# Remission Achieved by 60%

**Infliximab** *from page 1*

than 220, and no prior treatment with a steroid or immunomodulator.

The study was sponsored by Centocor and Schering-Plough. Centocor markets infliximab (Remicade) in the United States, and Schering-Plough markets the drug in all other countries. Dr. D'Haens has served as a consultant and speaker for both companies.

The 65 patients in one group were randomized to treatment that started with three infusions of infliximab at weeks 0, 2, and 6, and daily treatment with 2-2.5 mg/kg azathioprine. Patients in this group who relapsed received another infusion of infliximab, and if they relapsed again they were treated with a steroid.

The remaining 64 patients were randomized to start treatment with either topical budesonide or oral prednisone, at a daily dose of 40 mg. Patients in this group who relapsed were again treated with a steroid plus azathioprine. If they relapsed a second time, they received a three-dose course of infliximab.

**'Steroids are not necessary for treating Crohn's disease.' Infliximab plus azathioprine is a superior regimen.**

**DR. D'HAENS**

The study's primary end point was the remission rate at 6 and 12 months after starting treatment. Remission was defined as having a Crohn's disease activity index of less than 150, with no ongoing need for steroid treatment and no surgical resection. After 6 months, the remission rate was 60% in the infliximab-first group and 41% in patients who received steroids first, a statistically significant difference. After 12 months, the remission rate was 61% in the infliximab-first patients and 50% in those given steroids first, a nonsignificant difference.

Of the infliximab-first patients, 59% required no additional infliximab beyond their initial three doses during the year of follow-up. In the steroid-first group, 62% of patients also required treatment with azathioprine.

The study also used a new measure of efficacy, the rate of overall treatment success. This measure tracked the number of patients who reached and maintained a remission after 14, 26, 39, and 52 weeks of treatment. This end point was reached by 29% of patients in the infliximab-first group and 5% of those treated with a steroid first, a statistically significant difference.

After the first 6 months of treatment, no patients in the infliximab-first group were on steroid treatment, while 31% in the steroid-first were on systemic prednisone (average dose, 26 mg/day). At 12 months, no patients in the infliximab-first group and 17% in the steroid-first group were on steroids, at an average daily dose of 23 mg.

A serious adverse event that led to withdrawal from treatment occurred in 9 patients in the infliximab-first group and 10 patients in the steroid-first group. ■

# Certolizumab Shows Safety, Efficacy for Crohn's Disease

BY MITCHEL L. ZOLER
*Philadelphia Bureau*

COPENHAGEN — A new, anti–tumor necrosis factor antibody was safe and effective for treating Crohn's disease for 26 weeks in a study with over 400 patients.

Certolizumab pegol was better than placebo for maintaining responses following induction in Crohn's disease patients, Stefan Schreiber, M.D., said at the 13th United European Gastroenterology Week.

A second Crohn's disease study of certolizumab (Cimzia), a pegylated form of a humanized antibody fragment, is in progress. Patients from both studies will continue to receive the drug for 2 years to gather further safety information. UCB, the Belgium company developing Cimzia, plans to submit all the data early next year to the Food and Drug Administration to apply for a new-drug approval.

Certolizumab is the third anti–tumor necrosis factor (TNF) antibody to be tested on patients with Crohn's disease. Infliximab (Remicade) is already approved for this indication. Adalimumab (Humira) is approved for treating rheumatoid arthritis and psoriatic arthritis, and is being studied in Crohn's disease.

Certolizumab and adalimumab are both administered by subcutaneous injection, making them more convenient treatments than infliximab, which must be administered by intravenous infusion. Studies are underway to assess certolizumab in rheumatoid arthritis.

The study reported by Dr. Schreiber began with 668 patients who had a Crohn's disease activity index (CDAI) score at baseline of 220-450 points, indicating active disease. All patients received three 400-mg doses of certolizumab, given at 2-week intervals. Following the induction phase, 428 patients (64%) had a clinical response, defined as a 100-point or better drop in their CDAI score. The fraction of patients who responded to certolizumab was similar in size to the fraction who responded in prior studies of infliximab and adalimumab.

The responders were then randomized to a maintenance regimen of 400-mg certolizumab injected every 4 weeks or placebo for an additional 22 weeks. After 26 weeks of treatment, 63% of patients who continued on certolizumab and 36% of patients on placebo remained responders, with at least a 100-point improvement in their CDAI score compared with baseline, said Dr. Schreiber, professor of medicine and gastroenterology at Christian-Albrechts University in Kiel, Germany.

