placebo groups, respectively (rate difference, 0.45 percentage point [CI, −6.6 to 7.5 percentage points]).

Patients who completed the trial were able to continue in an extension study and receive 40 mg of open-label adalimumab every other week. Patients who participated in the extension study did not receive 70-day follow-up telephone calls because safety events were recorded as part of the extension study and will be reported separately. Fourteen patients did not participate in the extension study and received follow-up telephone calls. Of these patients, 1 in the placebo group reported an adverse event (pneumonia).

Adalimumab Concentrations and Immunogenicity

The mean adalimumab concentration at week 4 in the adalimumab group was 12.6 µg/mL (SD, 6.0) (median, 12.2 µg/mL; range, 0.0 to 36.4 µg/mL). None of the 159 patients treated with adalimumab had positive results for antidalimumab antibodies at week 4, although the presence of serious adverse events in the adalimumab group was lower than in the placebo group (rate difference, 7.1 percentage points [CI, 2.2 to 12.0 percentage points]).
of measurable adalimumab precluded determination of these antibodies in most patients treated with adalimumab.

**DISCUSSION**

Adalimumab therapy was superior to placebo for inducing remission and response in patients with moderate to severe Crohn disease who were intolerant of infliximab or had previously responded to infliximab and then lost response. Patients who received adalimumab were more likely than patients who received placebo to achieve remission, 70-point response, and 100-point response at 4 weeks. Patients who received adalimumab had greater decreases in disease activity as measured by changes in mean CDAI scores, mean IBDQ total scores, and median C-reactive protein concentrations. We observed statistically significant responses in some measures (70-point response and mean CDAI score) as early as week 1. Subgroup analyses demonstrated consistent benefit of adalimumab when the results were stratified for corticosteroid therapy, immunosuppressive therapy, baseline C-reactive protein concentration, previous loss of response to infliximab, and previous intolerance of infliximab.

These results suggest that the remission and response rates observed for patients with Crohn disease treated with adalimumab who had previously responded to infliximab therapy and then lost response or became intolerant are proximally similar to those reported previously for infliximab-naive patients who were treated with adalimumab and infliximab, although results from different studies cannot be fully or directly compared (2, 8). These data confirm uncontrolled results of earlier pilot studies suggesting that adalimumab is safe and effective in this patient population (14–16). Placebo-controlled trials of adalimumab, certolizumab pegol, and natalizumab that enrolled mixed samples of patients with Crohn disease, including infliximab-naive patients and patients previously treated with...
infliximab, have demonstrated efficacy in subgroups of patients with Crohn disease who had been treated with infliximab (10, 11, 17–19). However, these patients were not selected for loss of response or intolerance of infliximab and many had simply discontinued therapy and then had relapse (10, 11, 17–19). Of note, the 70-point response and remission rates at week 4 in the adalimumab group are very similar to the results observed in CHARM (Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) (10) at the same time point (clinical response [CR]–70 rate, 52% in GAIN vs. 60% in CHARM; remission rate, 21% in GAIN vs. 25% in CHARM). The study sample in CHARM included infliximab–experienced and infliximab–naive patients (10). For patients with rheumatoid arthritis, studies that have reported on the effectiveness of switching among TNF antagonists (etanercept, infliximab, and adalimumab) have used nonrandomized, uncontrolled, observational study designs (20–24). Other placebo-controlled studies of patients with rheumatoid arthritis have evaluated efficacy after patients switched from TNF inhibitors to drugs with other mechanisms of action (for example, abatacept and rituximab) (25, 26).

After a search of the medical literature and clinical trial registries, such as www.ClinicalTrials.gov, we believe that the GAIN study was the first randomized, double-blind, placebo-controlled trial in any immune-mediated disease in which TNF plays a central role to evaluate the efficacy of administering a second TNF antagonist to patients in whom a first TNF antagonist had failed. On the basis of baseline disease measures, such as CDAI and IBDQ scores and C-reactive protein concentrations, our study sample was representative of patients who had stopped infliximab treatment because they were deriving inadequate therapeutic benefit and patients who had experienced reactions or other adverse events that prevented them from continuing therapy. The categories for loss of response were sufficiently broad to reflect a wide population of infliximab–experienced patients with Crohn disease, although some very specific forms of infliximab reactions and failure may not have been captured. Nonetheless, our study covered a clinically relevant sample, and from the efficacy and safety results presented here, we conclude that adalimumab is a viable treatment option for these patients.

