Human Anti–Tumor Necrosis Factor Monoclonal Antibody (Adalimumab) in Crohn's Disease: the CLASSIC-I Trial

STEPHEN B. HANAUER,* WILLIAM J. SANDBORN,† PAUL RUTGEERTS,§ RICHARD N. FEDORAK,¶ MILAN LUKAS,‖ DONALD MACINTOSH,# REMO PANACCIONE,** DOUGLAS WOLF,†† and PAUL POLLACK§§

*Division of Gastroenterology, University of Chicago Medical Center, Chicago, Illinois; †Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; §Department of Gastroenterology, Universitaire Ziekenhuizen Leuven, UZ Gasthuisberg, Leuven, Belgium; ¶Division of Gastroenterology, University of Alberta, Edmonton, Alberta, Canada; ‖Clinical Department of Gastroenterology and Hepatology, Charles University, Prague, Czech Republic; #Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada; **Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta, Canada; ††Atlanta Gastroenterology Associates, Atlanta, Georgia; and §§Abbott Laboratories, Parsippany, New Jersey

Background & Aims: **Tumor necrosis factor blockade has been shown to be an effective treatment strategy in Crohn's disease (CD). Adalimumab is a human immunoglobulin G1 (IgG_1) monoclonal antibody targeting tumor necrosis factor (TNF). A randomized, double-blind, placebo-controlled, dose-ranging trial was performed to evaluate the efficacy of adalimumab induction therapy in patients with CD.** ***Methods:*** **A total of 299 patients with moderate to severe CD naive to anti–TNF therapy were randomized to receive subcutaneous injections at weeks 0 and 2 with adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo. The primary endpoint was demonstration of a significant difference in the rates of remission at week 4 (defined as a Crohn's Disease Activity Index score <150 points) among the 80 mg/40 mg, 160 mg/80 mg, and placebo groups.** ***Results:*** **The rates of remission at week 4 in the adalimumab 40 mg/20 mg, 80 mg/40 mg, and 160 mg/80 mg groups were 18% ($P = .36$), 24% ($P = .06$), and 36% ($P = .001$), respectively, and 12% in the placebo group. Adverse events occurred at similar frequencies in all 4 treatment groups except injection site reactions, which were more common in adalimumab-treated patients.** ***Conclusions:*** **Adalimumab was superior to placebo for induction of remission in patients with moderate to severe Crohn's disease naive to anti–TNF therapy. The optimal induction dosing regimen for adalimumab in this study was 160 mg at week 0 followed by 80 mg at week 2. Adalimumab was well tolerated.**

Tumor necrosis factor (TNF) is recognized as an important cytokine in the pathogenesis of Crohn's disease[1,2] and is elevated in the stool, mucosa, and blood of patients with Crohn's disease.[3–5] Clinical trials have shown that the chimeric monoclonal antibody to TNF, infliximab, is effective for both induction and maintenance therapy of patients with moderate to severe Crohn's disease, including patients with draining fistulas.[6–10] However, infliximab is immunogenic, and intermittent administration results in the development of human antichimeric antibodies (HACAs, also known as antibodies to infliximab) that lead to infusion reactions, loss of efficacy, and delayed hypersensitivity reactions.[11–15]

Adalimumab (D2E7, Humira; Abbott Laboratories, Chicago, IL) is a recombinant human immunoglobulin G1 (IgG_1) monoclonal antibody that binds with high affinity and specificity to human soluble TNF but not to lymphotoxin. Clinical trials in patients with rheumatoid arthritis have shown that adalimumab is effective when administered at a dosage of 40 mg every other week, with or without a concomitant disease-modifying antirheumatic drug such as methotrexate, and that dose escalation to 40 mg weekly is effective in patients not receiving concomitant methotrexate who have had an incomplete response or who failed to respond.[16–23] We conducted a 4-week, randomized, double-blind, placebo-controlled, dose-ranging induction trial (CLASSIC-I: Clinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn's disease) in which patients with moderate to severe Crohn's disease naive to anti-TNF therapy received induction treatment at weeks 0 and 2 with adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo and were followed through week 4.

Abbreviations used in this paper: CRP, C-reactive protein; IBDQ, inflammatory bowel disease questionnaire; IgG_1, immunoglobulin G1; IVRS, interactive voice response system; TNF, tumor necrosis factor.

0016-5085/06/$32.00
doi:10.1053/j.gastro.2005.11.030

Patients and Methods

Patients

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 55 centers between July 24, 2002, and December 18, 2003. The protocol was approved by the institutional review board or ethics committee at each center. All patients gave written informed consent.

Eligible patients included men and women (18–75 years of age) with Crohn's disease for at least 4 months who had moderate to severe disease as defined by a Crohn's Disease Activity Index (CDAI)[24] score of 220–450 points, inclusive. Radiologic or endoscopic studies were required to confirm the diagnosis of Crohn's disease. Concurrent therapies for Crohn's disease, including 5-aminosalicylates, prednisone (≤20 mg/day), budesonide (≤9 mg/day), azathioprine, 6-mercaptopurine, methotrexate, and antibiotics, were permitted at stable dosages. Female patients with childbearing potential were required to use a highly effective form of birth control. All patients were required to have adequate cardiac, renal, and hepatic function as defined by the investigator. Patients were excluded if they had a history of malignancy; had a history of active tuberculosis, listeriosis, or human immunodeficiency virus; had ulcerative colitis; had symptomatic obstructive strictures; underwent surgical bowel resection within 6 months; had an ostomy; underwent extensive bowel resection (>100 cm) or had short bowel syndrome; were currently receiving total parenteral nutrition; had received investigational chemical agents within 30 days; had received investigational biologic therapy within 4 months; had received antibiotic treatment within 3 weeks for infections not related to Crohn's disease; were pregnant or breast-feeding; had a history of clinically significant drug or alcohol abuse within 1 year; had poorly controlled medical conditions (including diabetes with history of recurrent infections or cerebrovascular accident within 3 months); had previously received infliximab or any other anti-TNF therapy; had received enema therapy within 2 weeks; had received cyclosporine or tacrolimus within 8 weeks; had a positive *Clostridium difficile* stool assay; or had clinically significant deviations in prespecified laboratory parameters.

Study Design

Patients were screened for eligibility 2 weeks before enrollment into the trial. At week 0, all eligible patients were randomly assigned in a 1:1:1:1 ratio 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. Patients were followed until week 4. An interactive voice response system generated and implemented the randomization sequence using a block size of 8 per center (see Appendix 1 for participating centers). The interactive voice response system (IVRS) assigned patients to their groups, and all participants remained blinded to group assignments. A pharmacist blinded to the identity of the study drug prepared each injection of adalimumab or an identical-appearing placebo.

