Once-Daily Mesalamine Stalls Ulcerative Colitis

BY BRUCE JANCIN
Denver Bureau

HONOLULU — A novel, once-daily high-strength formulation of 5-aminosalicylic acid proved effective for the induction of remission and other end points in patients with active, mild to moderate ulcerative colitis in two large, multicenter, phase III clinical trials presented at the annual meeting of the American College of Gastroenterology.

Mesavance, an investigational agent, has two key advantages over standard mesalamine, noted Gary R. Lichtenstein, M.D. It is released throughout the colon, creating the potential for enhanced efficacy, and can be given once daily, rather three or four times per day as with current oral formulations of mesalamine.

Mesavance is an investigational agent offering two key advantages over conventional mesalamine.

DR. LICHTENSTEIN

"Once-daily administration is likely to increase patient convenience and compliance, and hence is likely to improve outcomes," observed Dr. Lichtenstein, professor of medicine at the University of Pennsylvania, Philadelphia.

The compliance issue has recently taken on increased visibility as a result of a study by Sunanda Kane, M.D., of the University of Chicago, who found up to 68% of ulcerative colitis patients don't take their prescribed mesalamine regularly (Practical Gastroenterology 2004;28:16-22).

Mesavance consists of 5-aminosalicylic acid incorporated into a proprietary drug delivery system. Each tablet contains 1.2 g of 5-aminosalicylic acid in a lipophilic matrix dispersed within a hydrophilic matrix. The tablet is coated with a polymer film that breaks down at pH 7 in the terminal ileum, where the hydrophilic matrix begins to erode, and the 5-aminosalicylic acid starts diffusing out of the lipophilic matrix.

William J. Sandborn, M.D., reported on 343 patients who were randomized to 8 weeks of Mesavance at 2.4 g or 4.8 g once daily, Asacol at 0.8 g t.i.d., or placebo.

The primary end point in the double-blind study was induction of remission, rigorously defined by an Ulcerative Colitis Disease Activity Index score of 1 or less, together with a rectal bleeding and stool frequency score of zero and at least a 1-point reduction in sigmoidoscopy score from baseline. Both doses of Mesavance proved to be more effective than placebo at achieving remission. In contrast, Asacol showed only a nonsignificant trend to be better than placebo. (See box.)

Patients in both Mesavance arms also showed significantly greater clinical improvement, clinical remission, and sigmoidoscopic improvement than did those in the placebo group. The clinical remission rate, as defined by complete resolution of symptoms, wasn't significantly greater with Asacol than with placebo.

The study was not large enough to allow statistically meaningful direct comparisons of efficacy between Mesavance and Asacol, said Dr. Sandborn, professor of medicine at the Mayo Medical School, Rochester, Minn.

Dr. Lichtenstein presented a separate, double-blind study involving 280 ulcerative colitis patients randomized to 8 weeks of Mesavance at 1.2 g b.i.d. or 4.8 g once daily, or placebo. The primary end point—induction of remission—was achieved in 34% of patients on twice-daily Mesavance, in 29% with once-daily Mesavance, and in 13% with placebo. The remission rate in the Mesavance groups diverged from placebo as early as week 2.

Physician global assessment ratings ranked 64% of patients as significantly improved on twice-daily Mesavance, as were 66% on once-daily Mesavance and 39% on placebo, the gastroenterologist said. Mesavance was well tolerated in both studies, exhibiting a minimal side effect profile similar to that of available oral mesalamine products.

Dr. Lichtenstein and Dr. Sandborn are consultants to Shire Pharmaceuticals Group. It plans to file for marketing approval for Mesavance with the Food and Drug Administration by year's end. ■

Mesalamine vs. Asacol for Ulcerative Colitis

End Point	Mesavance 2.4 g once daily	Mesavance 4.8 g once daily	Asacol 0.8 g t.i.d.	Placebo
Sigmoidoscopic improvement	70%	77%	61%	42%
Clinical improvement	61%	65%	56%	40%
Clinical remission	42%	41%	34%	22%
Induction of remission	41%	41%	33%	22%
Complete mucosal healing	33%	37%	33%	18%

Note: Based on a study of 343 patients.
Source: Dr. Sandborn

KEVIN FOLEY, RESEARCH

Doubled Mesalazine Dosage Boosts Ulcerative Colitis Efficacy

BY MITCHEL L. ZOLER
Philadelphia Bureau

COPENHAGEN — Doubling the dose of mesalazine increased the drug's efficacy for moderately active ulcerative colitis in an analysis of more than 400 patients enrolled in two separate trials.

