INFLAMMATORY BOWEL DISEASE

Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial

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Background: Adalimumab induced clinical remission after four weeks in patients with active Crohn's disease in the CLASSIC I trial.
Objective: To evaluate long term efficacy and safety of adalimumab maintenance therapy in Crohn's disease in a follow-on randomised controlled trial (CLASSIC II).
Methods: In the preceding CLASSIC I trial, 299 patients with moderate to severe Crohn's disease naive to tumour necrosis factor antagonists received induction therapy with adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg, or placebo, at weeks 0 and 2. In all, 276 patients from CLASSIC I enrolled in CLASSIC II and received open-label adalimumab 40 mg at weeks 0 (week 4 of CLASSIC I) and 2; 55 patients in remission at both weeks 0 and 4 were re-randomised to adalimumab 40 mg every other week, 40 mg weekly, or placebo for 56 weeks. Patients not in remission at both weeks 0 and 4 were enrolled in an open-label arm and received adalimumab 40 mg every other week. With non-response or flare, these patients could have their dosages increased to 40 mg weekly. Patients in the randomised arm with continued non-response or disease flare could switch to open-label adalimumab 40 mg every other week and again to 40 mg weekly. The primary end point 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 every other week and 83% who received 40 mg weekly were in remission at week 56, *v* 44% for placebo ($p<0.05$). In all, 204 patients entered the open-label arm. Of these, 93 (46%) were in clinical remission at week 56. Adalimumab was generally well-tolerated in all patients.
Conclusions: Adalimumab induced and maintained clinical remission for up to 56 weeks in patients with moderate to severe Crohn's disease naive to anti-TNF treatment.

Crohn's disease 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.[1] Increased production of TNF by macrophages in patients with Crohn's disease results in raised concentrations of TNF in the stool, blood, and mucosa.[2–4] Tumour necrosis factor is thought to play a critical role in the inflammation of Crohn's disease.[5 6] Clinical trials have shown that infliximab, a chimeric anti-TNF monoclonal antibody, is effective for inducing and maintaining clinical response and remission in patients with moderate to severe Crohn's disease,[7–9] as well as inducing and maintaining fistula closure.[10 11] Unfortunately, infliximab may be immunogenic, and episodic as well as continuous administration may result in the formation of antibodies to the agent that can cause infusion reactions, loss of efficacy, and delayed hypersensitivity reactions.[12–16]

As noted in a review of therapeutic monoclonal antibodies published in 2000, fully human monoclonal antibodies are frequently less immunogenic than chimeric monoclonal antibodies.[17] Adalimumab (HUMIRA®, Abbott Laboratories, Abbott Park, Illinois, USA) is a fully human IgG_1 monoclonal antibody that binds with high affinity and specificity to membrane and soluble TNF, but not to lymphotoxin. Controlled trials have shown that adalimumab is safe and effective for treating rheumatoid arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis.[18–25] Adalimumab is approved by multiple regulatory authorities for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Adalimumab was approved in the United States in February 2007 for the treatment of moderate to severe Crohn's disease. A four-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 of 80 mg/40 mg and 160 mg/80 mg given at weeks 0 and 2 for patients with moderately to severely active Crohn's disease who were naive to anti-TNF therapy.[26] Adalimumab 160 mg/80 mg showed the greatest efficacy.[26]

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

Abbreviations: ANA, antinuclear antibodies; CDAI, clinical disease activity index; CLASSIC: Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease trial, ; IBDQ, inflammatory bowel disease questionnaire; LOCF, last observation carried forward

