Natalizumab Helps Normalize Life With Crohn's

Maintenance therapy produced quality of life scores that were similar to those in normal populations.

BY MITCHEL L. ZOLER
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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 in November (N. 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Natalizumab was approved by the Food and Drug Administration in late 2004 for treating multiple sclerosis, and then was withdrawn from the U.S. market in February 2005 following reports that associated its use with cases of multifocal leukoencephalopathy.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 α_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 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 of the 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.

In contrast, the scores of patients in the placebo arm were consistently and significantly lower than scores of the normal, general population, Dr. Feagan said. ■

Safety Issues Call for Selective Use

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 the drug was withdrawn from the market, the two companies that comarket it as Tysabri 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, one of the two companies jointly developing and marketing natalizumab.

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

"That's good news," Dr. Feagan said. "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 (N. 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.

Sargramostim Improves Quality of Life in Crohn's Disease

BY MITCHEL L. ZOLER
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COPENHAGEN — Daily treatment with sargramostim led to significantly improved quality of life in patients with moderate to severe Crohn's disease in a study with 124 patients.

"In addition to reducing disease severity scores, sargramostim appears to significantly improve quality of life," as measured with both the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Short Form-36, Joshua R. Korzenik, M.D., said at the 13th United European Gastroenterology Week.

Treatment with sargramostim, a yeast-derived, recombinant human granulocyte-macrophage colony-stimulating factor, is a striking departure from therapy with the immunosuppressive agents usually used to treat Crohn's disease.

The rationale is that sargramostim may help maintain the innate intestinal immune barrier and may also augment host defenses and reduce the inflammation associated with Crohn's.

The main efficacy end point of the study was a change in disease severity as measured with the Crohn's Disease Activity Index (CDAI) score.

A report published last May by Dr. Korzenik and his associates said that daily treatment with 6 mcg/kg sargramostim administered by subcutaneous injection failed to achieve the study's primary end point, a 70-point or greater drop in the score after 57 days of treatment. The 54% rate of this response with sargramostim wasn't significantly better than the 44% rate in the placebo group.

Remissions occurred in 40% of the sargramostim patients and 19% of the placebo group; clinical response occurred in 48% and 26%, respectively.

But sargramostim treatment did achieve two secondary end points: It produced a significant increase in clinical response, defined as a 100-point or greater decline in the CDAI score by day 57. By this measure, responses occurred in 48% of the sargramostim-treated patients, compared with 26% in the control arm. The drug also produced more remissions at day 57, defined as a CDAI score of 150 points or less, the researchers reported (N. Engl. J. Med. 2005;352:2193-201).

Remissions occurred in 40% of the sargramostim patients and 19% of the placebo group.

The study was sponsored by Berlex, which markets sargramostim (Leukine). The drug has several approved indications in the United States: following induction chemotherapy in patients with acute myelogenous leukemia; before and after transplantation of autologous peripheral blood progenitor cells; for myeloid reconstitution after autologous or allogenic bone marrow transplantation; and for bone marrow transplant failure or engraftment delay.

Dr. Korzenik has been a consultant to and lecturer for Berlex and for several other companies. He is codirector of the Massachusetts General Hospital Crohn's and Colitis Center, Boston.

In the new quality of life analysis, IBDQ scores were significantly better in the sargramostim group than in the placebo group by 29 days after the start of treatment, and this advantage was maintained throughout the 57-day treatment period and out to 30 days following the end of treatment. After 57 days, the IBDQ scores, which measure quality of life, had risen by a mean of 15% in the placebo group and 24% in patients taking sargramostim.

Sargramostim treatment also produced notable improvements in vitality and social subscores, suggesting that the treatment increased energy for everyday activities. The vitality subscore of the SF-36 increased by 68% over baseline by day 57. The social subscore of the IBDQ improved by an average of 14% when measured 30 days after stopping treatment, compared with a 4% increase in the placebo group. The social score of the SF-36 improved by 25% in the sargramostim group.

Drug treatment also led to improvements in systemic pain and bowel symptom scores, variables of great concern to patients with Crohn's disease, he added. Bowel symptoms decreased by 23%-33%. The degree of improvement varied depending on when measurements were made during the study. Systemic pain scores had decreased 39% after 57 days of treatment and 45% at 30 days after treatment ended. ■