Adalimumab Maintains Crohn's Disease Remission

The subcutaneously injected drug is currently approved by the FDA for the treatment of arthritis.

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COPENHAGEN — Regular treatment with adalimumab maintained remission in patients with Crohn's disease during a year of follow-up, in a controlled study with 55 patients.

A larger study that's powered to definitively assess the long-term efficacy of adalimumab is in progress, William J. Sandborn, M.D., said at the 13th United European Gastroenterology Week.

Adalimumab is a fully humanized, anti–tumor necrosis factor monoclonal antibody that's administered by subcutaneous injection. It's currently approved in the United States for treating rheumatoid arthritis and psoriatic arthritis, and is marketed as Humira by Abbott Laboratories, which is sponsoring development of the drug for Crohn's disease. Dr. Sandborn is a consultant to Abbott and several other companies.

Assessment of adalimumab's ability to maintain remission in patients with moderately to severely active Crohn's disease began with a study of 299 patients who received two doses of the drug to induce remission, defined as a Crohn's Disease Activity Index score of less than 150.

After induction efficacy was assessed 2 weeks following the second dose, patients were given the option of receiving two more doses on an open-label basis.

Fifty-five patients were in clinical remission at both the start and end of the 4-week open-label phase, and these patients were then rerandomized for the long-term maintenance phase.

Another 221 patients who were not in remission after both the induction phase and the open-label phase were continued on long-term, open-label treatment.

In the randomized group, 18 patients received 40 mg of adalimumab once a week for 1 year. Nineteen patients received the same dose every other week, and 18 patients received placebo.

After a year, remission continued in 83% of patients on the weekly dose, compared with 44% of those on placebo, a statistically significant difference. Remission was maintained in 74% of patients who received the drug every other week, which was not significantly different from placebo.

The failure to reach statistical significance was probably due to the small number of patients in the study, said Dr. Sandborn, a professor of medicine at the Mayo Medical School, Rochester, Minn.

Serious adverse events occurred in two patients in the placebo group, in one patient who got adalimumab every other week, and in no patients who got the drug weekly.

Antiadalimumab antibodies were found in one patient in the placebo group and one in the group that received adalimumab every other week. Injection-site reactions occurred in three patients, one of whom was in the placebo group. No patient in the study had an opportunistic infection.

Among the 221 patients who received long-term treatment with adalimumab on an open-label basis, 131 (59%) remained on the drug after 1 year. Seventy of these patients were receiving one dose of adalimumab every 2 weeks, and 60 patients were receiving it weekly.

Of the patients who entered the open-label phase, 43% were in remission after a year of treatment, Dr. Sandborn said in a separate report at the meeting.

Serious adverse events occurred in 17% of patients, including 5% who had an infection while receiving treatment. Antibodies to the drug were measured in six patients.

The first phase of this study showed that adalimumab was more effective than placebo for inducing an initial remission. The 299 patients enrolled in the induction phase were randomized to receive 160 mg, 80 mg, 40 mg, or placebo as their initial dose. For their second induction dose, these groups received 80 mg, 40 mg, 20 mg, or placebo, respectively.

Two weeks after the second dose, 36% of patients in the highest-dose group were in remission, compared with 24% in the 80 mg/40 mg group and 12% in the placebo group.

The remission rate in the highest-dose group (160 mg followed by 80 mg) was significantly higher than that in the placebo group. The response rate in the 80 mg/40 mg group just missed statistical significance, compared with the control group ($P = .06$). ■

Natalizumab Boosts Quality of Life in Crohn's Disease

COPENHAGEN — Maintenance therapy with natalizumab in patients with Crohn's disease led to improved quality of life compared with placebo, and normalized quality of life measures in a study with 339 patients.

"We're trying to normalize" patients with Crohn's disease, Brian G. Feagan, M.D., said at the 13th United European Gastroenterology Week.

Maintenance therapy with natalizumab produced quality of life scores that were similar to scores measured in normal populations.

Dr. Feagan presented findings from a secondary analysis of data collected in the pivotal, phase III trial for natalizumab in patients with active Crohn's disease—the Efficacy of Natalizumab as Active Crohn's Therapy (ENACT) trial.

