Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis

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BACKGROUND & AIMS: Adalimumab is a fully human monoclonal antibody that binds tumor necrosis factor (TNF)-α. Its efficacy as maintenance therapy for patients with ulcerative colitis has not been studied in a controlled, double-blind trial. **METHODS:** Ulcerative colitis long-term remission and maintenance with adalimumab 2 (ULTRA 2) was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of adalimumab in induction and maintenance of clinical remission in 494 patients with moderate-to-severe ulcerative colitis who received concurrent treatment with oral corticosteroids or immunosuppressants. Patients were stratified based on prior exposure to TNF-α antagonists (either had or had not been previously treated with anti–TNF-α) and randomly assigned to groups given adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week or placebo. Primary end points were remission at weeks 8 and 52. **RESULTS:** Overall rates of clinical remission at week 8 were 16.5% on adalimumab and 9.3% on placebo ($P = .019$); corresponding values for week 52 were 17.3% and 8.5% ($P = .004$). Among anti–TNF-α naïve patients, rates of remission at week 8 were 21.3% on adalimumab and 11% on placebo ($P = .017$); corresponding values for week 52 were 22% and 12.4% ($P = .029$). Among patients who had previously received anti-TNF agents, rates of remission at week 8 were 9.2% on adalimumab and 6.9% on placebo ($P = .559$); corresponding values for week 52 were 10.2% and 3% ($P = .039$). Serious adverse events occurred in 12% of patients given adalimumab or placebo. Serious infections developed in 1.6% of patients given adalimumab and 1.9% given placebo. In the group given adalimumab, 1 patient developed squamous cell carcinoma and 1 developed gastric cancer. **CONCLUSIONS: Adalimumab was safe and more effective than placebo in inducing and maintaining clinical remission in patients with moderate-to-severe ulcerative colitis who did not have an adequate response to conventional therapy with steroids or immunosuppressants.**

Keywords: Antibody Targeted Therapy; IBD; Clinical Trial Result; Inflammation; Colon.

The proinflammatory cytokine tumor necrosis factor-α (TNF-α) plays an important role in the pathogenesis of ulcerative colitis (UC).[1] Intravenous administration of infliximab, a chimeric IgG1 monoclonal antibody to TNF-α, is effective for induction and maintenance of remission in outpatients with moderate-to-severe UC who fail conventional therapy with steroids and/or immunosuppressive agents.[2] In a related condition, Crohn's disease, 2 subcutaneously administered anti–TNF-α agents are approved in the United States, and are preferred by some patients because they can be self-administered.[3–7] At present, no subcutaneously administered anti–TNF-α agents are approved for patients with UC.

Adalimumab is a fully human IgG1 monoclonal antibody directed against TNF-α that inhibits activity of this cytokine by blocking the interaction of TNF-α with its p55 and p75 cell surface receptors. Adalimumab is approved in the United States, Europe, and Japan for Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis, and psoriasis. Several small open-label trials and case reports have suggested that adalimumab might be effective therapy for UC.[8–11] Recently, an 8-week randomized controlled trial demonstrated the ability of adalimumab to induce clinical remission in patients with moderate-to-severe UC, and demonstrated that an induction regimen of subcutaneous adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg every other week (EOW) was more effective than placebo or adalimumab 80 mg at week 0, 40 mg at week 2, and then 40 mg EOW ulcerative colitis long-term remission and maintenance with adalimumab 1 (ULTRA 1).[12] Although this trial established the safety and efficacy of adalimumab for inducing clinical remission, higher than expected response rates were seen in placebo patients for several secondary end points, including clinical response and mucosal healing. To date, no controlled data regarding long-term (1 year) efficacy of adalimumab in patients with UC are available, and

Abbreviations used in this paper: EOW, every other week; IBDQ, Inflammatory Bowel Disease Questionnaire; NNT, number needed to treat; TNF, tumor necrosis factor; UC, ulcerative colitis; ULTRA 1, ulcerative colitis long-term remission and maintenance with adalimumab 1; ULTRA 2, ulcerative colitis long-term remission and maintenance with adalimumab 2.

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additional data regarding the induction efficacy of adalimumab for therapy in UC would be of interest. Accordingly, we designed the ulcerative colitis long-term remission and maintenance with adalimumab 2 (ULTRA 2) trial, a 52-week placebo-controlled induction and long-term treatment study in patients with moderate-to-severe UC.

Materials and Methods

Patients

This phase 3, multicenter, randomized, double-blind, placebo-controlled trial was conducted at 103 centers in North America, Europe, Australia, New Zealand, and Israel between November 2006 and March 2010. The protocol was approved by the institutional review board for each center. All patients gave written consent.

