Adalimumab for Maintenance Treatment of Crohn’s Disease: Results of the CLASSIC II Trial

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ABSTRACT

Objective: Adalimumab induced clinical remission after 4 weeks in patients with active Crohn’s disease (CD) in the CLASSIC I trial. A follow-on randomised controlled trial (CLASSIC II) evaluated long-term efficacy and safety of adalimumab maintenance therapy in CD.

Methods: In the preceding CLASSIC I trial, 299 patients with moderate to severe CD naïve to tumour necrosis factor antagonists received induction therapy with adalimumab 40 mg/20 mg, 80 mg/40mg, or 160 mg/80 mg; or placebo at Weeks 0 and 2. A total of 276 patients from CLASSIC I enrolled in CLASSIC II and received open-label (OL) adalimumab 40 mg at Weeks 0 (Week 4 of CLASSIC I) and 2. Fifty-five patients in remission at both Weeks 0 and 4 were re-randomised to adalimumab 40 mg every other week (eow), 40 mg weekly, or placebo through 56 weeks. Patients not in remission at both Weeks 0 and 4 were enrolled in an OL arm and received adalimumab 40 mg eow. With non-response or flare, these patients were permitted to have their dosages increased to 40 mg weekly. Patients in the randomised arm with continued non-response or disease flare were able to switch to OL adalimumab 40 mg eow and again to 40 mg weekly. Primary endpoint was maintenance of remission (CDAI<150) in randomised patients through Week 56.

Results: Of 55 patients randomised at Week 4, 79% who received adalimumab 40 mg eow and 83% who received 40 mg weekly were in remission at Week 56, vs. 44% for placebo (p<0.05). A total of 204 patients entered the OL arm. Of these, 93 (46%) were in clinical remission at Week 56. Adalimumab was generally well-tolerated in all patients.

Conclusion: Adalimumab induced and maintained clinical remission for up to 56 weeks in patients with moderate to severe CD naïve to anti-TNF therapy.
INTRODUCTION
Crohn’s disease (CD) is a T-helper Type 1 (Th 1) disease, which has a characteristic immune response pattern that includes an increased production of interleukin-12, tumour necrosis factor (TNF), and interferon γ. Increased production of TNF by macrophages in patients with Crohn’s disease results in elevated concentrations of TNF in the stool, blood, and mucosa. Tumour necrosis factor is thought to play a critical role in the inflammation of Crohn’s disease. Clinical trials have demonstrated that infliximab, a chimeric, anti-TNF monoclonal antibody, is efficacious for induction and maintenance of clinical response and remission in patients with moderate to severe CD, as well as inducing and maintaining fistula closure. Unfortunately, infliximab may be immunogenic, and episodic as well as continuous administration may result in the formation of antibodies to infliximab that can cause infusion reactions, loss of efficacy, and delayed hypersensitivity reactions.

As noted in a review of therapeutic monoclonal antibodies published in 2000, fully human monoclonal antibodies are frequently less immunogenic than chimeric monoclonal antibodies. Adalimumab (HUMIRA®, Abbott Laboratories, Abbott Park, IL, USA) is a fully human, IgG1 monoclonal antibody that binds with high affinity and specificity to membrane and soluble TNF, but not lymphotoxin. Controlled trials have shown that adalimumab is safe and efficacious for the treatment of rheumatoid arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis. Adalimumab is approved by multiple regulatory authorities for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. A 4-week, randomised controlled induction trial (CLASSIC I: Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease) demonstrated clinical efficacy at Week 4 with loading dose regimens of adalimumab 80 mg/40 mg and 160 mg/80 mg administered at Weeks 0 and 2 for patients with moderately to severely active CD who were naïve to anti-TNF therapy. Adalimumab 160 mg/80 mg demonstrated the greatest efficacy.