The doses of adalimumab were selected based on pharmacokinetic data from clinical trials in patients with rheumatoid arthritis. Adalimumab serum concentrations of 4–8 μg/mL achieved at a dosage of adalimumab 40 mg every other week were found to be effective in rheumatoid arthritis. On this basis, a dosage of adalimumab 40 mg every other week was selected as the target for efficacy in Crohn's disease. Two additional dose groups were included: one with a lower dosage regimen (target dosage 20 mg every other week) and one with a higher dosage regimen (target dosage 40 mg weekly or 80 mg every other week). Based on results from pharmacokinetic modeling of data from patients with rheumatoid arthritis who received adalimumab in the absence of concomitant methotrexate, a loading dose twice the treatment dose (ie, 40-, 80-, and 160-mg loading doses) was selected to provide rapid and sustained adalimumab target serum concentrations in each dosage group. Simulation of serum adalimumab concentrations in the low-dose group (40-mg loading dose followed by a second induction dose of 20 mg at week 2) was expected to yield an adalimumab concentration >2 μg/mL, which was anticipated to be subtherapeutic. The high-dose group (160-mg loading dose followed by a second induction dose of 80 mg at week 2) was expected to yield an adalimumab concentration slightly >10 μg/mL, which was the serum concentration that produced a near-maximal response in efficacy in patients with rheumatoid arthritis on adalimumab monotherapy. The patients, study coordinators, and study investigators were all blinded to treatment assignment. The dosage of all concurrently taken medications remained constant. A response was defined as a reduction of ≥70 points (70-point response) or of ≥100 points (100-point response) from week 0 in the CDAI score, and remission was defined as a CDAI score <150 points.[24]

Patient Schedule, Efficacy, and Safety Evaluations

Patients were assessed at weeks −2, 0, 1, 2, and 4. The CDAI score was calculated at each postscreening visit; scores range from 0 to 600, with higher scores indicating more severe disease activity. The Inflammatory Bowel Disease Questionnaire (IBDQ)[25] was administered to assess patient-reported outcomes at weeks 0, 1, 2, and 4. IBDQ total scores range from 32 to 224, with higher scores indicating better patient function and quality of life. Data for all 299 randomized patients were included in the safety analysis. At each visit, adverse events and concomitant medications were recorded and samples were collected for laboratory evaluations. Safety assessments included vital signs, physical examinations, hematologic analysis, serum biochemistry analysis, and urinalysis. A high-sensitivity C-reactive protein (CRP) assay (typically used to determine cardiovascular risk) was used in this study, enabling accurate measure of CRP concentrations down to 0.02 mg/dL (or 0.2 mg/L). Under normal conditions, the baseline CRP concentration in the plasma is approximately 0.8 mg/dL.[26]

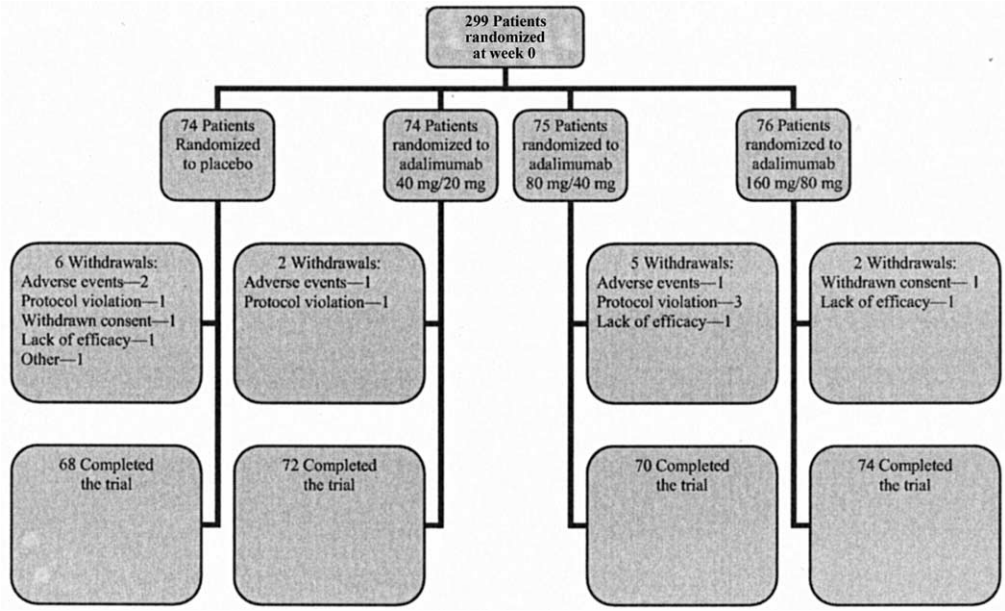


Figure 1. Enrollment and treatment of patients in the CLASSIC-I trial.

Statistical Analysis

A planned sample size of 272 patients randomized in a 1:1:1:1 ratio to adalimumab (each dose group, n = 68) or placebo (n = 68) using Pearson's χ^2 test with a .05 2-sided significance level had 80% power to detect the difference between the response rates of the 2 highest doses of adalimumab (80 mg/40 mg and 160 mg/80 mg) and placebo for induction of remission. This was based on the assumption of a 45% induction of remission rate for the 2 adalimumab groups and a 20% induction of remission rate for the placebo group. The primary endpoint was chosen to assess a robust measure of effect (remission), to demonstrate a rapid effect (at 4 weeks), and to incorporate doses that had been previously shown to be effective in another inflammatory disorder, rheumatoid arthritis (the 2 highest dose groups).

The primary analysis using Pearson's χ^2 test evaluated the difference in the proportion of patients in clinical remission at week 4 among those patients receiving the 2 highest doses of adalimumab (80 mg/160 mg and 160 mg/80 mg) and placebo. Those with missing primary endpoint data at week 4 were classified in the "no induction of clinical remission" category. An initial overall comparison of the 3 treatment groups (adalimumab 80 mg/40 mg, 160 mg/80 mg, and placebo) was tested. If a significant difference among the 3 groups was detected, pairwise comparisons of each adalimumab dose group (80 mg/40 mg and 160 mg/80 mg) versus the placebo group were performed.