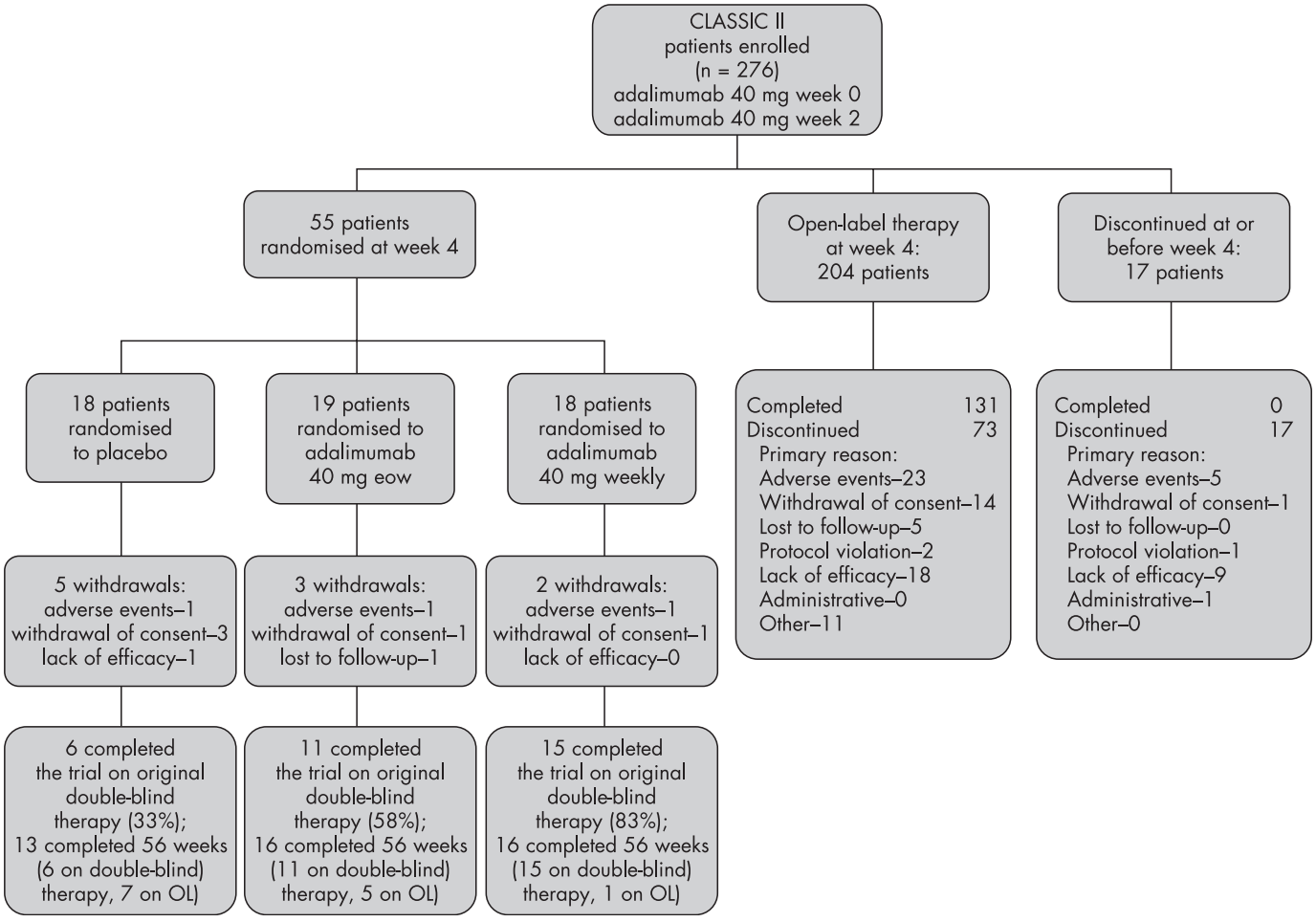

Figure 1 Enrolment and treatment of patients in CLASSIC II. eow, every other week; OL, open-label.

METHODS

Patients

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

All patients who met study entry criteria and successfully completed CLASSIC I[26] were eligible to enrol 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 the 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.[27] Patients were eligible for enrolment in the randomised cohort of CLASSIC II if they were in 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 treatment with adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo from weeks 4 to 55. Patients not in remission at both time points entered the open-label cohort and received 40 mg every other week. All patients were followed to the end of week 56. Assignment to randomised treatment was done 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 on the basis of 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 every other week were found to be effective in rheumatoid arthritis. On this basis, a dosage of 40 mg of adalimumab every other week was selected as the target maintenance dosage for efficacy in Crohn's disease. 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 to $\geqslant$70 points above the CLASSIC II week-4 value and a total CDAI score of $>$220 points) or had continued non-response (defined as a decrease in CDAI $\leqslant$70 points *v* week-0 value in CLASSIC I), they were permitted to switch to open-label adalimumab 40 mg every other week. These patients were considered failures in the primary efficacy analysis. If patients receiving open-label adalimumab 40 mg every other week flared or had continued non-response, their dosages could be increased to 40 mg weekly. Patients on weekly open-label dosing who continued to flare were discontinued from the study. For the randomised