The predefined hypothesis of this study was that sustained adalimumab therapy would maintain long-term clinical remission in a greater proportion of patients with moderate to severe CD than would placebo. In CLASSIC II, patients who achieved remission after the 4-week induction regimen in CLASSIC I and then maintained remission for an additional 4 weeks with open-label (OL) adalimumab 40 mg every other week (eow) were re-randomised to receive blinded adalimumab therapy or placebo through 56 weeks. Patients not in remission at both Weeks 0 and 4 of CLASSIC II entered the OL arm and received adalimumab 40 mg eow, with the potential to have their dosages increased to 40 mg weekly with non-response or disease flare.
METHODS

Patients

This multicentre, randomised, double-blind, placebo-controlled trial was conducted at 53 centres between August 28, 2002, and January 12, 2005. The protocol was approved by the institutional review board or ethics committee at each center. All patients provided written informed consent.

All patients who met study entry criteria and successfully completed CLASSIC I were eligible to enroll in CLASSIC II. Female patients of childbearing potential were required to use a highly effective form of birth control, and all patients were required to demonstrate adequate cardiac, renal and hepatic function as determined by principal investigator.

Study Design

In the CLASSIC I trial, patients were randomly assigned to receive one of the following subcutaneous induction regimens: placebo at Weeks 0 and 2; adalimumab 40 mg at Week 0 and 20 mg at Week 2; adalimumab 80 mg at Week 0 and 40 mg at Week 2; or adalimumab 160 mg at Week 0 and 80 mg at Week 2. Clinical remission was defined as a Clinical Disease Activity Index (CDAI) score of less than 150 points. Patients were eligible for enrollment in the randomised cohort of CLASSIC II if they demonstrated clinical remission at both Week 0 (Week 4 in CLASSIC I) and Week 4. At Week 4, those in remission were randomly assigned in a 1:1:1 ratio to receive blinded subcutaneous maintenance therapy with adalimumab 40 mg eow, adalimumab 40 mg weekly, or placebo from Weeks 4–55. Patients not in remission at both time points entered the OL cohort and received 40 mg eow. All patients were followed through Week 56. Assignment to randomised treatment was performed centrally. A pharmacist or designee dispensed the study drug according to detailed instructions provided by Abbott Laboratories to each of the study sites.

Dosages employed in this study were selected based on pharmacokinetic data from clinical trials of adalimumab in patients with rheumatoid arthritis. Adalimumab serum concentrations of 4–8 µg/mL achieved with dosages of 40 mg eow were found to be efficacious in rheumatoid arthritis. On this basis, a dosage of 40 mg of adalimumab eow was selected as the target maintenance dosage for efficacy in CD. An additional dosage, 40 mg weekly, was also included. This 40-mg weekly dosage was expected to yield adalimumab concentrations slightly greater than 10 µg/mL. If randomised patients experienced a flare (defined as both an increase in CDAI ≥70 points above the CLASSIC II Week-4 value and a total CDAI score >220 points) or had continued non-response (defined as a decrease in CDAI ≤70 points vs. Week-0 value in CLASSIC I), they were permitted to switch to OL adalimumab 40 mg eow. These patients were considered failures in the primary efficacy analysis. If patients receiving OL adalimumab 40 mg eow flared or had continued non-response, their dosages could be increased to 40 mg weekly. Patients on weekly OL dosing who continued to flare were discontinued from the study. For the randomised cohort, patients, study coordinators, and study investigators were all blinded to treatment assignments.

Patients’ dosages of all concurrent medications were required to remain constant, with the exception of corticosteroids. Steroid tapering was mandated for randomised patients at Week 8 and was permitted in the OL cohort for those patients who were responders (i.e., experienced a reduction of ≥70 points in CDAI score from Week 0 in CLASSIC I). After Week 8, daily dosages for randomised patients receiving prednisone >10 mg was reduced by...
5 mg weekly until a dosage of 10 mg/day was reached. Thereafter, dosage was reduced by 2.5 mg weekly to the point of discontinuation. Similarly, budesonide dosage was decreased by 3 mg every week until discontinuation.

Remission was defined as a CDAI <150 points. Response was defined as a reduction of ≥70 points (70-point response) or of ≥100 points (100-point response) in the CDAI score from Week 0 in CLASSIC I.

