Infliximab

Results of a study of infliximab (Remicade, Centocor) in patients with ulcerative colitis (UC) led professor William Sandborn, MD, of the Mayo Clinic in Rochester, Minnesota, to conclude that steroid sparing should be an important goal of therapy. Although remission remains the primary goal, steroid sparing is of primary importance in terms of maintaining health-related quality of life.

Dr. Sandborn presented an analysis of data from two pivotal Active Ulcerative Colitis Trials (ACT 1 and ACT 2) of infliximab. He noted that both preclinical and clinical data suggest that tumor necrosis factor–alpha (TNF-α), by mediating chronic inflammation, might be important in the pathogenesis of UC.

Infliximab is an anti–TNF-α monoclonal antibody that was developed as a therapeutic agent for various diseases in which TNF-α–mediated inflammation is thought to play a role.

ACT 1 and ACT 2 included 728 patients with active UC that was unresponsive to standard UC therapy consisting of oral corticosteroids, immunosuppressants, or aminosalicylates (5-ASAs, or 5-aminosalicylic acid). Patients had been randomly assigned to receive placebo or infliximab infusions (5 or 10 mg/kg at baseline, at weeks two and six and every eight weeks through week 22 in ACT 2 and through week 46 in ACT 1).

The analysis involved patients who had received steroids at baseline in the infliximab trial and who achieved remission at week 30 (91 of 408 patients). The 70 patients who discontinued steroids by week 30 were then compared with those who continued steroid use (n = 21). Outcome measures included scores from the Inflammatory Bowel Disease Quality of Life Index (IBDQ) and the 36-item Short Form Health Survey Questionnaire (SF-36). Baseline scores for these measures had been similar for both groups.

In an interview, Dr. Sandborn noted that expecting steroid-free remission “sets a very high bar.” Among patients who achieved remission, the mean reduction in IBDQ scores was 64.7 in the group of patients discontinuing steroids and 55.2 in the group continuing to receive steroids. (A larger reduction in scores shows greater improvement.)

Mean changes in SF-36 scores were similar in both patient groups at 30 weeks for the mental component (11.4 with continued steroids vs. 11.0 for discontinued therapy) but were significantly better on the physical component for patients discontinuing steroid therapy (5.9 for patients continuing and 9.8 for patients discontinuing) (P < .05).

Reviewing the side effects of the steroids, Dr. Sandborn listed emotional lability, “hyperness,” insomnia, weight gain, acne, “moon-face,” osteoporosis, vulnerability to infection, and an increased risk of diabetes. He said also that patients coming off steroid therapy need to taper their doses over eight to 12 weeks so that the adrenal glands can gradually re-establish cortisol production.

A second, longer-term analysis examined the impact of infliximab therapy on UC-related hospitalizations in ACT 1 and on hospitalizations requiring high-dose corticosteroids of 40 mg/day or more in ACT 1 and ACT 2. In this analysis, the reduction in the number of hospitalizations observed through 30 weeks of treatment was sustained through one year. The number of hospitalizations was reduced in the combined infliximab groups of patients in ACT 1 and ACT 2 by about half (12 per 100 patients), compared with the placebo group (22 per 100) (P = .061). At 54 weeks in ACT 1, 8.3% of the placebo patients were hospitalized and required high-dose steroids, compared with 3.7% of those in the infliximab groups. In both trials, the time to the first hospitalization was longer in patients receiving the combined infliximab regimen (P = .032).

The importance of avoiding hospitalization was borne out by the fact that among 32 patients hospitalized in ACT 1 and ACT 2 trials, 11 required colectomies. According to Dr. Sandborn:

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We’ve been seeing a raising of the bar as far as what we expect from medications. Now we’re expecting remissions and discontinuation of steroids. Ultimately, we want to avoid colon surgery.

Although randomized trials have not yet verified a reduced need for surgery through the use of biologic agents, Dr. Sandborn speculated that based on clinical observations, such a reduction would be anticipated. Even though two other biologic agents are nearing approval, he was aware of at least eight biologic agents that will be in phase 2 or 3 clinical trials by the first quarter of 2007.

Co-investigator Gary R. Lichtenstein, MD, from the University of Pennsylvania, spoke of the costs of UC-related hospitalizations:

The majority of the costs for patients with UC have been the huge costs incurred through hospitalizations and surgery. If we can limit these with appropriate medications, we can certainly make a dent in the cost of caring for these patients.

In the week before the ACG meeting, primarily on the basis of ACT 1’s one-year finding of a doubling of remission rates with infliximab (35% vs. 17%), the U.S. Food and Drug Administration (FDA) approved infliximab for maintaining clinical remission and mucosal healing in patients with moderately to severely active UC who were responding inadequately to conventional therapy.

**Adalimumab**

A clinical trial of adalimumab (Humira, Abbott), another anti–TNF-α monoclonal antibody, used for patients with moderate-to-severe Crohn’s disease, demonstrated efficacy in inducing responses and remissions. All of the patients in the trial had stopped responding to or had adverse reactions from infliximab.

This study, also presented by Dr. Sandborn, was unique in being the first randomized, controlled trial that involved switching within the class of anti–TNF-α agents. At this time, infliximab remains the only anti–TNF-α agent with an FDA indication for Crohn’s disease. Dr. Sandborn said that adalimumab, because it is a fully human antibody structurally identical to naturally occurring human antibodies, is thus “theoretically less likely to stimulate an immune response than other agents.”

The 12- to 14-day half-life of adalimumab allows for subcutaneous administration.

The objective of the four-week trial was to test the efficacy and safety of adalimumab in patients who did not respond to infliximab. Thirty-five subjects (mean age, 38 years; 35% male) received placebo or adalimumab 160 mg at week zero and 80 mg at the second week.

To be included in the study, patients had to score between 220 and 450 (moderate to severe) on the Crohn’s Disease Activity Index (CDAI); they also had to have discontinued receiving infliximab at least eight weeks before the study because they had stopped responding to the drug, had experienced adverse reactions, or both.

The primary endpoints were induction of remission at the fourth week, defined as a CDAI score below 150 and a decrease in CDAI scores of either 70 or greater (CR-70) or 100 points or more (CR-100).

The mean CDAI score at baseline was 313, and the mean score on the Inflammatory Bowel Disease Questionnaire (IBDQ) was 122. That score, Dr. Sandborn commented, was quite low; normal would be above 170. About 50% of the patients had stopped responding to infliximab, and 58.5% had experienced adverse reactions.

At four weeks, the rates of remission (indicated by a CDAI score below 150) were 21% in the adalimumab group and 7% in the placebo group ($P < .001$). CR-70 responses were reported in 52% of adalimumab patients, in contrast to 34% of placebo patients ($P < .001$). Differences were already significant ($P < .005$) by the first week.

Remission rates were similar among patients with and without human anti-chimeric antibodies at the baseline evaluation. Similarly, the use of immunosuppressants at baseline did not affect remission rates, and infliximab use did not affect loss of response or intolerance. Remission rates were somewhat lower among patients who were both intolerant of infliximab and who had stopped responding at baseline.

The safety profile of adalimumab was similar to that in other trials of the drug for rheumatoid arthritis and Crohn’s disease. Adverse events were actually lower in the adalimumab group than in the placebo group. However, Dr. Sandborn said that one wouldn’t expect many adverse events in such a short-term trial.

He concluded that adalimumab was efficacious in inducing clinical remission and responses in subjects with moderate-to-severe Crohn’s disease who had stopped responding to or who had adverse reactions to infliximab.

On February 27, 2007, adalimumab was approved by the FDA for the treatment of moderate-to-severe Crohn’s disease.