Table 1 Baseline characteristics of CLASSIC II patients

	Randomised cohort			
	Placebo	Adalimumab 40 mg every other week	Adalimumab 40 mg weekly	OL cohort total
Characteristic	n = 18	n = 19	n = 18	n = 204††
Female patients (n (%))	12 (67)	12 (63)	9 (50)	104 (51)
Male patients (n (%))	6 (33)	7 (37)	9 (50)	100 (49)
Age (years) (mean (SD))	36 (13)	34 (12)	38 (10)	40 (12)
Body weight (kg) (mean (SD))	70 (13)	69 (19)	72 (20)	77 (18)
Duration of Crohn's disease (years) (mean (SD))	8.24 (8.3)	7.73 (6.5)	9.13 (9.8)	9.58 (8.8)
Patients who smoked (n (%))	12 (67)	13 (68)	19 (56)	120 (59)
Enterocutaneous or perianal fistula* (n (%))	3 (17)	2 (11)	0 (0)	30 (15)
CDAI score* (mean (SD))	107 (62)	106 (33)	88 (50)	245 (73)
IBDQ* (median (range))†	191 (138 to 224)	188 (128 to 213)	200 (138 to 216)	149 (58 to 216)
CLASSIC I week-0 CRP (mg/dl)‡				
Mean (SD)	0.9 (1.0)	3.0 (3.0)	2.5 (3.3)	1.6 (2.4)
Median (range)	0.5 (0.0 to 3.0)	2.2 (0.0 to 11.3)	0.7 (0.1 to 9.3)	0.8 (0.0 to 17.3)
CRP* (mg/dl)‡				
Mean (SD)	0.2 (0.2)	0.8 (0.8)	0.6 (0.9)	1.3 (2.9)
Median (range)	0.2 (0.0 to 0.6)	0.5 (0.0 to 2.7)	0.2 (0.0 to 3.6)	0.5 (0.0 to 34.0)
Concomitant drug treatment (n (%))				
Any corticosteroid	10 (56)	8 (47)	9 (50)	74 (36)
Systemic corticosteroid§	6 (33)	4 (21)	5 (28)	34 (17)
Budesonide	4 (22)	4 (21)	4 (22)	23 (11)
Any immunosuppressive agent	3 (17)	4 (21)	5 (28)	67 (33)
Azathioprine	1 (6)	4 (21)	2 (11)	33 (16)
6-Mercaptopurine	1 (6)	0 (0)	3 (17)	25 (12)
Methotrexate	1 (6)	0 (0)	0 (0)	6 (3)
Crohn's-related antibiotics**	1 (6)	0 (0)	(0)	25 (12)
5-Aminosalicylates¶	8 (44)	14 (74)	12 (67)	110 (54)

*Baseline of CLASSIC II corresponds to week 4 of CLASSIC I.
†Scores for the IBDQ can range from 32 to 224; greater scores indicate a better quality of life.
‡High sensitivity cardiology assay for C-reactive protein; normal range is <0.283 mg/dl.
§Prednisone, prednisolone, methylprednisolone.
¶Aminosalicylic acid, mesalazine, and sulfasalazine.
**Metronidazole and ciprofloxacin.
††Excludes 17 patients who discontinued at or before week 4.
CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; OL, open-label.

cohort, the patients, study coordinators, and study investigators were all blinded to treatment assignments.