**Efficacy and Safety Evaluations**

Patients were assessed at Weeks 0, 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56, and CDAI scores were calculated for each visit. CDAI scores range from 0–600, with higher scores indicating greater disease activity. The Inflammatory Bowel Disease Questionnaire (IBDQ) was administered to assess patient-reported outcomes at each visit. IBDQ total scores range from 32–224, with higher scores indicating better patient function and quality of life. At each visit, adverse events and concomitant medications were recorded, and samples were collected for standard laboratory evaluations, including antibodies to adalimumab as well as C-reactive protein (CRP) values. Safety assessments included vital signs, physical examinations, haematology, serum biochemistry, and urinalysis.

**Sample Size and Statistical Analysis**

Sample size calculation for the lead-in CLASSIC I study, which called for enrollment of at least 300 patients, has been published. All patients who completed CLASSIC I were eligible to participate in CLASSIC II, and no additional statistical powering for this follow-on study was conducted. Thus, the analyses described here were exploratory in nature. Approximately 90% of patients from CLASSIC I (270 patients) were anticipated to enroll.

The primary analysis using Pearson’s Chi-square test evaluated the proportion of patients demonstrating remission at Week 56 in each arm of the randomized cohort (adalimumab 40 mg eow, 40 mg weekly, and placebo). Those with missing primary endpoint data at Week 56 or those who had moved to open-label dosing were classified in a “no maintenance of remission” category. An initial overall comparison of the three treatment groups (adalimumab 40 mg eow, adalimumab 40 mg weekly, and placebo) was tested. If significant differences between the three groups were detected, pairwise comparisons of each adalimumab group vs. the placebo group were performed.

The Pearson’s chi-square test, Fisher’s exact test, ANCOVA, Kruskal-Wallis test, and Kaplan-Meier survival analysis were used as appropriate to provide nominal p-values for secondary endpoints. Pre-specified secondary analyses included the percentages of patients in remission at Week 24; 70-point and 100-point clinical responses at Weeks 24 and 56; changes in IBDQ total score from baseline to Weeks 24 and 56; and percentages of patients who completely discontinued steroids without loss of remission at Weeks 24 and 56. A subgroup efficacy analysis of patients receiving and not receiving concomitant immunosuppressive agents was also performed. All secondary analyses were performed using last observation carried forward (LOCF).

Analyses of the results for patients who received OL therapy were imputed, and patients who discontinued treatment before Week 56 were counted as primary treatment failures.
RESULTS

Patient Characteristics

A total of 276 patients participated in the study. Fifty-five patients had achieved remission at Weeks 0 and 4 and were randomised (Figure 1). In this 55-patient randomised cohort, 18 patients received placebo, 19 patients received adalimumab 40 mg eow, and 18 patients received adalimumab 40 mg weekly. The baseline characteristics of the randomised patients who received placebo were similar to those who received adalimumab (Table 1). In the randomised group, 5 patients (28%) withdrew prematurely from the placebo group, vs. 3 patients (16%) in the adalimumab 40 mg eow group and 2 patients (11%) in the adalimumab 40 mg weekly group.

A total of 204 patients were ineligible for randomization and began receiving OL adalimumab 40 mg eow at Week 4. In addition, 17 patients discontinued at or before Week 4 for the reasons cited in Figure 1. Baseline characteristics of patients who received OL adalimumab were similar to those who were randomised (Table 1). In the OL group, 36% of patients discontinued, 11.3% because of adverse events and 9% because of lack of efficacy (Figure 1).
### Table 1. Baseline Characteristics of CLASSIC II Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomised Cohort</th>
<th>OL Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=18</td>
<td>n=19</td>
</tr>
<tr>
<td>Male patients, no. (%)</td>
<td>6 (33)</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Age in yrs, mean (SD)</td>
<td>36 (13)</td>
<td>34 (12)</td>
</tr>
<tr>
<td>Body weight in kg, mean (SD)</td>
<td>70 (13)</td>
<td>69 (19)</td>
</tr>
<tr>
<td>Duration of CD in yrs, mean (SD)</td>
<td>8.24 (8.3)</td>
<td>7.73 (6.5)</td>
</tr>
<tr>
<td>Patients who smoked, no. (%)</td>
<td>12 (67)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Enterocutaneous or perianal fistula*, no. (%)</td>
<td>3 (17)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>CDAI score*, mean (SD)</td>
<td>107 (62)</td>
<td>106 (33)</td>
</tr>
<tr>
<td>CLASSIC I Week 0 CRP, mg/dL‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.9 (1.0)</td>
<td>3.0 (3.0)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.5 (0.0–3.0)</td>
<td>2.2 (0.0–11.3)</td>
</tr>
<tr>
<td>CRP*, mg/dL.§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.2 (0.2)</td>
<td>0.8 (0.8)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.2 (0.0–0.6)</td>
<td>0.5 (0.0–2.7)</td>
</tr>
<tr>
<td>Concomitant medication, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any corticosteroid</td>
<td>10 (56)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Systemic corticosteroid§</td>
<td>6 (33)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>4 (22)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Any immunosuppressive agent</td>
<td>3 (17)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 (6)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>6-mercaptopurine</td>
<td>1 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Crohn’s-related antibiotics§</td>
<td>1 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5-aminosalicylates§</td>
<td>8 (44)</td>
<td>14 (74)</td>
</tr>
</tbody>
</table>

