Digestive Disease Week is the largest international gathering of physicians, researchers, and academicians in the fields of gastroenterology, hepatology, endoscopy, and gastrointestinal surgery. Jointly sponsored by the American Association for the Study of Liver Diseases, the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the Society for Surgery of the Alimentary Tract, the meeting took place from May 20 to 25, 2006, in Los Angeles, California.

Gastroduodenal and Esophageal Ulceration

The ASTERIX study showed that both gastroduodenal ulcers and esophageal ulcers occur less often in at-risk patients who add esomeprazole (Nexium, AstraZeneca) to low-dose aspirin than in those who add placebo. Low-dose aspirin reduces recurrent events in patients with cardiovascular or cerebrovascular disease, but it is also associated with an 11% prevalence of gastroduodenal ulcer, said Angel Lanas, MD, from Clinical University Hospital in Zaragoza, Spain.

The aim of ASTERIX was to compare the incidence of gastroduodenal ulcers among patients taking low-dose, enteric-coated aspirin (75–325 mg/daily) plus either 20 mg daily of esomeprazole or placebo for six months. The double-blind, randomized, parallel-group study was conducted in 80 centers in 11 countries.

Endoscopy was performed at the baseline evaluation, at two months, and at six months. To be enrolled, the patients:

- had to have a medical condition requiring low-dose aspirin.
- had to be 60 years of age or older.
- could not have _Helicobacter pylori_ infection.
- could not have any current or active gastroduodenal ulcers, reflux esophagitis greater than Los Angeles (LA) grade A, or upper gastrointestinal (GI) symptoms calling for treatment.

The main study endpoint was the incidence of gastroduodenal ulcer.

At six months, an analysis among 991 patients (with a mean age of 70) revealed an ulcer-free rate of 98.2% in esomeprazole patients and a 93.8% rate with placebo patients (P < .007). Among patients who did develop ulcers (nine with esomeprazole, 31 with placebo), the size of the ulcer was generally smaller in the esomeprazole group. Furthermore, more esomeprazole patients were free of esophageal lesions at six months (95.6%), compared with those receiving placebo (81.7%) (P < .0001). The esomeprazole patients were significantly less likely to have GI symptoms of epigastric burning, epigastric discomfort, or heartburn.

Esomeprazole 20 mg was well tolerated in these older patients, and discontinuation of therapy by ulcer-free patients was more frequent in the placebo group (13.6% vs. 18.9%).

Dr. Lanas concluded that in this at-risk population, esomeprazole was more effective than placebo in preventing gastroduodenal ulcers, esophageal lesions, and GI symptoms. He also noted that age was the most significant risk factor for GI complications.

Ulcerative Colitis

The Mesalamine Study

A formulation of mesalamine designed to provide both sustained and late release in the colon may increase compliance and thus promote better outcomes compared with existing 5-aminosalicylic acid (5-ASA) therapies. William J. Sandborn, MD, Professor of Medicine at the Mayo Clinic in Rochester, Minnesota, noted that existing 5-ASA formulations require inconvenient multiple-daily dosing with high pill burdens, which are known to be a factor in noncompliance, leading to relapse.

The Sandborn trial evaluated the MMX Multi-Matrix System mesalamine (SPD 476), a novel once-daily 5-ASA formulation with a gastro-resistant pH-dependent coating allowing transit of the tablet to the distal ileum. The hydrophilic and lipophilic matrices also afford gradual 5-ASA release throughout the colon.

The aim of the study was to assess the efficacy of MMX mesalamine in a pooled population from two phase 3 randomized, double-blind trials (SPD 476-301 and SPD 476-302). These patients had mild-to-moderate ulcerative colitis (UC) with scores of 4 to 10 on the modified Ulcerative Colitis Disease Activity Index (UC–DAI). All patients experienced relapses six weeks or less before their baseline evaluations.

Patients received either 2.4 g/day (n = 172) or 4.8 g/day (n = 174) of MMX mesalamine or placebo (n = 171) over an eight-week treatment period. In both studies, the primary endpoint was clinical and endoscopic remission at eight weeks. The UC–DAI modification included a more stringent definition than was customary for remission. The mean age of the patients was approximately 43 years; 60% of the participants had moderate-severity UC and 40% had mild-severity UC.

The rate of remission was significantly increased, compared with placebo, in both MMX mesalamine groups (with a dose of 2.4 g/day, 37.2%; with 4.8 g/day, 35.1%; P < .001 for both doses). Clinical improvement, indicated as a reduction in modified UC–DAI scores of three or more points from the baseline, was significantly higher as well for MMX mesalamine (with a dose of 2.4 g/day, 58.1%; with 4.8 g/day, 62.1%; and with placebo, 32.7%; P < .001 for both doses).