Patients' dosages of all concurrent drugs 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 open-label cohort for those patients who were responders (that is, who experienced a reduction of ⩾70 points in CDAI score from week 0 in CLASSIC I). After week 8, daily doses for randomised patients receiving prednisone >10 mg were 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.[27] 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 to 600, with greater scores indicating greater disease activity. The inflammatory bowel disease questionnaire (IBDQ)[28] was administered to assess patient-reported outcomes at each visit. IBDQ total scores range from 32 to 224, with greater scores indicating better patient function and quality of life. At each visit, adverse events and concomitant drug treatments were recorded, and samples were collected for standard laboratory evaluations, including antibodies to adalimumab as well as C-reactive protein values. Safety assessments included vital signs, physical examination, haematology, serum biochemistry, and urinalysis.

Sample size and statistical analysis

Sample size calculations for the lead-in CLASSIC I study, which called for enrolment of at least 300 patients, have been published.[26] 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. It was anticipated that approximately 90% of the patients from CLASSIC I (270 patients) would enrol.

The primary analysis using Pearson's χ^2 test evaluated the proportion of patients in remission at week 56 in each arm of the randomised cohort (adalimumb 40 mg every other week, adalimumb 40 mg weekly, and placebo). Those with missing primary end point 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 every other week, adalimumab 40 mg weekly, and placebo) was tested. If significant differences between the three groups were detected, pairwise comparisons of each adalimumab group *v* the placebo group were conducted.

The Pearson's χ^2 test, Fisher's exact test, analysis of covariance (ANCOVA), the Kruskal–Wallis test, and Kaplan–Meier survival analysis were used as appropriate to provide nominal p values for secondary end points. Prespecified secondary analyses included the percentages of patients in remission at week 24; 70-point and 100-point clinical responses