*Baseline of CLASSIC II corresponds to Week 4 of CLASSIC I.
†Scores for the IBDQ can range from 32–224; higher scores indicate a better quality of life.
‡High sensitivity cardiology assay for CRP; normal range is <0.283 mg/dL.
§Prednisone, prednisolone, methylprednisolone.
‖Metronidazole and ciprofloxacin.
¶Aminosalicylic acid, mesalamine, and sulfasalazine.
#Excludes 17 patients who discontinued at or before Week 4.
Efficacy

Randomised patients

All 55 patients were included in the efficacy analyses of the randomised patient group. For the primary analysis at Week 56, there was a significant difference in the remission rates between the adalimumab 40-mg eow (15/19, 79%), adalimumab 40-mg weekly (15/18, 83%), and placebo (8/18, 44%) groups (p<0.05 for each adalimumab group vs. placebo) (Figure 2A). The rates of remission at Week 56 were similar for patients receiving concomitant immunosuppressants such as azathioprine, 6-mercaptopurine, or methotrexate (adalimumab 40 mg eow [4/4, 100%], adalimumab 40 mg weekly [4/5, 80%], and placebo [1/3, 33%); and patients not receiving concomitant immunosuppressants (adalimumab 40 mg eow [11/15, 73%], adalimumab 40 mg weekly [11/13, 85%], and placebo [7/15, 47%]). Significant differences in remission and 100-point clinical response compared with placebo were demonstrated as early as Week 12 in both adalimumab groups (Figures 2A and 2B). The 70-point clinical response rates were numerically greater for the two active treatment groups vs. placebo (Figure 2C).

At Week 56, patients in the adalimumab groups had greater mean decreases (improvements) from baseline in CDAI score than patients in the placebo group: 150.8 (95% CI, –202, –99.8) and 197.7 (95% CI, –248, –147) for the eow and weekly groups, respectively, vs. 119.6 (95% CI, –174, –65.1) for placebo, (LOCF, p<0.05 for each adalimumab group vs. placebo).

In the randomised group, 49% of patients (27 of 55) were receiving systemic steroids or budesonide at baseline of CLASSIC II. At Week 56, 57% (4/7) of the placebo patients had completely discontinued steroids, compared with 67% (4/6) of patients in the adalimumab 40 mg eow group and 88% (7/8) in the adalimumab 40 mg weekly group (LOCF). The mean total IBDQ score at the start of CLASSIC II was 186.4. A score ≥170 corresponds to clinical remission. A mean total IBDQ score ≥170 was maintained in the groups of randomised patients treated with adalimumab 40 mg eow or weekly (Figure 3), while IBDQ scores declined rapidly in patients receiving placebo. Median CRP concentrations (mg/dL [range]) at Week 24 were 0.5 [0–1.2], 0.4 [0–1.9], and 0.1 [0–1.6] in the placebo, adalimumab 40-mg eow, and adalimumab 40-mg weekly groups, respectively. At Week 56, these CRP values were 0.4 [0–0.9], 0.3 [0–2.8], and 0.3 [0–1.2], respectively.

