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

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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.

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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]

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