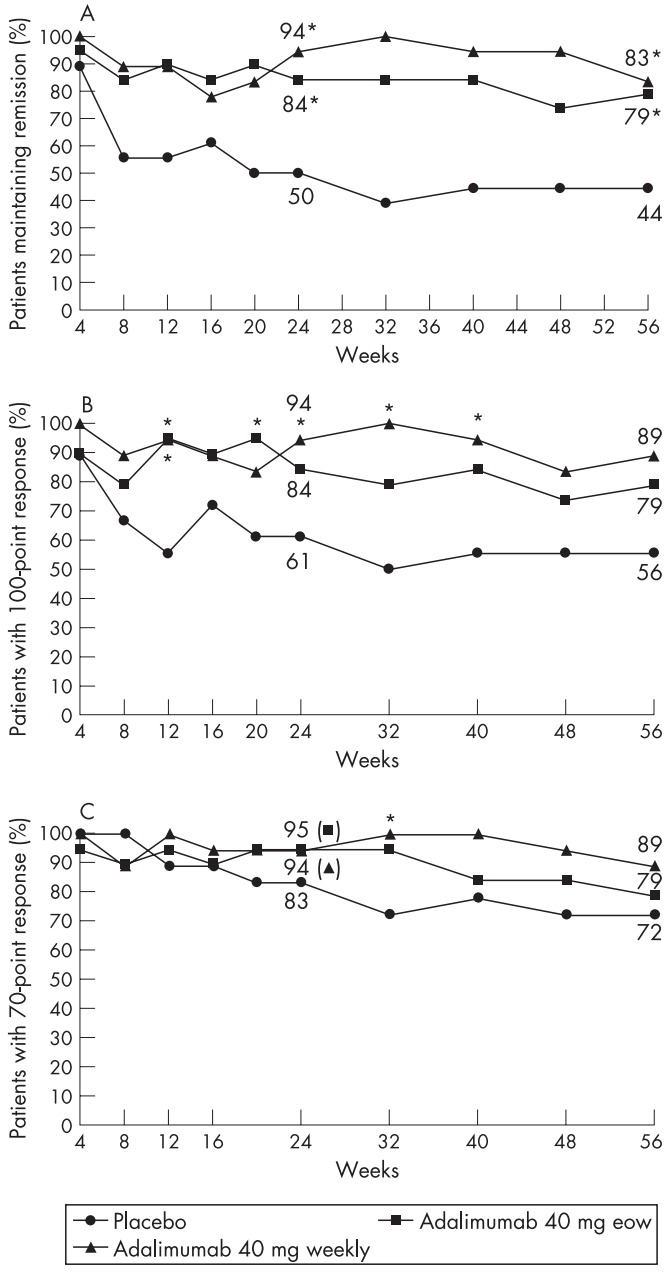

Figure 2 Efficacy of adalimumab as maintenance treatment in Crohn's disease in the randomised cohort. Remission was defined as a decrease in the CDAI score of <150 points; 100-point response was defined as a decrease from CLASSIC I baseline in the CDAI score of ⩾100 points; and 70-point response was defined as a decrease from CLASSIC I baseline in the CDAI score of ⩾70 points. Significance was assessed *v* placebo. (A) The percentage of patients in each adalimumab dose group and the placebo group achieving remission at weeks 4, 8, 12, 16, 24, 32, 40, 48, and 56. *p<0.05 *v* placebo, last observation carried forward (LOCF) for 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 *v* placebo at weeks 12 and 20; p<0.05 for adalimumab weekly *v* placebo at weeks 12, 24, 32, and 40. LOCF for 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 *v* placebo at week 32. All data are LOCF for ITT population, n = 55. CDAI, Clinical Disease Activity Index; eow, every other week.

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 conducted. All secondary analyses were carried out using last observation carried forward (LOCF).

Analyses of the results for patients who received open-label treatment were imputed, and patients who discontinued treatment before week 56 were counted as primary treatment failures.

RESULTS

Patient characteristics

In all, 276 patients participated in the study. Fifty-five had achieved remission at weeks 0 and 4 and were randomised (fig 1). In this 55-patient randomised cohort, 18 patients received placebo, 19 received adalimumab 40 mg every other week, and 18 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, five patients (28%) withdrew prematurely from the placebo group, *v* three patients (16%) in the adalimumab 40 mg every other week group, and two patients (11%) in the adalimumab 40 mg weekly group.

In all, 204 patients were ineligible for randomisation and began receiving open-label adalimumab 40 mg every other week at week 4. In addition, 17 patients discontinued at or before week 4 for the reasons given in fig 1. Baseline characteristics of patients who received open-label adalimumab were similar to those who were randomised (table 1). In the open-label group, 36% of patients discontinued, 11.3% because of adverse events and 9% because of lack of efficacy (fig 1).

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 every other week group (15/19, 79%), the adalimumab 40-mg weekly group (15/18, 83%), and the placebo group (8/18, 44%) (p<0.05 for each adalimumab group *v* placebo) (fig 2A). The rates of remission at week 56 were similar for patients receiving concomitant

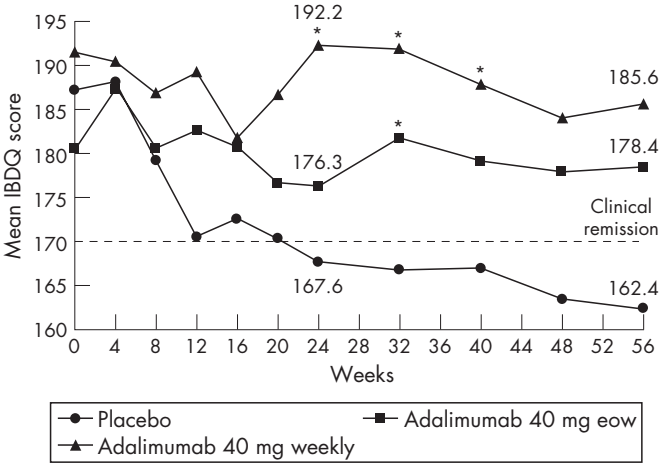

Figure 3 Mean total Inflammatory Bowel Disease Questionnaire (IBDQ) scores by visit: randomised cohort of CLASSIC II. Mean total IBDQ scores in each adalimumab dosage group and the placebo group at weeks 4, 8, 12, 16, 24, 32, 40, 48, and 56. IBDQ values ⩾170 correlate with clinical remission. All data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