Open-label patients

A total of 204 patients who were not in remission at both Weeks 0 and 4 entered the OL cohort. Of these, 131 (64%) completed 56 weeks of therapy, 71 remained on their initial regimens of adalimumab 40 mg eow, and 60 had their dosages increased to 40 mg weekly at some point before Week 56. Ninety-three (46%) of the 204 patients receiving OL adalimumab were in remission at Week 56, including 56/115 (49%) of those receiving 40 mg eow and 37/89 (42%) of those receiving 40 mg weekly.

A total of 132 (65%) of the 204 patients receiving OL adalimumab achieved 100-point clinical response at Week 56 or last visit, including 73/115 (64%) with 40 mg eow and 59/89 (66%) with 40 mg weekly (LOCF). Moreover, 147/204 patients receiving OL adalimumab (72%) achieved a 70-point clinical response at Week 56, including 80/115 (70%) with 40 mg eow and 67/89 (75%) with adalimumab 40 mg weekly. In the OL cohort, rates of remission and 100-point clinical response (CR-100) at Week 56 were similar for patients receiving concomitant immunosuppressants (remission, 48%; CR-100, 68%) and for patients who did not receive concomitant immunosuppressants (remission, 45%; CR-100, 63%).
At Week 56, patients in the open-label cohort had a mean decrease from baseline in CDAI score of 158.4. In addition, at Week 56, 58% (21/36) of patients receiving steroids at baseline in the OL cohort had discontinued them.

Safety
The most frequently reported treatment-emergent adverse events (AEs) (≥5% of patients) in the total population of CLASSIC II (n=276) were nasopharyngitis, aggravated CD, and sinusitis (Table 2). The most frequently reported infectious adverse events were nasopharyngitis, sinusitis not otherwise specified (NOS), upper respiratory tract infection NOS, and influenza. No cases of tuberculosis, coccidiomycosis, histoplasmosis, aspergillosis, listeria, pneumocystis, or blastomycosis were reported. One placebo patient reported a malignancy (squamous cell carcinoma). No lymphomas occurred during the study, and no patients died. Also, no events of interest for anti-TNF agents, including demyelinating events, lupus-like reactions, or congestive heart failure, were reported. Injection-site reaction NOS and burning were the most commonly reported of injection-site reactions, none of which led to patient withdrawal.

In the randomised cohort, greater percentages of patients randomised to placebo experienced adverse events, serious adverse events, severe adverse events, and adverse events leading to discontinuation than did patients randomised to either dosage of adalimumab.

In total, blood concentrations of both adalimumab and antibodies to adalimumab were collected for 269 of the 276 patients in CLASSIC II. Of these 269, 7 (2.6%) were determined to have developed antibodies to adalimumab. Of the 269, 84 received concomitant immunosuppressants, none of whom were positive for antibodies to adalimumab. Seven of the 185 patients (3.8%) who developed the antibodies did not receive concomitant immunosuppressants. Further, 3 of the 7 patients positive for antibodies to adalimumab (43%) were in remission at Week 24, and 2 of 7 (29%) were in remission at week 56.

A total of 185 patients had both baseline and Week-56 (or last-visit) measurements for anti-nuclear antibodies (ANAs). Of these 185 patients, 172 were determined to be ANA-negative at baseline, and 33/172 (19%) were ANA-positive at their final visits. Further, all 33 were positive for antibodies to double-stranded DNA (dsDNA), also at their final visits. Of the 13/185 patients determined to be positive for ANAs at baseline, 4/13 (31%) were ANA-negative at their final visits, and all of these were negative for antibodies to dsDNA at baseline. Overall, there were no significant findings of clinical laboratory abnormalities, including concentrations of ANAs, and there were no correlations between laboratory findings and clinical efficacy.
Table 2. Summary of Safety Analyses for CLASSIC II Patients through Week 56