This study had an induction phase, ENACT-1, with 905 patients randomized to natalizumab or placebo, and a maintenance phase, ENACT-2, that included the 339 patients who had a response to the drug in ENACT-1.

The studies were sponsored by Elan Pharmaceuticals and Biogen Idec, the two companies that jointly market natalizumab (Tysabri).

Dr. Feagan has served as a consultant to Elan Pharmaceuticals.

The results from ENACT-1 failed to show an advantage for natalizumab over placebo for producing clinical responses, but the ENACT-2 data showed that continued treatment with 300 mg natalizumab once every 4 weeks led to a 61% rate of sustained responses during 36 weeks of follow-up, significantly higher than the 28% rate of sustained responses in the placebo group.

These primary end point results were reported last month (New Engl. J. Med. 2005;353:1912-25).

Natalizumab was approved by the Food and Drug Administration in late 2004 for treating multiple sclerosis, and then was withdrawn from the U.S. market in February following reports that associated its use with cases of multifocal leukoencephalopathy.

In September, the companies submitted a supplemental application to the FDA in a move to resume selling the drug for treating multiple sclerosis.

Natalizumab is a humanized, IgG monoclonal antibody that binds alpha-4 integrin and thereby blocks the adhesion of leukocytes to the gut and the migration of these cells into the gut.

The quality of life analysis led by Dr. Feagan used data collected on the inflammatory bowel disease questionnaire (IBDQ) and on the Short Form–36 (SF-36).

Starting with the first maintenance dose, patients receiving natalizumab had significantly higher IBDQ scores than did those treated with placebo.

After 1 year of treatment, patients who took natalizumab had an average score of 181, compared with an average score of 157 in the placebo group, a statistically significant difference, said Dr. Feagan, a professor of medicine at the University of Western Ontario, London.

After 1 year, patients on maintenance therapy with natalizumab also showed significantly better scores than did placebo patients for all physical and mental component scores of the SF-36, including bodily pain, social function, and mental health.

In addition, the analysis showed no significant differences between individual component scores for patients in the active-treatment arm and scores from an age-adjusted sample of normal Americans, except for the categories of vitality and general health, Dr. Feagan reported.

In contrast, the scores of patients in the placebo arm were consistently and significantly lower than scores of the normal, general population, he noted in his presentation. ■

A Promising Future, Despite Safety Issues

Despite natalizumab's safety issues, the drug remains a viable option for treating selected patients with Crohn's disease, Dr. Feagan said at the meeting.

After Tysabri was withdrawn from the market, the two companies that comarket it offered an extensive safety evaluation to the more than 3,500 patients who had participated in the drug's trials.

This offer was accepted by about 90% of all patients in the multiple sclerosis, rheumatoid arthritis, and Crohn's disease trials—a total of more than 3,000 patients—said a spokeswoman for Biogen Idec.

The investigation turned up no additional cases beyond the three patients that had been reported previously, noted Biogen Idec and Elan Pharmaceuticals in written statements.

That's good news," said Dr. Feagan. "What it comes down to is, will we, as physicians, accept this rare but serious and often fatal complication? I think we will pick our spots, and focus on patients who fail other treatments, at least until there are more safety data."

"Do I think that the drug will come back for Crohn's disease? Yes I do," he said.

In an editorial that accompanied the published report of the primary efficacy and safety data for natalizumab in 905 patients with Crohn's disease, Daniel K. Podolsky, M.D., wrote that natalizumab treatment may interfere with immune control of the endemic JC virus, and that this may be the trigger for progressive, multifocal leukoencephalopathy (New Engl. J. Med. 2005; 353:1965-8).

Dr. Podolsky suggested that natalizumab therapy be targeted to patients with frequent and debilitating recurrences of inflammatory bowel disease, in concert with close surveillance by MRI, which may be able to identify the leukoencephalopathy complication at an early stage in patients who are still asymptomatic for this adverse effect.

The precedent exists for treating patients with more severe inflammatory bowel disease with other agents that can cause potentially life-threatening immunodeficiency, such as infliximab, said Dr. Podolsky, chief of gastroenterology at Massachusetts General Hospital in Boston.