Rosiglitazone Found to Quell Ulcerative Colitis

In a study of 105 patients, 44% of those taking Avandia had clinical remission, vs. 23% on placebo.

BY KERRI WACHTER
Senior Writer

WASHINGTON — Rosiglitazone shows some promise in reducing ulcerative colitis activity and may offer an alternative to conventional therapy for patients who fail to respond to the latter approach or can't tolerate it, said Dr. James D. Lewis at the annual Digestive Disease Week.

Rosiglitazone (Avandia) reduced disease activity significantly, compared with placebo in patients with mild to moderate ulcerative colitis activity.

In the study of 105 patients, 44% of those taking rosiglitazone achieved clinical remission—defined as at least a 2-point drop in the disease activity index at 12 weeks—compared with 23% of those on placebo.

Fifty-two patients were randomized to receive 4 mg rosiglitazone twice daily, and 53 received placebo. Most of the patients were male (79%), with an average age of 44 years.

"Rosiglitazone may represent a novel approach to the treatment of mild to moderately active ulcerative colitis and conceivably has a role in those patients who fail to respond to or are unable to tolerate 5-aminosalicylic acid therapy," said Dr. Lewis, associate director of the University of Pennsylvania Health System's Inflammatory Bowel Disease Program in Philadelphia.

Dr. Lewis disclosed that he has received grants and research support from GlaxoSmithKline, maker of Avandia. The company also supplied rosiglitazone for this study.

Patients had to have been treated with at least 2 g/day of 5-aminosalicylic acid for at least 4 weeks prior to randomization, or they had to have documented intolerance to this therapy. Corticosteroids were allowed, as long as the patient was on a stable dose for at least 4 weeks or taking no more than 20 mg/day of prednisone or the equivalent.

Immunomodulators (azathioprine and 6-mercaptopurine) were also allowed if the patient had been treated with these for at least 4 months and was on a stable dose for at least 2 months. Rectal therapies were also allowed, as long as the dose had been stable for at least 2 weeks prior to randomization.

Patients were excluded if they had diabetes mellitus requiring treatment with a hypoglycemic agent or had New York Heart Association class III or IV heart failure. Patients were also excluded if they were taking cyclosporine, anti–tumor necrosis factor–α drugs, or methotrexate within 2 months of the study.

The researchers used a modified version of the Sutherland and Mayo disease activity indices to assess disease activity. This index (DAI) included four components: stool frequency, physician global assessment, rectal bleeding, and mucosal appearance. Each component could be scored 0-3. Patients were included if they had a score that was at least 4 but no more than 10.

Mucosal appearance could only be assessed at the time of sigmoidoscopy, so the researchers also used a modified disease activity index (mDAI) that excluded mucosal appearance and ranged from 0 to 9 points.

At baseline, patients had a complete DAI calculated and then were randomized. Follow-up occurred at weeks 4, 8, and 12. At weeks 4 and 8, an mDAI was calculated, and at week 12 (study end point) a complete DAI was calculated. During the course of the study, patients were not allowed to increase their usual medications, nor were corticosteroids tapered.

Clinical remission was defined as a final DAI score of no more than 2. Endoscopic remission required a final DAI score of less than 2 and a mucosal appearance score of 0. The researchers defined response as a reduction in DAI score of at least 3 points, as this definition has been used in other trials. Response at weeks 4 and 6 was defined as a reduction from baseline of at least 2 points on the mDAI.

With the more stringent definition of response, more patients on rosiglitazone (37%) responded than patients in the placebo group (13%). Likewise, more patients on rosiglitazone had clinical remission—17%, compared with 2% in the placebo group. In terms of endoscopic remission, 8% in the rosiglitazone group met the criteria, compared with 2% in the placebo group; this difference was not statistically significant.

Rosiglitazone 'conceivably has a role in those patients who fail to respond to or are unable to tolerate 5-aminosalicylic acid therapy.'

In terms of adverse events, lower extremity edema was significantly more common among patients on rosiglitazone—17% vs. 2% for placebo. Patients were more likely to withdraw early because of worsening disease if they were in the placebo arm: 11 patients vs. 4 in the rosiglitazone arm.

In a post hoc analysis, the researchers excluded patients with lower extremity edema during the course of the study. They were concerned that such edema could have unmasked the treatment assignments for these patients because this is a common side effect of rosiglitazone. However, "the results are almost identical to those from our primary intention to treat analysis," Dr. Lewis said.