Pearson's χ^2 test, Fisher's exact test, and analysis of covariance (ANCOVA) were used as appropriate to provide nominal *P* values for secondary endpoints. Prespecified secondary analyses included the proportions of clinical response (70-point response and 100-point response) in each adalimumab dose group and placebo at week 4, changes in IBDQ total score from baseline, and achievement of clinical remission (defined as CDAI $<$150 points) in the 20-mg dose arm at week 4. Subgroup analyses describing the proportion of patients who demonstrated induction of response and remission in subgroups of patients with elevated CRP levels $>$1.0 mg/dL at baseline and those using immunosuppressive agents were performed. Subgroup analyses describing the proportion of patients with improvement in the number of draining fistulas at week 4 (defined as a decrease in the number of draining fistulas $\geq$50% for at least 2 consecutive visits) and fistula remission at week 4 (defined as closure of all draining fistulas for at least 2 consecutive visits) among patients with fistulas consistently noted at both screening and baseline visits were also performed. All analyses were as observed with the exception of the IBDQ data that assessed the last observation carried forward (LOCF).

Role of the Funding Source

This study was designed by Abbott Laboratories staff members and 2 of the investigators who are authors of this report (S.B.H. and W.J.S.). Abbott Laboratories staff members and selected investigators, including those who designed the study and analyzed and interpreted the data, wrote this manuscript and agreed to submit this manuscript for publication. The principal investigator (S.B.H.) approved the content of the report before submission.

Results

Characteristics of the Patients

A total of 299 patients were available for randomization at week 0 (Figure 1). The 299 patients were randomly assigned to receive placebo induction (74 patients) or adalimumab induction with 40 mg/20 mg (74 patients), 80 mg/40 mg (75 patients), or 160 mg/80 mg

Table 1. Baseline Characteristics of the Patients

Characteristic	Placebo (n = 74)	Adalimumab 40 mg/ 20 mg (n = 74)	Adalimumab 80 mg/ 40 mg (n = 75)	Adalimumab 160 mg/ 80 mg (n = 76)
Male subjects, no. (%)	37 (50)	39 (53)	25 (33)	36 (47)
Age (*y*), mean (SD)	37 (13)	39 (13)	38 (12)	39 (11)
Body weight (*kg*) mean (SD)	74 (19)	75 (16)	74 (20)	78 (18)
Involved intestinal area, no. (%)				
Colonic	14 (19)	23 (31)	17 (23)	22 (29)
Ileal	50 (68)	45 (61)	47 (63)	40 (53)
Ileocolonic	7 (9)	4 (5)	7 (9)	8 (11)
Perianal	0 (0)	0 (0)	1 (1)	1 (1)
Small bowel	0 (0)	1 (1)	0 (0)	2 (3)
Unclassifiable	3 (4)	1 (1)	3 (4)	3 (4)
Enterocutaneous or perianal fistula at screening and baseline, no. (%)	6 (8)	4 (5)	10 (13)	12 (16)
Baseline CDAI score, mean (SD)	296 (60)	299 (57)	301 (61)	295 (52)
IBDQ, median (range)[a]	131 (52–200)	129 (81–218)	128 (63–200)	127 (37–192)
CRP (*mg/dL*)				
Mean (SD)	1.8 (2.6)	1.6 (2.1)	2.0 (2.8)	1.4 (1.9)
Median (range)	0.9 (0.0–17.3)	0.9 (0.0–11.3)	0.9 (0.0–14.9)	0.7 (0.0–9.3)
CRP concentration ≥1.0 mg/dL (10 mg/L), no. (%)[b]	28 (38)	31 (42)	33 (44)	27 (36)
Concomitant medication, no. (%)				
Any corticosteroid	25 (34)	17 (23)	32 (43)	24 (32)
Systemic corticosteroid[c]	17 (23)	11 (15)	20 (27)	12 (16)
Budesonide	8 (11)	6 (8)	12 (16)	12 (16)
Any immunosuppressive agent	22 (30)	23 (31)	21[d] (28)	22 (29)
Azathioprine	13 (18)	13 (18)	9 (12)	11 (14)
6-Mercaptopurine	8 (11)	6 (8)	10 (13)	10 (13)
Methotrexate	1 (1)	4 (5)	3 (4)	1 (1)
Crohn's disease–related antibiotics[e]	5 (7)	10 (14)	7 (9)	4 (5)
5-Aminosalicylates[f]	37 (50)	37 (50)	40 (53)	39 (51)
Current smoker, no. (%)	28 (38)	25 (34)	32 (43)	32 (42)

[a]Scores for the IBDQ can range from 32 to 224; higher scores indicate a better quality of life.
[b]High sensitivity cardiology assay for CRP; normal range is <0.283 mg/dL (2.83 mg/L).
[c]Prednisone, prednisolone, hydrocortisone, and methylprednisolone.
[d]One patient was receiving azathioprine and methotrexate at baseline.
[e]Metronidazole, levofloxacin, and ciprofloxacin.
[f]Mesalamine, sulfasalazine, and olsalazine.

(76 patients). The baseline characteristics of the patients who received placebo were similar to those who received adalimumab (Table 1). Overall, premature withdrawal from the study occurred in 6 patients (8%) in the placebo group versus 2 patients (3%) in the adalimumab 40 mg/20 mg group, 5 patients (7%) in the adalimumab 80 mg/40 mg group, and 2 patients (3%) in the adalimumab 160 mg/80 mg group.

Efficacy

All 299 patients were included in the efficacy analyses. For the primary analysis at week 4 (following a loading dose injection at week 0 and a second induction injection at week 2), there was a significant difference ($P = .004$) in the remission rates between the adalimumab 80 mg/40 mg (24% [18/75]), adalimumab 160 mg/80 mg (36% [27/76]), and placebo (12% [9/74]) groups (Figure 2*A*). There was a linear dose response across the 3 adalimumab treatment groups at week 4 for the endpoints of remission and 100-point response, with the highest dose group demonstrating statistical significance in the pairwise comparisons with placebo (Figure 2*B* and *C*). All 3 adalimumab treatment groups demonstrated significant results for the pairwise comparisons with placebo at week 4 for the endpoint of 70-point response (Figure 2*D*). Significant differences in response compared with placebo were demonstrated as early as week 1 in the 80 mg/40 mg dose group.