The findings "prove that 4.8 g/day mesalazine produced a clinically meaningful and statistically significant benefit over the standard 2.4 g/day," Stephen B. Hanauer, M.D., said at the 13th United European Gasteroenterology Week. "The results support starting treatment at the higher dose in patients with moderately active ulcerative colitis," said Dr. Hanauer, professor of medicine and clinical pharmacology at the University of Chicago.

Both studies were sponsored by Procter and Gamble, which now markets a 400-mg formulation of mesalazine (Asacol) that is used in a 2.4-g/day regimen for patients with ulcerative colitis.

The results of each study alone, which enrolled patients with either mild or moderate disease, were unable to show statistically that a 4.8-g daily dose, given as six 800-mg tablets, was superior to the 2.4-g dosage. But the results suggested that the higher dosage was especially effective in patients with moderate active disease, leading to a new analysis combining data from both studies. Dr. Hanauer is a consultant and speaker for Procter & Gamble and also receives research support from the company.

The combined studies enrolled 687 patients, of whom 423 had moderate disease and were evaluable after 6 weeks of treatment. Among 223 patients treated with 2.4 g/day mesalazine, 58% had treatment success, compared with a 72% rate among 200 patients treated with 4.8 g/day, a statistically significant difference, reported Dr. Hanauer, who is also chief of the section of gastroenterology and nutrition at the University of Chicago.

Treatment success was defined as an improvement from baseline in physician's global assessment with improvement in at least one of four categories of clinical assessment: stool frequency, rectal bleeding, sigmoidoscopy findings, and patient's functional assessment. Among the over 200 patients with mild disease, the 2.4-g/day dosage led to treatment success in 41% of patients, while 34% had success on the 4.8-g/day regimen, a nonsignificant difference. The results indicate that it's specifically patients with moderate disease who benefit from the higher dose, Dr. Hanauer said. Both dosages had similar safety profiles and were well tolerated.

The 4.8-g dose was clearly superior, but its advantage over lower dosages was "marginal," suggesting the impact of boosting the dose levels off at 4.8 g/day and little would probably be gained by raising the dose further, he said. The FDA told Procter & Gamble last summer that the 800-mg formulation was approvable for ulcerative colitis; the company and the agency are resolving final issues before approval is granted. ■

Topical Beclomethasone May Relieve Moderate UC

BY MITCHEL L. ZOLER
Philadelphia Bureau

COPENHAGEN — Treatment of mild to moderate, distal ulcerative colitis with topical beclomethasone was about as effective and safe as use of topical mesalazine in a pilot study with 99 patients.

The results suggest that if a patient does not tolerate or respond to topical mesalazine, administered as an enema or as foam, topical beclomethasone may be an option, Livia Biancone, M.D., said at the 13th United European Gastroenterology Week.

But the results are not definitive because the study was small and was done on an open-label basis. Before beclomethasone becomes an alternative to mesalazine, the findings must be confirmed in a larger randomized controlled trial, said Dr. Biancone, a professor of medicine at the University of Rome.

The study was done at 15 centers in Italy. The patients were treated with one of the two study drugs in either an enema or foam formulation once daily, at night, for 8 weeks, meaning they were split into four different treatment groups of 24-26 patients each.

Patients received a daily dose of either 3 mg beclomethasone or 2 mg mesalazine. Beclomethasone is a steroid with high local activity when used topically, but with low systemic activity.

After 4 weeks of treatment, almost 80% of the patients had a partial or complete remission. After 8 weeks, 84% of patients treated with beclomethasone had responded, as had 90% of those treated with mesalazine. About half the patients in each group had a complete remission at 8 weeks.

Disease activity index scores also fell in both groups, from an average score of about 6 at baseline to an average of about 2 after 8 weeks of treatment.

The rates of adverse events associated with the two drugs were also similar. Adverse events occurred in 33% of the beclomethasone patients and in 21% of those on mesalazine. Three patients on each drug withdrew because of an adverse event. No patient treated with beclomethasone showed changes in cortisol levels during or after treatment. ■

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