Similar responses were seen in patients who entered the study with high serum levels of C-reactive protein, in patients who were on immunosuppressive drugs at baseline, and in patients who had previously failed treatment with infliximab.

The percentage of patients who reached remission, defined as a CDAI score of 150 or less, was 47.9% of those maintained on certolizumab, compared with 28.6% of those who received placebo. In addition, 60% of patients maintained on certolizumab had an improved quality of life, compared with 43% in the placebo group.

The rate of serious adverse events was similar in the two groups, and certolizumab was generally well tolerated, said Dr. Schreiber. One patient treated with the drug developed active tuberculosis.

An antibody reaction to certolizumab developed in 8%. Allthough not yet assessed, the major potential impact is that the antibody might blunt the drug's benefit. Certolizumab has a lower protein content than infliximab and adalimumab and is the only pegylated agent. ■

# *Genetic Mutations Linked to Need for Ileocolic Resection in Crohn's Disease*

PHILADELPHIA — More than half of patients with Crohn's disease who required an ileocolic resection carried at least one mutation in a gene known as *NOD2*, according to a pilot study of 50 patients.

The 52% prevalence of one or more *NOD2* mutations in patients who needed surgery contrasts with the 10%-35% prevalence of *NOD2* mutations in all Crohn's disease patients previously reported to have had *NOD2* testing. This finding suggests *NOD2* mutations predispose these patients to a more severe disease that requires surgical management, Lisa S. Poritz, M.D., said at the annual meeting of the American Society of Colon and Rectal Surgeons.

The apparent link between mutations in the *NOD2* gene and more severe Crohn's disease is unexpected because people with these mutations have reduced levels of nuclear factor (NF) kappa B, a transcription factor that raises levels of cytokines and other molecules that enhance immune responses. Results from other studies had indicated that levels of NF kappa B are higher in patients with Crohn's disease, and hence *NOD2* gene mutations were expected to reduce NF kappa B levels and produce less severe forms of Crohn's disease.

The study involved screening for *NOD2* mutations in blood samples from all patients who underwent ileocolic resections for Crohn's disease at the Milton S. Hershey Medical Center in Hershey, Pa., during 1992-2004; so far, tests have been completed on the first 50 of these patients.

*NOD2* mutations were found in 26 of the 50 patients (52%), Dr. Poritz said. When the clinical characteristics of patients with *NOD2* mutations were compared with those of the 24 patients without mutations, there was no significant difference in the age of Crohn's disease onset, time to first surgery, or percentage of patients needing more than one abdominal surgical procedure. The findings suggest *NOD2* mutations do not affect the incidence of recurrent Crohn's disease after ileocolic resection, said Dr. Poritz, chief of colon and rectal surgery research at the Hershey Medical Center.

**—Mitchel L. Zoler**

# Curbing Inflammation May Reduce Gastrointestinal Ca Risk in Crohn's

MONTREAL — The risk for gastrointestinal cancer in Crohn's disease appears to be higher among patients who continue to have inflammatory disease and lower among those treated with steroids, the immunosuppressive agent azathioprine, or surgery.

The findings in an 11-year retrospective analysis "suggest controlling the inflammation, or the disease activity, can reduce or eliminate any risk of GI-related cancer," Elizabeth Strevel, M.D., of the University of Toronto, said in an interview.

The investigation, which she presented as a poster at the World Congress on Gastroenterology, used databases to review the cases of 1,351 Crohn's disease patients hospitalized at the city's teaching centers. Of those patients, 65 had one or more malignancies, 37 of which originated in the gastrointestinal tract.

Patients who had a surgical intervention were at a decreased risk of malignancy of all types (odds ratio [OR] 0.4), as were patients who were given azathioprine (OR 0.4). A similar association was found for the use of steroids (OR 0.5).

"When we looked at all malignancies, indicators of increased inflammation, such as fistula, increased the risk of cancer," said Dr. Strevel, noting an odds ratio of 1.7. "That became more prevalent when we did a subgroup analysis, just in the GI cancer group. It indicated that what we found in the whole group was probably just an effect of the GI cancers. Also, we found that the effect of the immunosuppressive agent azathioprine became more strongly protective in the subgroup, indicating that the effect is mostly on GI cancers," Dr. Strevel said.

"While malignancy isn't overly present in Crohn's disease, it is obviously a complication with a lot of morbidity and mortality," she explained.

"Given the numbers, it would be hard to do a randomized controlled trial. But a prospective cohort study following these people in a database, seeing what happens and assessing, will provide more accurate information," she added.

**—Bob Babinski**