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Adalimumab 40 mg every other week</th>
<th>Adalimumab 40 mg weekly</th>
<th>Patients Who Received Open-Label Therapy or Discontinued by Week 4</th>
<th>Total Safety Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=18</td>
<td>N=19</td>
<td>n=18</td>
<td>n=221</td>
<td>N=276</td>
</tr>
<tr>
<td>Adverse events, no. of patients (%)</td>
<td>18 (100)</td>
<td>15 (79)</td>
<td>14 (78)</td>
<td>207 (94)</td>
<td>254 (92)</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation of study drug, no. of patients (%)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>1 (6)</td>
<td>39 (18)</td>
<td>43 (16)</td>
</tr>
<tr>
<td>Most frequently reported treatment-emergent adverse events, ≥5% of patients, no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7 (39)</td>
<td>5 (26)</td>
<td>2 (11)</td>
<td>37 (17)</td>
<td>51 (19)</td>
</tr>
<tr>
<td>Crohn’s disease aggravated</td>
<td>5 (28)</td>
<td>4 (21)</td>
<td>2 (11)</td>
<td>48 (22)</td>
<td>59 (21)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1 (6)</td>
<td>4 (21)</td>
<td>1 (6)</td>
<td>20 (9)</td>
<td>26 (9)</td>
</tr>
<tr>
<td>Patients with any type of injection site reactions, no. (%)</td>
<td>2 (12)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>26 (12)</td>
<td>29 (12)</td>
</tr>
<tr>
<td>Patients with treatment-emergent infectious adverse events, no. (%)</td>
<td>15 (83)</td>
<td>14 (74)</td>
<td>6 (33)</td>
<td>127 (58)</td>
<td>162 (59)</td>
</tr>
<tr>
<td>Malignancies, no. patients (%)</td>
<td>1 (5)**</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Serious adverse events, no. patients (%)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>37 (17)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>Serious infections, no. patients (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*All patients entered the open-label period receiving adalimumab 40 mg eow. Patients who flared or demonstrated continued non-response were permitted to have their dosages escalated to 40 mg weekly. **Squamous cell carcinoma.
DISCUSSION

The results of this study support the efficacy of adalimumab, administered subcutaneously 40 mg eow or weekly, for inducing and maintaining remission in infliximab-naïve CD patients with moderate to severe disease activity, vs. placebo. Of the randomised patients, those who received adalimumab were approximately 1.5–2.0 times more likely to have maintained remission at 56 weeks. Consistent with these results, randomised patients who received either dosage of adalimumab also had numerically greater rates of 100-point and 70-point responses, and lower disease activity as measured by mean CDAI scores and mean IBDQ total scores, compared with patients who received placebo. However, this study was not powered to detect statistical differences in these measures, and there were relatively small numbers (<20) of patients in each of the three groups of the randomised cohort. Furthermore, the majority of randomised patients in the adalimumab treatment groups and patients in the open-label cohort who were receiving corticosteroids at baseline of CLASSIC I were without relapse and steroid-free at Week 56. The relatively small number of patients in the randomised cohort receiving steroids at baseline and the open-label nature of the other cohort did not permit statistical comparison. Statistically significant differences in remission and 100-point clinical response could be observed as early as Week 12 (8 weeks after randomization), vs. placebo. In addition, while remission rates were similar between randomised patients receiving concomitant immunosuppressants and patients who did not receive concomitant immunosuppressants, the relatively small sample size of the randomized group, as well as the lack of a placebo control in the OL group, preclude definitive conclusions regarding the effect of concomitant immunosuppression on clinical efficacy.

Patients who had not achieved remission at both Weeks 0 and 4 and entered the OL cohort represent a more difficult-to-treat population. Adalimumab therapy resulted in progressive increases in clinical remission at Week 56 for 46% of these patients. Moreover, approximately two-thirds of patients who received adalimumab OL therapy achieved 100-point improvement in CDAI at Week 56, and close to three-quarters achieved 70-point improvement. Again, response rates were similar between patients who received concomitant immunosuppressants and those who did not.