Eligible patients were adults with moderately-to-severely active UC for at least 3 months with a Mayo score of 6−12 points (endoscopy subscore of at least 2), despite concurrent therapy with steroids and/or azathioprine or 6-mercaptopurine. The Mayo score is a composite score of 4 items (ie, rectal bleeding, stool frequency, physician's global assessment, endoscopy).[13] For the scoring of the rectal bleeding and stool frequency items, the worst score from the previous 3 days before the study visit was used. The diagnosis of UC was confirmed by biopsy obtained at the screening colonoscopy or flexible sigmoidoscopy. Patients concurrently treated with oral corticosteroids were to receive a stable dose (prednisone ≥20 mg/day for at least 2 weeks, or <20 mg/day for at least 40 days) before baseline. Patients treated with immunomodulators were to receive at least a consecutive 3-month course of azathioprine (at least 1.5 mg/kg/day, or highest tolerated dosage) or 6-mercaptopurine (at least 1 mg/kg/day, or highest tolerated dosage) before baseline (with stable dosage for at least 4 weeks). Concurrent therapy was not required for patients who failed to respond to or could not tolerate previous corticosteroid or immunomodulator treatment, as judged by the investigator. Previous use of anti-TNF agents other than adalimumab was permitted if the patient had discontinued its use due to a loss of response or intolerance to the agent for longer than 8 weeks. Patients were allowed stable dosages of 5-aminosalicylates as concurrent therapy, but 5-aminosalicylate use was not an entry criterion for the trial.

Patients were excluded if they had the following: history of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for UC, or planned bowel surgery; previous treatment with adalimumab; receipt of intravenous corticosteroids within 2 weeks of screening; receipt of cyclosporine, tacrolimus, or mycophenolate mofetil within 1 month of baseline; receipt of therapeutic enema or suppository, other than required for endoscopy, within 2 weeks of the screening endoscopy and during the screening period; or receipt of any investigational agent within 30 days or 5 half-lives before baseline. Patients were also excluded for the following: a current diagnosis of fulminant colitis or toxic megacolon, disease limited to the rectum (ulcerative proctitis), current diagnosis of indeterminate colitis, or current diagnosis or history of Crohn's disease, current total parenteral nutrition, positive *Clostridium difficile* stool assay, previous use of infliximab and no clinical response at any time ("primary nonresponder"), history of an infection requiring intravenous antimicrobial therapy within 1 month or oral antimicrobial therapy within 2 weeks, history of listeria, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus, immunodeficiency syndrome, or untreated tuberculosis, history of central nervous system demyelinating disease, history of malignancy other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix, or evidence of dysplasia or malignancy on the screening colonoscopy/flexible sigmoidoscopy with biopsy.

Study Design

Patients were randomly assigned in a 1:1 ratio to receive subcutaneous injections of adalimumab 160 mg at week 0, 80 mg at week 2 and then 40 mg EOW beginning at week 4, or matching placebo. They were followed through week 52. Randomization was performed centrally and was stratified by prior exposure to infliximab or other anti-TNF agents. Concomitant medication doses remained constant except steroids, which could be tapered after week 8 at the discretion of the investigator in patients who had a satisfactory clinical response. The taper consisted of reducing the prednisone dosage by 5 mg weekly until a dosage of 10 mg/day was reached. Thereafter, the dosage was reduced by 2.5 mg weekly until discontinuation. Patients demonstrating inadequate response could switch to open-label adalimumab (40 mg EOW) starting at week 12. Inadequate response was defined as: (1) partial Mayo score equal to or above baseline score on 2 consecutive visits at least 14 days apart (for patients with a partial Mayo score of 4−7 at baseline); (2) partial Mayo score ≥7 on 2 consecutive visits at least 14 days apart (for patients with a partial Mayo score of 8 or 9 at baseline). Patients who demonstrated inadequate response at 2 consecutive visits at least 14 days apart while on open-label administration 40 mg EOW were permitted to escalate dosage to adalimumab 40 mg weekly.

Efficacy Evaluations

Patients were evaluated at weeks 0, 2, 4, 8, 12, 16, 20, 26, 32, 38, 44, and 52/early termination. The Mayo score was determined at weeks 0, 8, 32, and 52/early termination. A partial Mayo Score (Mayo Score without endoscopy) was determined at all visits. Health-related quality of life, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ),[14] was determined at weeks 0, 4, 8, 20, 32, and 52/early termination. Clinical remission was defined as a total Mayo score ≤2 points, with no individual subscore exceeding 1 point. Clinical response was defined as a decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. Mucosal healing was defined as an endoscopy subscore of 0 or 1. Clinical response, clinical remission, and mucosal healing were assessed at weeks 8, 32, and 52/early termination. Patients who achieved clinical remission or clinical response at both weeks 8 and 52 were considered to be in sustained clinical remission or sustained clinical response, respectively. Partial Mayo score clinical remission was defined as a partial Mayo score ≤2 points, with no individual subscore exceeding 1 point. IBDQ response was defined as an increase from baseline of at least 16 points.

Safety Evaluations

At each clinic visit from baseline (week 0) through week 52/early termination, patients underwent physical examination, vital signs, previous (at baseline) and concomitant medications, and adverse events were recorded, and general laboratory tests including C-reactive protein and urinalysis were performed. Sera