Baseline mean CDAI and IBDQ total scores were similar across all dose groups. Patients in the adalimumab 80 mg/40 mg and 160 mg/80 mg treatment groups had significantly lower mean CDAI scores (Figure 3*A*) and higher mean IBDQ total scores than patients in the placebo group (Figure 3*B*) as early as week 1. Patients in all 3 adalimumab groups had significantly lower median CRP concentrations (Figure 3*C*) compared with

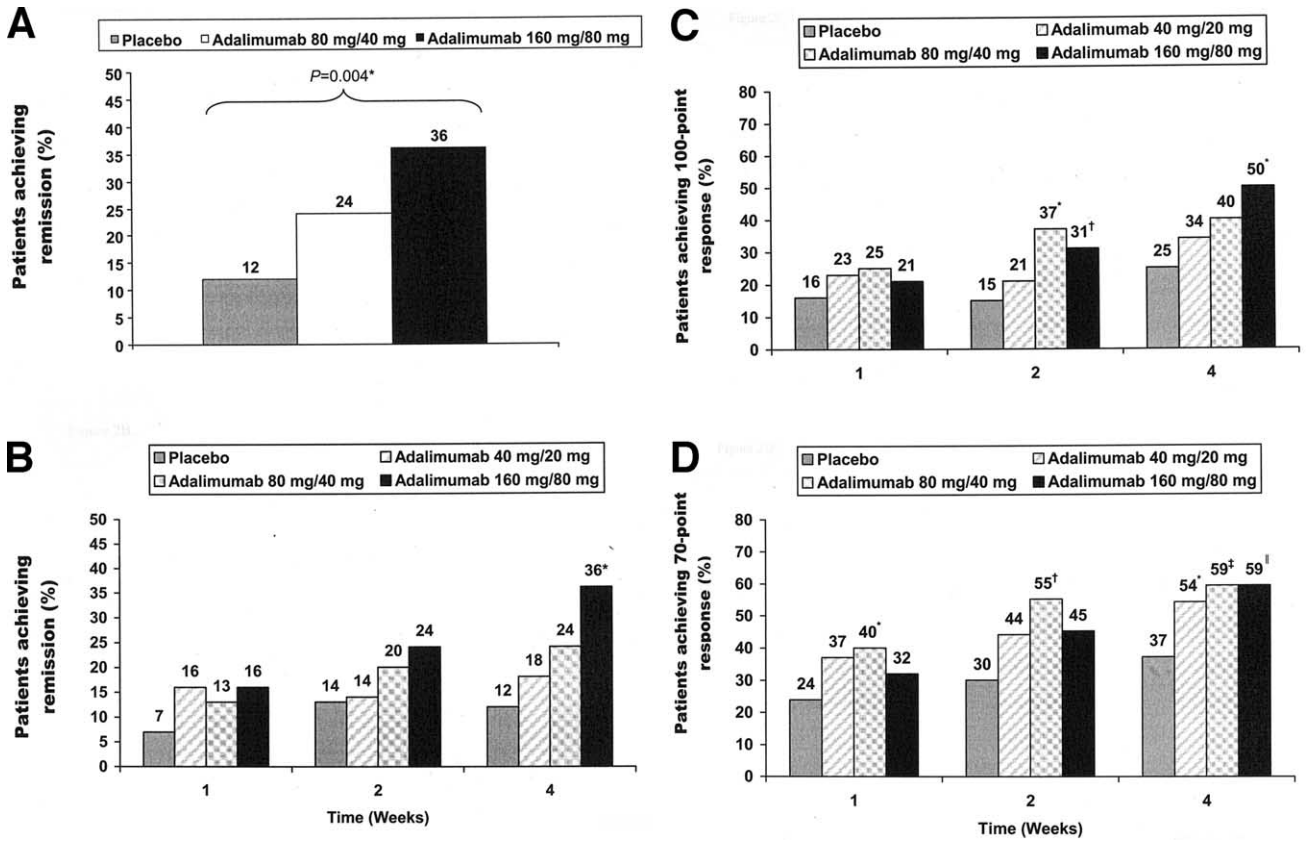


Figure 2. Efficacy of adalimumab as induction therapy in Crohn's disease. Remission was defined as a decrease in the CDAI score to <150 points, 70-point response was defined as a decrease from baseline in the CDAI score of ≥70 points, and 100-point response was defined as a decrease from baseline in the CDAI score of ≥100 points. Significance was assessed compared with placebo. (*A*) Percentage of patients in the 2 highest adalimumab dose groups and the placebo group achieving remission at week 4 (*$P = .004$ for a significant difference among the 3 groups). (*B*) Percentage of patients in each adalimumab dose group and the placebo group achieving remission at weeks 1, 2, and 4 (*$P = .001$ vs placebo). (*C*) Percentage of patients in each adalimumab dose group and the placebo group achieving a 100-point response at weeks 1, 2, and 4 (*$P = .002$; †$P = .019$; both vs placebo). (*D*) Percentage of patients in each adalimumab dose group and the placebo group achieving a 70-point response at weeks 1, 2, and 4 (*$P < .05$; †$P = .003$; ‡$P = .01$; ‖$P = .007$; all vs placebo).

patients in the placebo group beginning at week 1. CRP concentrations in the placebo group did not change signficantly throughout the study.

Only 11% of the randomized patients (32/299) had draining enterocutaneous or perianal fistulas at screening and at baseline and were unevenly distributed across the treatment groups. The rates of fistula improvement and remission for the adalimumab-treated patients and those receiving placebo were not significantly different (Table 2). The difference in rates of remission between the adalimumab-treated patients and those receiving placebo was greater in the subgroup of patients who had week 0 CRP concentrations ≥1.0 mg/dL than in patients with week 0 CRP concentrations <1.0 mg/dL (Table 2). However, logistic regression analysis failed to show a relationship between the CRP concentration at week 0 and induction of remission at week 4. The difference in rates of remission between the adalimumab-treated patients and those receiving placebo was similar when stratified for concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate (Table 2). Logistic regression analysis failed to show a relationship between concomitant immunosuppressive therapy and induction of remission at week 4.

Safety

Adverse events occurred at similar frequencies in the adalimumab and placebo groups. One percent of patients (1/74) in the adalimumab 40 mg/20 mg group, 1% of patients (1/75) in the adalimumab 80 mg/40 mg group, and none of 76 patients in the adalimumab 160 mg/80 mg group discontinued treatment because of an adverse event, compared with 3% of patients (2 of 74) in the placebo group (Table 3). The most common adverse events were injection site reactions, which occurred in 26% of patients (19/74) in the adalimumab 40 mg/20 mg group, 24% of patients (18/75) in the adalimumab 80 mg/40 mg group, and 38% of patients (29/76) in the

