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Combination Therapy With Infliximab and Azathioprine Is Superior to Monotherapy With Either Agent in Ulcerative Colitis

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BACKGROUND & AIMS: The comparative efficacy and safety of infliximab and azathioprine therapy alone or in combination for ulcerative colitis (UC) have not been evaluated previously. **METHODS:** This randomized, double-blind trial evaluated the efficacy and safety of 16 weeks of treatment with infliximab monotherapy, azathioprine monotherapy, or the 2 drugs combined in tumor necrosis factor-α antagonist-naive adults with moderate to severe UC. Patients were assigned randomly to receive intravenous infusions of infliximab 5 mg/kg at weeks 0, 2, 6, and 14 plus daily oral placebo capsules; oral azathioprine 2.5 mg/kg daily plus placebo infusions on the infliximab schedule; or combination therapy with the 2 drugs. Corticosteroid-free clinical remission (primary end point, week 16) was evaluated at weeks 8 and 16. The study was terminated before the enrollment target was reached. **RESULTS:** A total of 239 patients were included in efficacy analyses. Baseline characteristics were similar between treatment groups. Corticosteroid-free remission at week 16 was achieved by 39.7% (31 of 78) of patients receiving infliximab/azathioprine, compared with 22.1% (17 of 77) receiving infliximab alone ($P = .017$) and 23.7% (18 of 76) receiving azathioprine alone ($P = .032$). Mucosal healing at week 16 occurred in 62.8% (49 of 78) of patients receiving infliximab/azathioprine, compared with 54.6% (42 of 77) receiving infliximab ($P = .295$) and 36.8% (28 of 76) receiving azathioprine ($P = .001$). Serious infections occurred in 2 patients (1 patient receiving infliximab, and 1 patient receiving azathioprine). **CONCLUSIONS:** Anti–tumor necrosis factor-α–naive patients with moderate to severe UC treated with infliximab plus azathioprine were more likely to achieve corticosteroid-free remission at 16 weeks than those receiving either monotherapy. Combination therapy led to significantly better mucosal healing than azathioprine monotherapy. ClinicalTrials.gov number, NCT00537316.

Keywords: Tumor Necrosis Factor Inhibitors; Purine Antimetabolites; Biologic Treatment.

Ulcerative colitis (UC) is a chronic inflammatory disorder of the large intestine characterized by bloody diarrhea, abdominal pain and cramping, and urgency and tenesmus, which can negatively affect daily functioning and quality of life.[1] The goals of therapy include the induction of remission and mucosal healing. For patients with mild to moderate disease, this may be achieved with mesalamines with or without corticosteroids (CSs). Mesalamine and steroids also may be useful in patients with more distal disease and may aid in symptom resolution in patients with more extensive disease.[2] For more severe disease and in hospitalized patients, CSs may be administered intravenously. Limitations of CS therapy include a high incidence of short- and long-term adverse effects and the inability to maintain remission.[3]

Patients who experience frequent disease relapse or are resistant to or dependent on CSs often are treated with purine antimetabolites, including azathioprine (AZA) or 6-mercaptopurine (6-MP), to maintain remission.[2] Such patients also may be candidates for treatment with monoclonal antibodies targeting tumor necrosis factor-α (TNF-α), which have shown efficacy in inducing and maintaining remission in patients with UC.[4] However, treatment guidelines routinely recommend the use of TNF-α antagonists only after failure of conventional nonbiologic therapy, including the purine antimetabolites AZA and 6-MP.[5–7] The comparative efficacies of TNF-α antagonists vs purine antimetabolites or vs the combination of TNF-α antagonists and purine antimetabolites are important questions relevant to management of UC. This trial was designed to compare the efficacy of the TNF-α antagonist infliximab (IFX), AZA, or the combination of the 2 drugs (IFX/AZA) in the treatment of patients with moderate to severe UC.

Methods

Ethical Issues

The study was conducted in accordance with Good Clinical Practices guidelines.[8] The institutional review board of each center approved the protocol, and all study participants provided informed written consent. All authors had access to the

Abbreviations used in this paper: **AEs, adverse events; ATI, antibodies to infliximab; AZA, azathioprine; CI, confidence interval; CS, corticosteroid; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; PBO, placebo; SF-36, 36-item Short Form Health Survey; 6-MP, 6-mercaptopurine; TNF-α, tumor necrosis factor α; UC, ulcerative colitis.**

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study data and were required to review and approve the final manuscript.

Study Design and Procedures

UC SUCCESS (NCT00537316, protocol number P04807) was a randomized, double-blind, double-dummy trial evaluating the safety and efficacy of 16 weeks of IFX monotherapy, AZA monotherapy, and IFX/AZA combination therapy in the treatment of patients with moderate to severe, active UC. The study was performed at 62 centers from November 2007 through February 2010.