The results of maintenance therapy with the fully human IgG1 monoclonal antibody adalimumab in patients with CD presented here are broadly similar to those reported for the chimeric IgG1 monoclonal antibody infliximab and for the humanized Fab’ antibody fragment conjugated to polyethylene glycol, certolizumab pegol (CDP-870).8, 9, 29 Infliximab, certolizumab pegol, and adalimumab have each demonstrated efficacy for maintenance of remission in patients with moderately to severely active CD who had previously responded to induction therapy with the same agent (drug withdrawal study design). However, while there are 1-year maintenance data for adalimumab and infliximab, published data for certolizumab pegol cover 6-month analyses only. In contrast, another anti-TNF therapy, the humanised IgG4 monoclonal antibody, CDP-571, failed to demonstrate efficacy for induction of remission at 24–26 weeks.30, 31 These differences in efficacy between anti-TNF antibodies may at least partially be related to study design. Adalimumab offers a patient advantage vs. other biologics for CD in that it can be self-administered through subcutaneous injection with either a pre-filled syringe or an autoinjection pen.

There was an apparent dosage response across the two randomised adalimumab groups for the endpoints of remission and 100-point response at Week 56, but no clinically important difference in dosage response was observed between the two maintenance regimens. With
either dosage, remission rates were significantly higher than for placebo at most time points after Week 12. For induction of remission, results of CLASSIC I suggested that a loading dose of adalimumab 160 mg at Week 0 followed by 80 mg at Week 2 (resulting in blood concentrations at Week 4 equivalent to 40 mg weekly dosing) is the optimal induction dose. For maintenance of remission, the results of CLASSIC II suggest that both 40 mg eow and weekly are efficacious. More conclusively, the results from a large maintenance trial comparing adalimumab 40 mg eow, adalimumab 40 mg weekly, and placebo (the CHARM study),\textsuperscript{32} demonstrate that adalimumab eow and weekly dosing are similarly efficacious in maintaining remission in patients with CD.

Maintenance therapy with adalimumab was generally well-tolerated. The rates of serious adverse events were low in patients treated with adalimumab and were similar to placebo. No patients developed serious infectious adverse events, opportunistic infections, tuberculosis, lupus, demyelinating neurologic diseases, or lymphoma, and no patients died.

The percentage of patients developing antibodies to the human antibody adalimumab was low (7/269, 2.6%). It should be acknowledged that this small study lacked adequate statistical power to accurately estimate the frequency of developing antibodies to adalimumab compared with placebo, and to explore whether concomitant immunosuppression with azathioprine, 6-mercaptopurine, or methotrexate was protective. However, the total number of patients exposed to adalimumab demonstrates that the immunogenicity of adalimumab in patients with CD is modest. In patients with rheumatoid arthritis, the rate of formation of antibodies to adalimumab was 5% (1% for patients receiving concomitant therapy with methotrexate and 12% for patients receiving adalimumab monotherapy).\textsuperscript{33} The rate of ANA formation observed in CLASSIC II was consistent with what has been observed in controlled and open-label trials of adalimumab in rheumatoid arthritis.\textsuperscript{33,34} As noted, there were no significant findings of clinical laboratory abnormalities, and there were no correlations between laboratory findings and clinical efficacy.

In conclusion, subcutaneous administration of adalimumab resulted in maintenance of remission and response, potential steroid-sparing effects, and improved quality of life over 1 year in infliximab-naïve CD patients with moderate to severe disease activity compared with placebo. Both 40-mg eow and 40-mg weekly dosages were efficacious. In this trial, adalimumab was generally well-tolerated. Adalimumab represents an important new therapeutic option for the treatment of Crohn’s disease.
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COMPETING INTERESTS

William Sandborn, Paul Rutgeerts, Douglas Wolf, and Remo Panaccione have served as consultants for Abbott Laboratories. William Sandborn, Stephen Hanauer, Paul Rutgeerts, and Remo Panaccione have participated in continuing medical education events supported by unrestricted educational grants from Abbott Laboratories. Jeffrey Kent, Barry Bittle, Ju Li, and Paul Pollack are Abbott employees.

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FIGURE LEGENDS

Figure 1. Enrollment and treatment of patients in CLASSIC II.