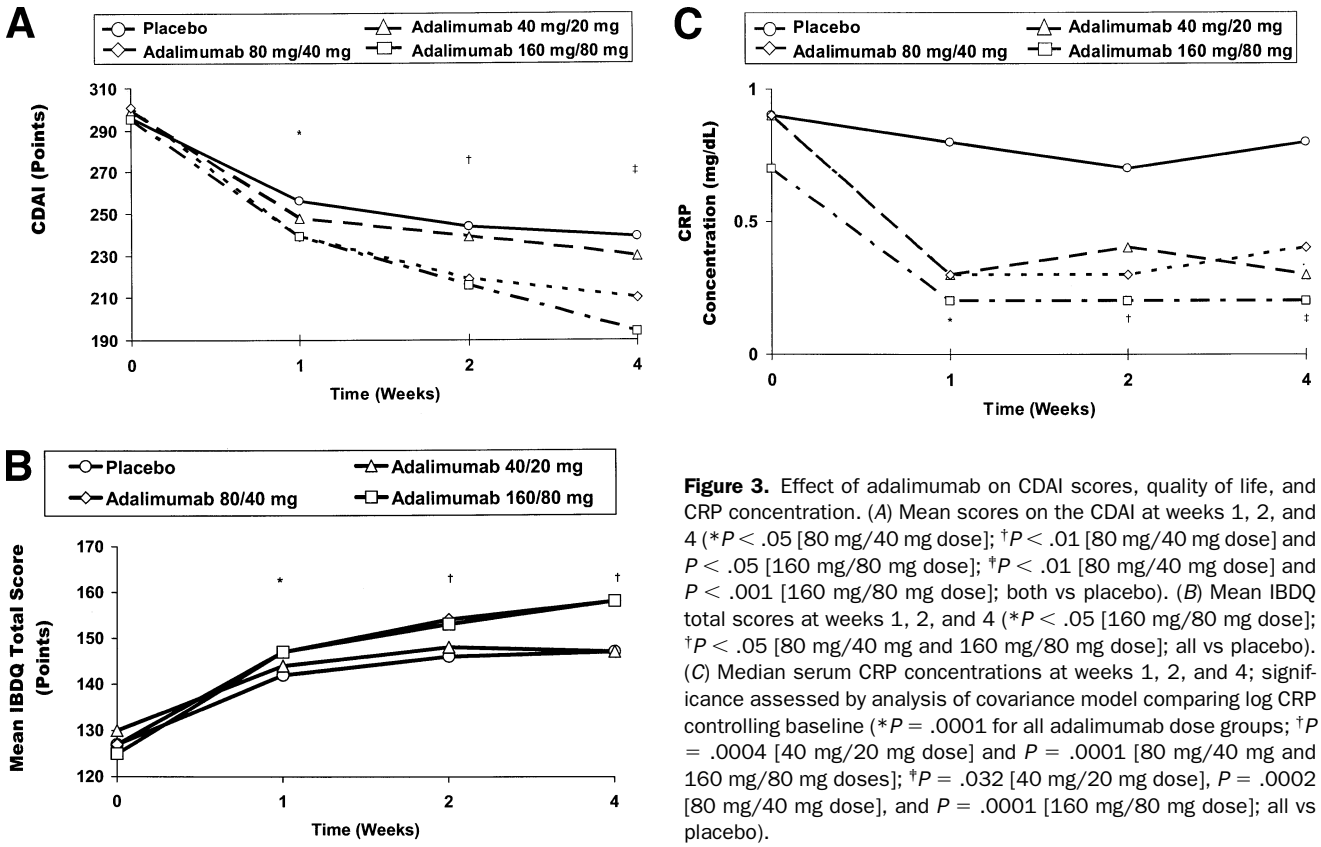


Figure 3. Effect of adalimumab on CDAI scores, quality of life, and CRP concentration. (*A*) Mean scores on the CDAI at weeks 1, 2, and 4 (*$P < .05$ [80 mg/40 mg dose]; †$P < .01$ [80 mg/40 mg dose] and $P < .05$ [160 mg/80 mg dose]; ‡$P < .01$ [80 mg/40 mg dose] and $P < .001$ [160 mg/80 mg dose]; both vs placebo). (*B*) Mean IBDQ total scores at weeks 1, 2, and 4 (*$P < .05$ [160 mg/80 mg dose]; †$P < .05$ [80 mg/40 mg and 160 mg/80 mg dose]; all vs placebo). (*C*) Median serum CRP concentrations at weeks 1, 2, and 4; significance assessed by analysis of covariance model comparing log CRP controlling baseline (*$P = .0001$ for all adalimumab dose groups; †$P = .0004$ [40 mg/20 mg dose] and $P = .0001$ [80 mg/40 mg and 160 mg/80 mg doses]; ‡$P = .032$ [40 mg/20 mg dose], $P = .0002$ [80 mg/40 mg dose], and $P = .0001$ [160 mg/80 mg dose]; all vs placebo).

adalimumab 160 mg/80 mg group, compared with 16% of patients (12/74) in the placebo group. The most common of these specific events were injection site burning and pain. The remaining adverse events that were reported by at least 5% of patients in 1 of the 4 treatment groups occurred in all groups at similar rates, including abdominal tenderness, Crohn's disease, aggravated Crohn's disease, nausea, flatulence, nasopharyngitis, pharyngitis, and headache.

Infections occurred in 10% of patients (8/74) in the adalimumab 40 mg/20 mg group, 17% of patients (13/75) in the adalimumab 80 mg/40 mg group, and 21% of patients (16/76) in the adalimumab 160 mg/80 mg group, compared with 16% of patients (12/74) in the placebo group (Table 4). Pneumonia occurred in 3 subjects: 1 in the placebo group and 2 in the 160 mg/80 mg group. One of the latter was reported as a serious adverse event.

Serious adverse events were infrequent and occurred at similar frequencies in the adalimumab and placebo groups (Table 4). None of the patients in the adalimumab 40 mg/20 mg group, 1% of patients (1/75) in the adalimumab 80 mg/40 mg group, and 4% of patients (3/76) in the adalimumab 160 mg/80 mg group experienced a serious adverse event, compared with 4% of patients (3/74) in the placebo group. No lymphomas occurred during the study, and no patients died.

Infections reported as serious adverse events occurred in 3% of patients (2/74) in the adalimumab 160 mg/80 mg group and none of the patients in the adalimumab 40 mg/20 mg, adalimumab 80 mg/40 mg, and placebo groups. The specific types of serious infections observed in the adalimumab 160 mg/80 mg group are shown in Table 4. No tuberculosis or opportunistic infections occurred during the study.

Immunogenicity and Pharmacokinetics

Only 2 patients developed antibodies against adalimumab. One patient in the placebo group had a positive assay for antibody to adalimumab at week 0, and 1 patient in the adalimumab 160 mg/80 mg group had a positive assay at week 2 with a subsequent negative assay at week 4.