immunosuppressants such as azathioprine, 6-mercaptopurine, or methotrexate (adalimumab 40 mg every other week (4/4, 100%), adalimumab 40 mg weekly (4/5, 80%), and placebo (1/3, 33%)); and patients not receiving concomitant immunosuppressants (adalimumab 40 mg every other week (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 (fig 2, panels A and B). The 70-point clinical response rates were numerically greater for the two active treatment groups *v* placebo (fig 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% confidence interval (CI), −202 to −99.8) and 197.7 (−248 to −147) for the every-other-week and weekly groups, respectively, *v* 119.6 (−174 to −65.1) for placebo (LOCF, $p<0.05$ for each adalimumab group *v* 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 the patients in the adalimumab 40-mg every other week 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 of ⩾170 was maintained in the groups of randomised patients treated with adalimumab 40-mg every other week or weekly (fig 3), while IBDQ scores declined rapidly in patients receiving placebo. Median C-reactive protein concentrations (mg/dl (range)) at week 24 were 0.5 (0 to 1.2), 0.4 (0 to 1.9), and 0.1 (0 to 1.6) in the placebo, adalimumab 40 mg every other week, and adalimumab 40-mg weekly groups, respectively. At week 56, these C-reactive protein values were 0.4 (0 to 0.9), 0.3 (0 to 2.8), and 0.3 (0 to 1.2), respectively.

Open-label patients

In all, 204 patients who were not in remission at both week 0 and week 4 entered the open-label cohort. Of these, 131 (64%) completed 56 weeks of treatment, 71 remained on their initial regimens of adalimumab 40 mg every other week, and 60 had their dosages increased to 40 mg weekly at some point before week 56. Ninety-three (46%) of the 204 patients receiving open-label adalimumab were in remission at week 56, including 56/115 (49%) of those receiving 40 mg every other week and 37/89 (42%) of those receiving 40 mg weekly.

One hundred and thirty-two (65%) of the 204 patients receiving open-label adalimumab achieved a 100-point clinical response at week 56 or last visit, including 73/115 (64%) with 40 mg every other week and 59/89 (66%) with 40 mg weekly (LOCF). Moreover, 147/204 patients receiving open-label adalimumab (72%) achieved a 70-point clinical response at week 56, including 80/115 (70%) with 40 mg every other week and 67/89 (75%) with adalimumab 40 mg weekly. In the open-label 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% of patients receiving steroids at baseline in the open-label cohort (21/36) had discontinued them.

Safety

The most frequently reported treatment-emergent adverse events (⩾5% of patients) in the total population of CLASSIC II (n = 276) were nasopharyngitis, aggravated Crohn's disease, 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, coccidioidomycosis, 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, and 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, larger percentages of patients randomised to placebo experienced adverse events, serious

Table 2 Summary of safety analyses for CLASSIC II patients to the end of week 56

	Randomised cohort			Patients who received open-label treatment or discontinued by week 4	
Variable	Placebo (n = 18)	Adalimumab 40 mg eow (n = 19)	Adalimumab 40 mg weekly (n = 18)	Adalimumab 40 mg every other week* (n = 221)	Safety set total (n = 276)
Adverse events (n (%))	18 (100)	15 (79)	14 (78)	207 (94)	254 (92)
Adverse events leading to discontinuation of study drug (n (%))	2 (11)	1 (5)	1 (6)	39 (18)	43 (16)
Most frequently reported treatment-emergent adverse events (⩾5% of patients)					
Nasopharyngitis	7 (39)	5 (26)	2 (11)	37 (17)	51 (19)
Crohn's disease aggravated	5 (28)	4 (21)	2 (11)	48 (22)	59 (21)
Sinusitis	1 (6)	4 (21)	1 (6)	20 (9)	26 (9)
Patients with any type of injection-site reactions (n (%))	2 (12)	1 (5)	0 (0)	26 (12)	29 (12)
Patients with treatment-emergent infectious adverse events (n (%))	15 (83)	14 (74)	6 (33)	127 (58)	162 (59)
Malignancies (n (%))	1 (5)†	0 (0)	0 (0)	0 (0)	1 (0.4)
Serious adverse events (n (%))	2 (11)	1 (5)	0 (0)	37 (17)	40 (15)
Serious infections (n (%))	0 (0)	0 (0)	0 (0)	9 (4)	0 (0)

*All patients entered the open-label period receiving adalimumab 40 mg every other week. Patients who flared or showed continued non-response could have their dosages increased to 40 mg weekly.
†Squamous cell carcinoma.
eow, every other week.

adverse events, severe adverse events, and adverse events leading to discontinuation than did patients randomised to either dosage of adalimumab.