Rosaglitazone has recently made headlines, based on an analysis of 42 published and unpublished randomized trials showing that patients who received rosiglitazone were 43% more likely to have an MI than were patients who received either an active comparator drug or placebo during the course of 24-52 weeks of treatment (N. Engl. J. Med. 2007 [Epub doi:10.1056/NEJMoa072761]).

In a separate study of more than 33,000 patients with type 2 diabetes, researchers found that the incidence of hospitalizations for heart attack and/or for coronary revascularization for patients on rosiglitazone was the same as for patients on metformin or sulfonylurea (Pharmacoepidemiol. Drug Saf. 2007 [Epub doi:10.1002/pds.1443]). The research involved an observational cohort study from a large U.S. managed care database and was commissioned by GlaxoSmithKline. The study populations were matched to ensure that the cohort groups were similar in terms of their baseline risk factors for cardiovascular disease. Patients were followed for an average of slightly over a year.

In May, the Food and Drug Administration issued a safety alert regarding potential safety issues related to the drug. The agency noted that its "analyses of all available data are ongoing. FDA has not confirmed the clinical significance of the reported increased risk in the context of other studies." ■

Surveillance Intervals After Polypectomy Should Be Narrowed

BY DENISE NAPOLI
Assistant Editor

WASHINGTON — Postpolypectomy surveillance should follow surgery far sooner than current guidelines recommend, according to a study presented at the annual Digestive Disease Week.

In a retrospective cohort study, Dr. Madhavi Rudraraju of the University of Oklahoma, Oklahoma City, and her colleagues including Dr. William Tierney found that the recurrence rate for advanced adenomas following polypectomy was 25.8%, and the time to recurrence was 6.4 months—much sooner than the 3-year follow-up surveillance period recommended by current guidelines (Gastroenterology 2006;130:1872-85).

The researchers analyzed medical records at the VA Medical Center in Oklahoma City from Jan. 1, 1990, to Dec. 31, 2002. The patients had had at least one surveillance colonoscopy following removal of a polyp with high-grade dysplasia (HGD).

Patients under 40 years of age and those with a history of colon cancer were excluded from the study.

There were two control groups: patients with tubular adenomatous polyps, who were matched for polyp size and had at least one surveillance colonoscopy; and those with normal colonoscopy findings who had undergone at least one subsequent colonoscopy. Both groups were also matched for age, gender, race, and year of index colonoscopy.

Polyps with advanced features (adenoma greater than 1 cm; villous histology; HGD; colon cancer) were counted as outcomes of interest. Polyps found in the same region of the colon within 6 months or after documented incomplete polypectomy were counted as residual, rather than incident, lesions, and were therefore excluded.

Most of the patients in all three groups were male and white, and the mean age was 66 years. A total of 89 patients met the study criteria for having HGD.

In the HGD group, the mean polyp size was 1 cm, the mean number of polyps was 4.1, all had complete resection, and 73% were sessile. Polyp characteristics for the tubular adenoma group were similar—mean size was also 1 cm, mean number was 4.4, 79.8% were sessile, and, as in the HGD group, 100% were completely resected.

"At the Oklahoma VA Medical Center, surveillance is performed at the least at 3 and 12 months, but most patients had it at 3 months, 6 months, 9 months, and 12 months," said Dr. Rudraraju. This practice of aggressive surveillance has continued at this facility despite the recent guidelines.

The study found that in the HGD group, 25.8% (23 of 89 patients) went on to develop advanced polyp recurrence, and among those 23 patients, the median time to recurrence was 6.4 months. In contrast, 16.8% (15 of 89) of the tubular adenoma group developed recurring advanced polyps at a median time of 36.6 months after initial polypectomy. In the group with no polyps on initial colonoscopy, 5.6% (5 of 89) developed advanced polyps at a median of 34.8 months later.

The range of advanced polyp development in the HGD group was 2.6-101 months. Overall, 5.6% (5 of 89) developed colon cancer at a median of 6 months after initial polypectomy.

"Until we have further prospective evidence about this group of patients with high-grade dysplasia, it would be very reasonable for clinicians to consider intense early surveillance, given [that] this represents the largest study to date looking at this particular group of patients," said Dr. Rudraraju in an interview.

"Our data demonstrate [that] this group likely has a high rate of synchronous advanced polyps, and an early 'second look' procedure may be necessary to achieve optimal prevention of colorectal cancer."

Dr. Rudraraju conceded that the study had limitations, such as the fact that the researchers did not know their patients' family histories of colorectal cancer, and that pathology specimens were unavailable for review, since it was a retrospective study. ■