Remission rates were not significantly higher among women. Treatment failures were significantly less common with MMX mesalamine (25% with 2.4 g/day; 22% with 4.8 g/day; 50.9% with placebo; P < .001 for both doses vs. placebo).

MMX was well tolerated; the rates of adverse events were comparable to those of placebo (with a dose of 2.4 g/day, 36.2%; with 4.8 g/day, 32.4%; and with placebo, 34.6%). Dr. Sandborn concluded that MMX mesalamine effectively induced remission in patients with mild-to-moderately active UC.

“Effective once-daily dosing with MMX mesalamine has the
potential to increase compliance relative to existing 5-ASA therapies. Increased compliance rates are expected to improve overall treatment outcomes,” he said.

**ACT 1 and ACT 2 Trials**

Dr. Sandborn also presented data on the impact of remission on employment status in study of ulcerative colitis (UC) in patients randomly assigned to receive, in a ratio of 1:1:1, placebo, infliximab (Remicade, Centocor) 5 mg/kg, or infliximab 10 mg/kg. In the overall study—the ACT 1 and ACT 2 trials among 728 patients with moderately to severely active UC—significantly more patients (P < .001) had clinical responses with either infliximab dose than with placebo. The current analysis of these studies looked at the impact of remission on patients’ employment and disability status, hours per week actually worked, productivity, and hours per week in which patients were fully productive.

At the baseline, 35.4% of patients were not employed; 7% were receiving disability compensation. Among patients not employed at the baseline, at the 30th week, 20.6% (14/68) of those in remission were employed; 8.3% (9/108) of those who were not in remission were employed.

In the ACT 2 trial, which followed patients up to 54 weeks, 30.4% (14/46) of those who were in remission were employed; 8.8% (3/34) of those who were not in remission were employed.

The differences between the remission and non-remission groups were significant in both cases (P < .05). Among patients who were receiving disability compensation at the baseline, a greater percentage of those in remission were no longer receiving such compensation than those not in remission at week 30 (58.8% [10/17 patients] vs. 20% [3/15 patients]) (P = .06). Furthermore, patients in remission at week 30 had significantly greater increases in hours per week actually worked (P < .001) and productivity (P < .05) than patients who were not in remission.

Dr. Sandborn concluded that remission in patients with UC is associated with improved employment and disability status, hours per week actually worked, productivity, and fully productive work hours.

When asked whether it was obvious that patients in remission would function better, he responded:

“At the most superficial level, it’s a ‘no-brainer’ that patients in remission should have improved their employment rates.” However, he said, no information is published as to whether the definitions of remission that have been used to approve drugs for UC would lead to an improved ability to work.

“The current study demonstrates that this is in fact the case. A study showing a significant impact of remission on employment validates the measure.”

**The important take-home message?**

“Achieving remission should be the key therapeutic goal in managing ulcerative colitis.”

**Crohn’s Disease**

A study of Crohn’s disease (CD) also evaluated the effect of treatment on patients’ ability to participate in work and leisure activities, with a double purpose of validating both the treatment strategy and the measure itself.

Brian K. Dieckgraefe, MD, PhD, Associate Professor of Medicine at Washington University School of Medicine in St. Louis, Missouri, and Joshua Korzenik, MD, at Massachusetts General Hospital in Boston, pioneered a counterintuitive treatment strategy. They based their approach on an understanding that in individuals with CD, the innate immune system mounts an inadequate response to the presence of bacteria and bacterial products. They hypothesized that CD ensues when the adaptive immune system produces a secondary T-cell response.

Their approach has been to fortify the innate immune system with sargramostim granulocyte–macrophage colony-stimulating factor (GM-CSF) (Leukine, Berlex). It is believed that this hematopoietic growth factor extends the lives of neutrophils, monocytes and macrophages, and dendritic cells, all of which are active as a first defense against infection.

Dr. Korzenik’s clinical trial showed that sargramostim induced a significant clinical response and promoted remission of symptoms in patients with moderately to severely active CD more often than placebo.

At the meeting, Dr. Dieckgraefe presented a study that examined the effects of sargramostim therapy on 124 CD patients’ attendance at work or school and their ability to engage in leisure and sport activities. The focus was on items 4 (work, school) and 12 (leisure, sports) in patients’ social function subscores of the Inflammatory Bowel Disease Questionnaire (IBDQ).

Dr. Dieckgraefe reported that sargramostim treatment significantly improved patients’ ability to attend work or school by up to 25% (1 point) in those receiving sargramostim and by 13% (0.6 points) in the placebo group. Participation in leisure and sport activities improved by 42% (1.4 points) with sargramostim versus 23% (0.8 points) with placebo. He underscored the significant improvements achieved with sargramostim in the questionnaire’s social function subscores, noting that, in previous research, this parameter had been the slowest to demonstrate significant progress.

He concluded: “The key point is that this paradoxical approach to treatment via stimulating innate immunity has favorable outcomes.”

**REFERENCES**