Blood concentrations of both adalimumab and antibodies to adalimumab were collected for 269 of the 276 patients in CLASSIC II. Of these 269, seven (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, three of the seven patients positive for antibodies to adalimumab (43%) were in remission at week 24, and two of seven (29%) were in remission at week 56.

One hundred and eighty-five patients had both baseline and week 56 (or last visit) measurements for antinuclear antibodies (ANA). Of these, 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.

DISCUSSION

The results of this study support the efficacy of adalimumab given subcutaneously at a dosage of 40 mg every other week or weekly versus placebo for inducing and maintaining remission in infliximab-naive Crohn's disease patients with moderate to severe disease activity. 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 of patients (<20) in each of the three groups of the randomised cohort. Furthermore, the majority of randomised patients in the adalimumab treatment groups and 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 in 100-point clinical response could be observed as early as week 12 (eight weeks after randomisation) *v* 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 randomised group, as well as the lack of a placebo control in the open-label group, preclude definitive conclusions on the clinical efficacy of concomitant immunosuppression.

Patients who had not achieved remission at both weeks 0 and 4 and entered the open-label 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 open-label therapy achieved 100-point improvement in CDAI at week 56, and close to three-quarters achieved a 70-point improvement. Again, response rates were similar between patients who received concomitant immunosuppressants and those who did not.

The results of maintenance treatment with the fully human, IgG_1 monoclonal antibody adalimumab in patients with Crohn's disease presented here are broadly similar to those reported for the chimeric IgG_1 monoclonal antibody infliximab and for the humanised Fab' antibody fragment conjugated to polyethylene glycol, certolizumab pegol (CDP-870).[8 9 29] Infliximab, certolizumab pegol, and adalimumab have each shown efficacy for maintenance of remission in patients with moderately to severely active Crohn's disease who had previously responded to induction treatment with the same agent (drug withdrawal study design). However, while there are one-year maintenance data for adalimumab and infliximab, published data for certolizumab pegol cover six-month analyses only. In contrast, another anti-TNF therapy—the humanised IgG_4 monoclonal antibody, CDP-571—failed to show efficacy for induction of remission at 24 to 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 over other biological agents for Crohn's disease in that it can be self-administered through subcutaneous injection with either a prefilled syringe or an autoinjection pen.

There was an apparent dosage response across the two randomised adalimumab groups for the end points of remission and the 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 greater 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 every other week and adalimumab weekly are effective. More conclusively, the results from a large maintenance trial comparing adalimumab 40 mg every other week, adalimumab 40 mg weekly, and placebo (the CHARM study)[32] showed that adalimumab every other week and adalimumab weekly are equally effective in maintaining remission in patients with Crohn's disease.

Maintenance treatment 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 neurological 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 estimate accurately how often antibodies developed to adalimumab compared with placebo, or to explore whether concomitant immunosuppression with azathioprine, 6-mercaptopurine, or methotrexate was protective. However, the results for the total number of patients exposed to adalimumab show that the immunogenicity of adalimumab in patients with Crohn's disease is modest. In patients with rheumatoid arthritis, the rate of formation of antibodies to adalimumab was 5% (1% for patients receiving concomitant treatment with methotrexate and 12% for patients receiving adalimumab monotherapy).[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 (data on file and[33]) As noted, there were

no significant findings of clinical laboratory abnormalities, and there were no correlations between laboratory findings and clinical efficacy.

Conclusions

Subcutaneous administration of adalimumab resulted in maintenance of remission and response, potential steroid sparing effects, and improved quality of life over one year in infliximab-naive Crohn's disease patients with moderate to severe disease activity compared with placebo. Both 40-mg every other week and 40-mg weekly dosages were effective. 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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