# Adalimumab Holds Crohn's Disease in Check

## *A larger study is underway to definitively assess the drug's long-term efficacy for preventing recurrence.*

BY MITCHEL L. ZOLER
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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, Dr. William J. Sandborn 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 adalimumab 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 gastroenterologist and 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.

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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 ($P = 0.06$). ■

# Prescription NSAIDs Did Not Trigger IBD Flares

BY BRUCE JANCIN
*Denver Bureau*

HONOLULU — The use of prescription NSAIDs did not promote flares of inflammatory bowel disease in a large observational study, Dr. Faten N. Aberra reported at the annual meeting of the American College of Gastroenterology.

This has been a controversial issue, as previous studies have yielded conflicting results. But those studies were uncontrolled and/or small in size, said Dr. Aberra of the University of Pennsylvania, Philadelphia.

She used data from the U.K. General Practice Research Database for the years 1988-1997 to conduct a matched, case-crossover study in which patients were their own controls. Dr. Aberra identified 1,205 patients with Crohn's disease who experienced a collective 2,622 flares requiring treatment after at least a 4-month period of remission, and 2,029 ulcerative colitis patients with 5,227 flares during 4 years of follow-up.

An NSAID was prescribed within the 60 days prior to 3.9% of the ulcerative colitis flares and 5.1% of the Crohn's disease flares. The adjusted odds ratio for exposure to a prescription NSAID within 60 days before a Crohn's disease flare was 0.85, and for an ulcerative colitis flare was 1.18, with neither being statistically significant.

Exposures to NSAIDs within 15, 30, and 45 days yielded similar results, as did prescription NSAID exposures 2-4 months before a disease flare.

The results of this study don't rule out the possibility that a small percentage of patients with inflammatory bowel disease are especially sensitive to NSAIDS, but the findings do indicate that most patients in remission can tolerate the drugs without raising their risk of a flare, Dr. Aberra said.

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**DR. ABERRA**

Audience members questioned the validity of the study results, given that the U.K. database didn't include any information on over-the-counter NSAIDs. Dr. Aberra replied that over-the-counter NSAIDs are taken in lower doses and for shorter durations than are prescription regimens, so if prescription NSAIDs weren't associated with inflammatory bowel disease flares, it's unlikely that over-the-counter NSAIDs would be. ■

# *Sargramostim Improves Quality Of Life in Patients With Crohn's*

BY BRUCE JANCIN
*Denver Bureau*

HONOLULU — Sargramostim shows considerable promise as a novel treatment for Crohn's disease, Dr. Suzanne Laplante reported at the annual meeting of the American College of Gastroenterology.

She reported on 124 patients with moderate to severe Crohn's disease who participated in the phase II New Opportunities to Verify Evolving Logic in Crohn's Disease (NOVEL) trial. They were randomized 2:1 to sargramostim (Leukine)—a granulocyte-macrophage, colony-stimulating factor—at 6 mcg/kg per day subcutaneously, or to placebo for 8 weeks. All patients also received background antibiotics and/or 5-aminosalicylic acid compounds as needed.

Sargramostim resulted in a significant reduction in disease severity. The remission rate at 8 weeks was 40% in the sargramostim group and 19% in the placebo group. The clinical response rate, as defined by at least a 100-point drop from baseline in the Crohn's Disease Activity Index, was 48% with sargramostim and 26% with placebo, said Dr. Laplante of Schering AG Germany in Berlin.

But her main focus was on the drug's impact on quality of life, increasingly seen as a major clinical end point in the management of chronic incurable diseases such as Crohn's disease, heart failure, and arthritis.

Clinically meaningful quality-of-life improvements were noted in the Inflammatory Bowel Disease Questionnaire (IBDQ) as early as day 29 in the sargramostim group. At 30 days after the conclusion of treatment, patients in the sargramostim group averaged a 20% improvement over baseline in their IBDQ scores, compared with a 7% gain in the placebo arm. Patients in the sargramostim group had moderate to large improvements in three of the four IBDQ subscales—social function, bowel symptoms, and systemic symptoms—with only the emotional subscale showing no significant change.

Quality of life was also measured by the Short Form-36 Health Survey. Moderate to large improvements in the general health, bodily pain, social function, vitality, and physical component summary scores were observed in the sargramostim group as early as day 15.

Sargramostim is classified as a biologic response modifier. Its FDA-approved indications are to accelerate recovery of white blood cells after chemotherapy and in conjunction with bone marrow or stem cell transplantation. Recent evidence that Crohn's disease results from impairments in innate immunity provided the rationale for developing sargramostim through the NOVEL clinical trials program as an alternative to antibiotics, corticosteroids, immunosuppressants, and tumor necrosis factor-α inhibitors.

Sargramostim activates intestinal immune defenses. The biologic response modifier promotes production of cytokines, including tumor necrosis factor-α and interleukin-1. Those cytokines are thought to play an important role in regulating intestinal inflammation secondary to the defects in mucosal epithelial barrier function that are believed to figure centrally in Crohn's disease, Dr. Laplante said. ■