Mean serum concentrations of adalimumab (μg/mL) at week 4 were 2.79 ± 1.48 (n = 66), 5.65 ± 3.06 (n = 65), and 12.61 ± 5.25 (n = 67) for the 40 mg/20 mg, 80 mg/40 mg, and 160 mg/80 mg groups, respectively.[27] Concomitant immunosuppressant therapy with azathioprine and 6-mercaptopurine did not produce a significant

Table 2. Subgroup Analyses

	Placebo	Adalimumab 40 mg/20 mg	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg
Enterocutaneous or perianal fistula improvement				
Week 4	2/6 (33)	3/4 (75)	2/10 (20)	1/12 (8)
Enterocutaneous or perianal fistula remission				
Week 4	1/6 (17)	3/4 (75)	0/10 (0)	0/12 (0)
Remission (CDAI score <150 points) in patients not receiving immunosuppressive agents				
Week 1	4/52 (8)	8/51 (16)	9/54 (17)	11/54 (20)
Week 2	7/52 (13)	6/51 (12)	14/54 (26)	14/54 (26)
Week 4	7/52 (13)	8/51 (16)	16/54 (30)	19/54 (35)
Remission (CDAI score <150 points) in patients receiving immunosuppressive agents				
Week 1	1/22 (5)	4/23 (17)	1/21 (5)	1/22 (5)
Week 2	3/22 (14)	4/23 (17)	1/21 (5)	4/22 (18)
Week 4	2/22 (9)	5/23 (22)	2/21 (10)	8/22 (36)
Remission (CDAI score <150 points) in patients with baseline CRP concentration <1.0 mg/dL				
Week 1	4/45 (9)	5/43 (12)	4/42 (10)	8/48 (17)
Week 2	5/45 (11)	6/43 (14)	7/42 (17)	9/48 (19)
Week 4	7/45 (16)	6/43 (14)	9/42 (21)	15/48 (31)
Remission (CDAI score <150 points) in patients with baseline CRP concentration ≥1.0 mg/dL				
Week 1	1/29 (3)	7/31 (23)	6/33 (18)	4/28 (14)
Week 2	5/29 (17)	4/31 (13)	8/33 (24)	9/28 (32)
Week 4	2/29 (7)	7/31 (23)	9/33 (27)	12/28 (43)

NOTE. All values are expressed as no. (%).

change in serum concentrations of adalimumab (Abbott Laboratories, data on file).

Discussion

We found that induction therapy with adalimumab, administered subcutaneously as a loading dose at week 0 followed by a second dose at week 2, is superior to placebo for inducing remission and response in infliximab-naive patients with moderate to severe disease activity despite the use of conventional therapy. Patients who received the highest dose (160 mg/80 mg) of adalimumab were 3 times more likely to achieve remission and approximately twice as likely to achieve a 100-point response and 70-point response at 4 weeks. Consistent with these results, patients who received the 2 highest doses of adalimumab also had significantly greater decreases in disease activity as measured by mean CDAI scores, median CRP concentrations, and mean IBDQ total scores compared with patients who received placebo. Statistically significant responses in some measures (70-point response, CDAI, IBDQ total score, and CRP) could be seen as early as week 1 versus placebo.

The results of induction therapy with the human IgG1 monoclonal antibody adalimumab in patients with Crohn's disease presented here are generally comparable to those observed with the chimeric IgG1 monoclonal antibody infliximab.[6] Both adalimumab and infliximab have demonstrated efficacy for induction of remission in the broad population of patients with moderate to severe Crohn's disease, without selecting for a subgroup of patients with elevated CRP concentration. In contrast, other anti-TNF therapies, including the humanized IgG4 monoclonal antibody CDP571 and, in a recently published phase 2 study, the pegylated humanized Fab′ antibody fragment certolizumab pegol (formerly known as CDP870), have only demonstrated efficacy in a subgroup of patients with CRP concentrations >1.0 mg/dL (10 mg/L).[28,29] The human p75 soluble TNF receptor fusion protein etanercept and the human soluble p55 TNF receptor onercept have failed to show any evidence of efficacy.[30,31] These apparent differences in efficacy between anti-TNF agents may in part be due to the ability of infliximab and adalimumab to induce T-cell apoptosis.[32,33]

There was a linear dose response across all 3 adalimumab dose groups for the more specific endpoints of remission and 100-point response at week 4. In contrast, for the more sensitive endpoints of 70-point response, CDAI score, and IBDQ total score, the results for the 2 highest adalimumab dose groups were similar and gen-

Table 3. Summary of Safety Analyses for All Randomized Patients up to Week 4

Variable	Placebo (n = 74)	Adalimumab 40 mg/ 20 mg (n = 74)	Adalimumab 80 mg/ 40 mg (n = 75)	Adalimumab 160 mg/ 80 mg (n = 76)
Adverse events, no. of patients (%)	55 (74)	50 (68)	51 (68)	57 (75)
Adverse events leading to discontinuation of study drug, no. of patients (%)	2 (3)	1 (1)	1 (1)	0 (0)
Adverse events occurring at a frequency of at least 5% in either the adalimumab or placebo groups, no. of patients (%)[a]				
Abdominal tenderness	1 (1)	1 (1)	0 (0)	4 (5)
Crohn's disease aggravated	4 (5)	2 (3)	3 (4)	2 (3)
Crohn's disease	2 (3)	4 (5)	2 (3)	3 (4)
Nausea	1 (1)	5 (7)	4 (5)	6 (8)
Flatulence	3 (4)	2 (3)	2 (3)	4 (5)
Nasopharyngitis	1 (1)	2 (3)	4 (5)	4 (5)
Pharyngitis	2 (3)	1 (1)	1 (1)	5 (7)
Headache	4 (5)	3 (4)	4 (5)	7 (9)
Patients with any type of injection site reactions, no. (%)	12 (16)	19 (26)	18 (24)	29 (38)
Specific types of injection site reactions, no. (%)				
Injection site burning[a]	6 (8)	9 (12)	8 (11)	11 (15)
Injection site pain[a]	6 (8)	6 (8)	4 (5)	6 (8)
Injection site reaction nonspecific[a]	0 (0)	3 (4)	5 (7)	6 (8)
Injection site erythema	0 (0)	1 (1)	0 (0)	3 (4)
Injection site bruising	0 (0)	0 (0)	1 (1)	2 (3)
Injection site pruritus	0 (0)	0 (0)	0 (0)	2 (3)

[a]Including specific injection site reactions as noted.

erally had greater improvements compared with the lowest adalimumab dose group and for placebo. The dose of 160 mg/80 mg results in adalimumab serum concentrations similar to those attained on long-term dosing with 40 mg weekly (10–13 μg/mL) or 80 mg every other week and is clearly effective for induction of remission.[27] The 80 mg/40 mg dose results in serum concentrations similar to dosing with 40 mg every other week (4–5 μg/mL).[27] This dosing regimen did not independently show efficacy for induction of remission or 100-point response, although differences in comparison with placebo did approach significance in both analyses ($P = .06$). Significant effects in the 80 mg/40 mg group were observed for 70-point response, IBDQ total score, and decreased CRP level. Thus, at present, there are insufficient data to determine whether an 80-mg loading dose of adalimumab followed by 40 mg every other week will be effective for induction and maintenance of remission in patients with Crohn's disease. The results from 2 ongoing maintenance trials comparing adalimumab 40 mg weekly, 40 mg every other week, and placebo should provide the answers to these questions.