Randomization was performed centrally using an adaptive randomization procedure stratified by whether patients previously used immunomodulators such as AZA and cyclosporine. Patients were randomized in a 1:1:1 ratio to receive IFX, AZA, or combination IFX/AZA treatment. Patients in the IFX group received 5 mg/kg intravenous IFX at weeks 0, 2, 6, and 14 plus daily oral placebo (PBO) capsules. Patients in the IFX group who were nonresponders at week 8 (partial Mayo score improvement from baseline of <1) also received PBO infusions at weeks 8 and 10. Patients in the AZA group received 2.5 mg/kg AZA oral capsules daily plus intravenous PBO infusions at weeks 0, 2, and 6. For patients who responded to AZA at week 8, a PBO infusion also was received at week 14. For patients who were nonresponders to AZA at week 8 (partial Mayo score improvement from baseline of <1), IFX rescue infusions were administered at weeks 8, 10, and 14 while continuing AZA therapy. Patients in the combination IFX/AZA group received IFX 5 mg/kg at weeks 0, 2, 6, and 14 and also received 2.5 mg/kg AZA capsules daily. Patients in this group who were nonresponders at week 8 also received PBO infusions at weeks 8 and 10. Thiopurine methyltransferase was not assayed at study enrollment. Patients with a known sensitivity to administered study medications were excluded from the study. A strategy for dose reduction and discontinuation of AZA was followed during the study if a patient developed leukopenia, transaminitis, or pancreatitis. Details of the study design are shown in Supplementary Figure 1*A*.

All concomitant therapies at baseline were held stable throughout the study. Patients taking CSs at baseline were tapered to 0 mg by week 14 unless medically contraindicated. It was recommended that for patients who were receiving a dosage of more than 20 mg/day of prednisone or equivalent at enrollment, the CS dose be tapered daily by 5 mg/week to 20 mg/day, then by 2.5 mg/week. For patients who were receiving 20 mg/day or less of prednisone or equivalent at enrollment, the daily dose was to be tapered by 2.5 mg/week.

After the initial randomized treatment phase of the study, a continuation study was planned to evaluate which of 2 open-label maintenance treatment regimens was superior for maintaining steroid-free remission. Patients who had achieved CS-free remission at week 16 or patients who were not enrolled in the study but had been treated with IFX for a maximum of 6 months with or without AZA/6-MP and were in CS-free remission could enter the follow-up study, which included a randomized portion and an observational portion (Supplementary Figure 1*B*). An enrollment target of 600 patients was planned for the initial randomized treatment phase to fully enroll 200 patients in the longer-term follow-up study. However, in October 2009, the sponsor decided to terminate enrollment in this study because of a higher-than-expected incidence of serious infusion reactions in patients who received an intermittent IFX regimen with re-induction in a separate, long-term study of patients with psoriasis (RESTORE2, NCT00358670).[9] As a result, only 239 patients were randomized to the initial treatment phase. Only 13 of the planned 200 patients were randomized for the follow-up study; therefore, the data are not reported here.

Patients

Eligible patients were at least 18 years of age (the minimum age was increased to 21 years of age after the study started) with moderate to severe UC as defined by Mayo score at baseline[10]; moderate and severe disease were defined as Mayo scores of 6–8 and 9–12, respectively. Patients had endoscopic evidence of UC, as determined by sigmoidoscopy, within 14 days before baseline. Patients were required to have responded inadequately to a course of CSs with or without mesalamine within the past 12 weeks. Patients who were taking CSs could enter the study if they were on a stable dose ($\leq$30 mg prednisone or equivalent) for at least 2 weeks before enrollment. All patients were required to be TNF-α antagonist-naive. Patients also were required to be either AZA-naive or free from AZA treatment for at least 3 months before enrollment. Prohibited medications at study entry included methotrexate, calcineurin inhibitors (tacrolimus, cyclosporine), antibiotics, rectal therapy with CSs or mesalamine, and antimotility agents or laxatives.

Patients were excluded if they had been hospitalized for extensive severe UC or had experienced recent gastrointestinal surgery, bowel obstruction, stricture of the colon, previous colonic resection, documented colonic dysplasia, previous tuberculosis or other granulomatous infection, a recent episode of an opportunistic infection (within 2 months of screening), active infection with hepatitis B or C, infection with the human immunodeficiency virus, history of a demyelinating disease, systemic lupus erythematosus, malignancy, congestive heart failure, or a transplanted organ.

Evaluation of Efficacy and Safety

The Mayo score,[10] Inflammatory Bowel Disease Questionnaire (IBDQ),[11] the Short-Form Health Survey (SF-36),[12] and fecal calprotectin levels were assessed at baseline and weeks 8 and 16. Sigmoidoscopy was performed at screening and week 16. Measurement of antibodies to IFX (ATI) was performed at baseline and week 16.

The primary end point of the study was the proportion of patients in CS-free remission, defined as a total Mayo score of 2 points or less, with no individual subscore exceeding 1 point, without the use of CSs at week 16. Secondary end points included the percentage of patients with partial Mayo response at week 8 (defined as a decrease from baseline in partial Mayo score [ie, Mayo score without endoscopy subscore] of $\geq$1 point); the percentage of patients with total Mayo response at week 16 (defined as a decrease in the total Mayo score of $\geq$3 points and at least a 30% decrease from baseline Mayo score); the percentage of patients with mucosal healing (Mayo endoscopy subscore of 0 or 1) at week 16; and changes in mean Mayo, IBDQ, and SF-36 scores from baseline to weeks 8 and 16. A more lenient definition of Mayo response was used at week 8 than week 16 to provide an earlier rescue treatment for patients with poor response. In post hoc analyses, response at week 8 also was assessed using a more stringent definition of response (decrease from baseline in partial Mayo score of $\geq$2).