Figure 2. Efficacy of adalimumab as maintenance therapy in Crohn’s disease in the randomised cohort. Remission was defined as a decrease in the CDAI score of <150 points; 100-point response was defined as a decrease from CLASSIC I baseline in the CDAI score of ≥100 points; and 70-point response was defined as a decrease from CLASSIC I baseline in the CDAI score of ≥70 points. Significance was assessed vs. placebo. (A) The percentage of patients in each adalimumab dosage group and the placebo group achieving remission at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 56. *p<0.05 vs. placebo, last observation carried forward (LOCF), intention-to-treat (ITT) population, n=55; (B) The percentage of patients in each adalimumab dosage group and the placebo group achieving a 100-point response at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 56. *p<0.05 for adalimumab every other week (eow) vs. placebo at Weeks 12 and 20; p<0.05 for adalimumab weekly vs. placebo at Weeks 12, 24, 32, and 40; LOCF, ITT population, n=55; (C) The percentage of patients in each adalimumab dosage group and the placebo group achieving a 70-point response at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 56. *p<0.05 for adalimumab 40 mg weekly vs. placebo at Week 32. All data are last observation carried forward for intention-to-treat population, n=55. eow=every other week.

Figure 3. Mean Total IBDQ Scores by Visit: Randomised Cohort of CLASSIC II. Mean total Inflammatory Bowel Disease Questionnaire (IBDQ) scores in each adalimumab dosage group and the placebo group at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 56. IBDQ values ≥170 correlate with clinical remission. All data are last observation carried forward for the intention-to-treat population, n=55. eow=every other week. *p<0.05 for adalimumab every other week (eow) vs. placebo at Week 32; p<0.005 for adalimumab 40 mg weekly vs. placebo at Weeks 24, 32, and 40.
REFERENCES


34. Data on file, Abbott Laboratories, North Chicago.
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Figure 1

CLASSIC II
Patients Enrolled
(N=276)
Adalimumab 40 mg Week 0
Adalimumab 40 mg Week 2

55 Patients
randomised at Week 4

18 Patients
randomised to placebo

5 Withdrawals:
- Adverse events – 1
- Withdrawal of consent – 3
- Lack of efficacy – 1

6 Completed the trial on original double-blind therapy (33%)
13 completed 56 weeks (6 on double-blind therapy, 7 on OL)

19 Patients
randomised to adalimumab 40 mg eow

3 Withdrawals:
- Adverse events – 1
- Withdrawal of consent – 1
- Lost to follow-up – 1

11 Completed the trial on original double-blind therapy (58%)
16 Completed 56 weeks (11 on double-blind therapy, 5 on OL)

18 Patients
randomised to adalimumab 40 mg weekly

2 Withdrawals:
- Adverse events – 1
- Withdrawal of consent – 1
- Lack of efficacy – 0

15 Completed the trial on original double-blind therapy (83%)
16 Completed 56 weeks (15 on double-blind therapy, 1 on OL)

Open-label Therapy
at Week 4
204 Patients

Completed 131
Discontinued 73
Primary reason
Adverse events – 23
Withdrawal of consent – 14
Lost to follow-up – 5
Protocol violation – 2
Lack of efficacy – 18
Administrative – 0
Other – 11

Discontinued at or before Week 4
17 Patients

Completed 0
Discontinued 17
Primary reason
Adverse events – 5
Withdrawal of consent – 1
Lost to follow-up – 0
Protocol violation – 1
Lack of efficacy – 9
Administrative – 1
Other – 0
Figure 2A

Patients maintaining remission (%)

Weeks

- Placebo
- Adalimumab 40 mg eow
- Adalimumab 40 mg weekly
Figure 2B

Patients with 100-point response (%)

Weeks

- Placebo
- Adalimumab 40 mg eow
- Adalimumab 40 mg weekly

* Significant difference
Figure 2C

Patients with 70-point response (%)

Weeks

- Placebo
- Adalimumab 40 mg eow
- Adalimumab 40 mg weekly

Legend
Figure 3

Mean IBDQ Score vs Weeks

- Placebo
- Adalimumab 40 mg eow
- Adalimumab 40 mg weekly

Clinical Remission
Adalimumab for Maintenance Treatment of Crohn's Disease: Results of the CLASSIC II Trial

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