Induction therapy with adalimumab was generally well tolerated. The overall rates of any type of injection reaction were 16% in the placebo group, 26% in the adalimumab 40 mg/20 mg group, 24% in the adalimumab 80 mg/40 mg group, and 38% in the adalimumab 160 mg/80 mg group. A burning sensation at the injection site was the most commonly reported of these reactions, none of which led to patient withdrawal. The rates of serious adverse events, serious infection, and pneumonia were low in patients treated with adalimumab and were similar to placebo. No patients developed opportunistic infection, lupus, neurologic disease,

Table 4. Infections and Serious Adverse Events

Variable	Placebo (n = 74)	Adalimumab 40 mg/20 mg (n = 74)	Adalimumab 80 mg/40 mg (n = 75)	Adalimumab 160 mg/80 mg (n = 76)
Infections, no. of patients (%)	12 (16)	8 (10)	13 (17)	16 (21)
Serious adverse events, no. of patients (%)	3 (4)	0 (0)	1 (1)	3 (4)
Serious infections, no. of patients (%)	0 (0)	0 (0)	0 (0)	2 (3)
Specific types of serious infections				
Perianal abscess	0 (0)	0 (0)	0 (0)	1 (1)
Pneumonia	0 (0)	0 (0)	0 (0)	1 (1)

or died. It should be acknowledged that this was a short 4-week trial and that additional trials of longer duration will be required to adequately evaluate the safety of adalimumab in patients with Crohn's disease. In patients with rheumatoid arthritis treated with adalimumab, drug-induced lupus, demyelination, possibly an increased rate of lymphoma, and serious and opportunistic infections have all been reported.[34] The rate of infections in placebo-controlled trials of adalimumab in patients with rheumatoid arthritis was 1.0 per patient-year in adalimumab-treated patients and 0.9 per patient-year in patients receiving placebo. Serious infections occurred at a rate of 0.04 per patient-year in adalimumab-treated patients and 0.02 per patient-year in placebo-treated patients. Pneumonia, tuberculosis, histoplasmosis, aspergillosis, and nocardiosis were all observed.[34]

The proportion of patients developing antibodies against the human antibody adalimumab was low (1 of 225 patients [0.04%]). It should be acknowledged that this short 4-week study might underestimate the frequency of developing anti-adalimumab antibodies. In patients with rheumatoid arthritis, the rate of formation of anti-adalimumab antibodies is 5% (1% for patients receiving concomitant therapy with methotrexate and 12% for patients not receiving methotrexate).[34]

In conclusion, induction therapy with adalimumab, administered subcutaneously as a loading dose at week 0 followed by a second dose at week 2, resulted in induction of response and remission in infliximab-naive patients with moderate to severe disease activity despite the use of conventional therapy compared with placebo. The efficacy and safety of adalimumab in the long-term management of patients with Crohn's disease are currently being evaluated in clinical trials.

Appendix 1. Participating Investigators and Location

Robert Bailey (Edmonton, Alberta, Canada), Peter Banks (Boston, MA), Charles Barish (Raleigh, NC), David Binion (Milwaukee, WI), Charles Birbara (Worcester, MA), Wlodzimierz Bolujko (Szczecin, Poland), William Chey (Rochester, NY), Kiron Das (New Brunswick, NJ), Petr Dite (Brno, Czech Republic), James Doyle (Spokane, WA), Robert Enns (Vancouver, British Columbia, Canada), David Eskreis (Lakes Success, NY), Richard Fedorak (Edmonton, Alberta, Canada), Stuart Frank (Chattanooga, TN), Bradley Freilich (Kansas City, MO), Daniel Geenen (Milwaukee, WI), Glenn Gordon (Mexico, MO), Stephen Hanauer (Chicago, IL), John Hanson (Charlotte, NC), Daniel Hommes (Amsterdam, The Netherlands), Kim Isaacs (Chapel Hill, NC), Bruce Johnson (San Diego, CA), Seymour Katz (Great Neck, NY), Radan Keil (Prague, Czech Republic), Alan Kivitz (Duncansville, PA), Milan Lukas (Praha, Czech Republic), Donald MacIntosh (Halifax, Nova Scotia, Canada), Philip Miner (Oklahoma City, OK), Mark Murphy (Savannah, GA), Daniel Pambianco (Charlottesville, VA), Remo Panaccione (Calgary, Alberta, Canada), Leszek Paradowski (Wroclaw, Poland), Pierre Pare (Quebec, Canada), Daniel Present (New York, NY), Michael Priebe (Tacoma, WA), Ronald Pruitt (Nashville, TN), Paul Rutgeerts (Leuven, Belgium), Alan Safdi (Cincinnati, OH), William Sandborn (Rochester, MN), Bruce Sands (Boston, MA), Ellen Scherl (New York, NY), Jerrold Schwartz (Arlington Heights, IL), Stephen Severance (Long Beach, CA), Ira Shafran (Winter Park, FL), Stanley Goldberg (Berkeley, CA), David Silvers (Metairie, LA), Hillary Steinhart (Toronto, Ontario, Canada), Stephan Targan (Los Angeles, CA), Harvey Tatum (Tulsa, OK), Emil Valle (Annapolis, MD), Gary Varilek (Lincoln, NE), Gary Wild (Montreal, Quebec, Canada), Douglas Wolf (Atlanta, GA), Strick Woods (Bridgeport, CT), and Bradley Zins (Billings, MT).