Types and frequencies of adverse events in our study were similar to those previously reported for patients naive to anti-TNF therapy (8). The overall rates of any type of injection-site reaction were 10% in the placebo group and 11% in the adalimumab group. Injection-site irritation and nonspecific injection-site reactions were the most commonly reported of these reactions, and none led to withdrawal. The rates of serious adverse events and serious infections in patients treated with adalimumab were similar to those of patients who received placebo. No patient developed opportunistic infections, lupus or lupus-like disease, neurologic diseases, lymphoma, or solid malignant tumors, and no patient died. We note that this was only a 4-week trial. The CHARM results (10) provide additional information about the safety of 56 weeks of adalimumab treatment in patients with Crohn disease and support the safety of adalimumab for patients in whom infliximab therapy has failed or who are naive to infliximab therapy. For patients with rheumatoid arthritis treated with adalimumab, serious and opportunistic infections, lymphoma, demyelination, congestive heart failure, and lupus-like syndrome have all been reported (27–29). Rates of infections in placebo-controlled trials of adalimumab in patients with rheumatoid arthritis were 1.0 infection per patient-year in patients who received adalimumab and 0.9 infection per patient-year in patients who received placebo. Serious infections occurred at a rate of 0.04 infection per patient-year in patients with rheumatoid arthritis who received adalimumab and 0.02 infection per patient-year in those who received placebo. Pneumonia, tuberculosis, histoplasmosis, aspergillosis, and nocardia were all observed during trials of patients with rheumatoid arthritis who received adalimumab (27, 28).

None of the 159 patients who received adalimumab in our short-term study developed antibodies to adalimumab.

### Table 3. Summary of Safety and Immunogenicity Analyses for All Randomly Assigned Patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Group</th>
<th>Adalimumab Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>n (% )</td>
<td>n (% )</td>
</tr>
<tr>
<td>Adverse events occurring in ≥5% of any treatment group</td>
<td>121 (73)</td>
<td>91 (57)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (7)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (7)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Injection-site irritation</td>
<td>7 (4)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (5)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>15 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Patients with any type of injection-site reactions</td>
<td>17 (10)</td>
<td>17 (11)</td>
</tr>
</tbody>
</table>

* Number and percentage of patients in whom an event, including exacerbations of Crohn disease and other preexisting conditions, occurred ≥1 time during the trial.
These results are similar to those reported previously for adalimumab in patients with Crohn disease, in which the frequency of antibodies to adalimumab ranged from 0.4% to 3.6% (8, 9). Again, the mean trough adalimumab concentration at week 4 was 12.6 μg/mL. An identical concentration was observed for infliximab-naive patients in the CLASSIC II (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease II) study (10).

Some important study limitations should be noted. Our trial was a short-term induction trial, and longer-term results are needed to evaluate the maintenance of response. The CHARM study (10) has published results demonstrating maintenance of clinical remission with adalimumab therapy in a mixed sample of both infliximab-naive and infliximab-experienced patients. Moreover, a longer study with additional doses of adalimumab may also demonstrate a greater rate of induction of remission. As a 4-week study, our trial was limited in providing data to assess important but uncommon adverse effects of adalimumab. Long-term safety and efficacy results for patients in the GAIN trial who participated in an extension study will be published as a follow-up to this article.

In addition, the definition of loss of response, although broad enough to reflect a clinically relevant population, was specific to this trial setting and allowed for a single criterion to be met to fulfill the definition. This should be taken into consideration when interpreting these results. Furthermore, assessment of infliximab failure in this study was retrospective rather than prospective. The study designers believed that a prospective assessment approach to determining failure of infliximab therapy would have made enrollment difficult and the study ultimately not feasible. Finally, the trial did not directly compare alternative active treatments.

In conclusion, adalimumab induces remission more frequently than placebo in adult patients with moderate to severe Crohn disease who cannot tolerate infliximab or who have symptoms despite receiving infliximab therapy.

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Adalimumab Induction Therapy for Crohn Disease

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