References

1. Van Deventer SJ. Tumour necrosis factor and Crohn's disease. Gut 1997;40:443–448.
2. Papadakis KA, Targan SR. Tumor necrosis factor: biology and therapeutic inhibitors. Gastroenterology 2000;119:1148–1157.
3. Murch SH, Lamkin VA, Savage MO, Walker-Smith JA, MacDonald TT. Serum concentrations of tumour necrosis factor alpha in childhood chronic inflammatory bowel disease. Gut 1991;32: 913–917.
4. Murch SH, Braegger CP, Walker-Smith JA, MacDonald TT. Location of tumour necrosis factor alpha by immunohistochemistry in chronic inflammatory bowel disease. Gut 1993;34:1705–1709.
5. Braegger CP, Nicholls S, Murch SH, Stephens S, MacDonald TT. Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. Lancet 1992;339:89–91.
6. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–1035.
7. Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, Mayer L, Van Hogezand RA, Braakman T, DeWoody KL, Schaible TF, Van Deventer SJ. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 1999; 117:761–769.
8. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–1549.
9. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340:1398–1405.
10. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance

therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876–885.
11. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, Plevy S. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 2003; 98:1315–1324.
12. Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601–608.
13. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 2003;124:917–924.
14. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, Olson A, Bao W, Rutgeerts P. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004; 2:542–553.
15. Hanauer S, Rutgeerts P, Targan S, Kam L, Present D, Mayer L, Wagner C, LaSorda J, Sands B, Livingston R. Delayed hypersensitivity to infliximab (Remicade) re-infusion after a 2-4 year interval without treatment (abstr). Gastroenterology 1999;116:A731.
16. den Broeder A, van de Putte L, Rau R, Schattenkirchner M, Van Riel P, Sander O, Binder C, Fenner H, Bankmann Y, Velagapudi R, Kempeni J, Kupper H. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol 2002;29:2288–2298.
17. van de Putte LB, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, Schattenkirchner M, Emery P, Burmester GR, Zeidler H, Moutsopoulos HM, Beck K, Kupper H. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis 2003;62:1168–1177.
18. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35–45.
19. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, Teoh LS, Velagapudi RB, Noertersheuser PA, Granneman GR, Fischkoff SA, Chartash EK. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther 2003;25:1700–1721.
20. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, Fischkoff SA, Chartash EK. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30: 2563–2571.
21. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P, Emery P, Walter N, Kaul M, Fischkoff S, Kupper H. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508–516.
22. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA, Chartash EK. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400–1411.
23. Rau R, Simianer S, van Riel PL, van de Putte LB, Kruger K, Schattenkirchner M, Allaart CF, Breedveld FC, Kempeni J, Beck K, Kupper H. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol 2004;33:145–153.
24. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439–444.
25. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JW. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology 1994;106:287–296.
26. Ford ES, Giles WH, Myers GL, Rifai M, Ridker PM, Mannino DM. C-reactive protein concentration distribution among US children and young adults: finding from the National Health and Nutrition Examination Survey, 1999-2000. Clin Chem 2003;49:1353–1357.
27. Paulson SK, Noertersheuser PA, Pollack P, Hoffman RS. Pharmacokinetics of adalimumab from CLASSIC, a randomized phase 3 trial for the induction of clinical remission in patients with Crohn's disease (abstr). Gastroenterology 2005;128(Suppl 2):A-585.
28. Sandborn WJ, Feagan BG, Radford-Smith G, Kovacs A, Enns R, Innes A, Patel J. CDP571, a humanised monoclonal antibody to tumour necrosis factor alpha, for moderate to severe Crohn's disease: a randomised, double-blind, placebo-controlled trial. Gut 2004;53:1485–1493.
29. Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, Bernstein CN, Staun M, Thomsen OO, Innes A; CDP870 Crohn's Disease Study Group. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005;129:807–818.
30. Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, Tremaine WJ, Johnson T, Diehl NN, Zinsmeister AR. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088–1094.
31. Rutgeerts P, Fedorak RN, Rachmilevich D, Tarabar D, Gibson P, Nielsen OH, Wild G, Schreiber S, Zignani M, Onercept Study Group T. Onercept (recombinant human p55 tumour necrosis factor receptor) treatment in patients with active Crohn's disease: randomized, placebo-controlled, dose-finding phase II study (abstr). Gut 2004;53(Suppl VI):A47.
32. van den Brande JMH, Braat H, van den Brink GR, Versteeg HH, Bauer CA, Hoedemaeker I, van Montfrans C, Hommes DW, Peppelenbosch MP, van Deventer SJH. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterology 2003;124:1774–1785.
33. Shen C, Van Assche G, Colpaert S, Maerten P, Geboes K, Rutgeerts P, Ceuppens JL. Adalimumab induces apoptosis of human monocytes: a comparative study with infliximab and etanercept. Aliment Pharmacol Ther 2005;21:251–258.
34. Humira [package insert]. Chicago, IL: Abbott Laboratories, 2004.

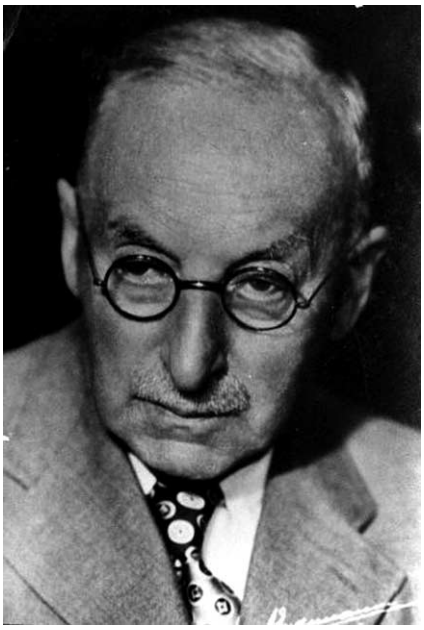
Received June 24, 2005. Accepted October 19, 2005.

Address requests for reprints to: Stephen B. Hanauer, MD, Division of Gastroenterology, University of Chicago Medical Center, 5841 South Maryland Avenue, Chicago, Illinois 60637. e-mail: shanauer@uchicago.edu; fax: (773) 702-2182.

Supported by a research grant from Abbott Laboratories (Abbott Park, IL).

S.B.H., W.J.S., P.R., R.N.F., R.P., and D.W. have served as consultants for Abbott Laboratories. S.B.H., W.J.S., P.R., R.N.F., and R.P. have participated in continuing medical education events supported by unrestricted educational grants from Abbott Laboratories.

Heller of the Heller Myotomy



Ernst Heller

Ernst Heller (1877–1964) was born in Eichenwalde, Germany, the son of a farmer. In the peregrine tradition of 19th century Germany, he pursued his medical studies in a circuit of Berlin, Munich, and Leipzig. Following advanced training in surgery, he was named chief surgeon at the Saint Georg County Hospital in Leipzig and later appointed professor of surgery at the University of Leipzig. In 1914, he published his first paper on esophagocardiomyotomy as a means of relieving dysphagia in cases of achalasia. The procedure was more readily adopted beyond the borders of Heller's own country. German authorities argued that myotomy could not possibly correct impaired esophageal motility. This is true, yet the operation proved to be remarkable effective in alleviating the symptoms and complications of achalasia. Another abiding concern of Heller was control of lighting in the operative field. It was he who introduced the use of colored drapes and nonreflecting instruments.

—Contributed by WILLIAM S. HAUBRICH, MD
The Scripps Clinic, La Jolla, California