

# Therapies for Celiac Disease Show Early Promise

BY ALICIA AULT

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SAN DIEGO — Two new therapeutic approaches to celiac disease modestly improved patients' gluten tolerance, based on the results of early studies reported at a press briefing at the annual Digestive Disease Week.

The results of a third trial suggested diagnostic criteria for the disease may be too strict, leaving many patients with early-stage disease undiagnosed and untreated.

Celiac disease is a T-cell-mediated autoimmune disorder that is characterized by small intestinal inflammation, injury, and intolerance to gluten found in wheat, rye, and barley products. It affects about 3 million people in the United States. The small intestine primarily is affected, but the disorder is associated with a range of other systemic effects includ-

ing malnutrition, bone mineral loss, anemia, and delayed growth. Treatment is limited to a gluten-free diet, but dietary adherence is difficult and response to diet is poor in up to 30% of patients.

Results were presented from a phase IIb study of larazotide acetate (AT-1001), a novel oral drug that inhibits intestinal barrier dysfunction being developed by Alba Therapeutics Corp. in Baltimore.

Dr. Daniel Leffler and his colleagues—from Beth Israel Deaconess Medical Center, Boston; the Mayo Clinic, Rochester, Minn.; and the South Hills Endoscopy Center in Pittsburgh—reported on 86 patients who had biopsy-proven celiac disease and were in remission for at least 6 months. They were randomized to one of seven treatment arms, including placebo and various doses of the active drug, with or without a gluten challenge, for 14 days. The drug

was taken three times daily.

The primary end point was intestinal permeability, as measured by the urinary lactulose/mannitol ratio. None of the 69 patients who completed the study met the primary outcome in the 14-day study period. In ad hoc analyses, however, permeability was significantly improved by day 21, said Dr. Leffler of the divisions of clinical nutrition and gastroenterology.

Alba aims to launch a larger phase II study, and planning for phase III has already begun, he said. The drug was well tolerated and undetectable in serum, making it a potentially safe addition or alternative to a gluten-free diet.

Working with Alvine Pharmaceuticals Inc., Dr. Peter Watson, of the Belfast City (Ireland) Hospital Trust performed a double-blind crossover study of another therapeutic designed to aid gluten di-

gestion. Twenty celiac disease patients were randomly assigned to receive 5 g of gluten pretreated with a combination of enzymes or 5 g of untreated enzymes. The enzymes, prolyl endopeptidase and endopeptidase-B2, were synthesized from microorganisms and barley. The enzymes hypothetically could help celiac disease patients fully digest gluten and so avoid inflammation and symptoms. After treatment, there was no significant difference in symptom profiles, but 10 patients had a decrease in fecal fat levels, indicating increased gluten tolerance.

Currently, the diagnosis of celiac disease is confirmed by a biopsy showing small bowel mucosal villous atrophy with crypt hyperplasia (Marsh III). But Dr. Markku Mäki of the University of Tampere (Finland) presented results of a randomized, prospective study indicating that celiac disease

damage occurs gradually with clinical symptoms appearing well before histologic damage.

He and his colleagues at Tampere and the University of Helsinki identified 23 patients (out of 145 consecutive cases) who had only intraepithelial lymphocytosis with or without crypt hyperplasia and randomized them either to a gluten-free diet or a normal diet.

A year later, clinical, serologic, and histologic exams were repeated. Villous architecture had deteriorated, and symptoms and antibody titers were unchanged in the normal diet group, whereas symptoms, antiglutin antibodies, and mucosal inflammation were all significantly reduced in those who restricted gluten.

He urged more studies before changing diagnostic criteria, but urged considering celiac disease in all symptomatic patients and a trial of dietary restriction. ■

## Fundoplication Beat Medical Treatment in Taming GERD

BY JEFF EVANS

Senior Writer

PHILADELPHIA — Laparoscopic Nissen fundoplication appears to offer better overall control of gastroesophageal reflux disease symptoms than does optimized medical therapy for patients who are stable and symptomatically controlled on long-term medical therapy, according to a randomized study of 101 patients.

At 3 years after the start of the trial, surgical patients generally had more symptom-free days, greater satisfaction with their control of symptoms, less esophageal acid exposure, and better quality of life than did patients who received optimal proton pump inhibitor (PPI) therapy throughout the trial, Dr. Mehran Anvari reported at the annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons.

In a randomized, nonblinded study, Dr. Anvari, director of the centre for minimal access surgery at McMaster University, Hamilton, Ont., and his colleagues compared the 3-year results of 101 patients who underwent either laparoscopic Nissen fundoplication or optimized PPI therapy.

The patients had controlled their GERD symptoms with PPIs but still required long-term PPI therapy. All of them had been taking PPIs continuously for at least 1 year and had good symptom control—a GERD symptom scale (GSS) score of less than 18 on a range of 0-60 and a visual analog scale score of greater than 70 on a range of 1-100.

The operations were done by four surgeons who each had performed more than 50 laparoscopic Nissen fundoplication procedures. Surgical patients stopped using PPIs after their operation. Patients randomized to medical therapy received treatment using a standardized management protocol based

on best evidence and published guidelines.

The average GSS scores were similar in both groups at 1 and 3 years. At 3 years, the 51 patients randomized to surgery had an average of nearly 7 symptom-free days a week, compared with about 6 a week in the 50 patients randomized to medical therapy. Unlike medical therapy, surgery was associated with normalization of lower esophageal sphincter pressure.

On 24-hour pH monitoring at 3 years, surgical patients spent a mean of 2% of the duration of monitoring with a distal esophageal pH less than 4, but patients on medical therapy spent more than 4% of the duration with a pH below 4 even though they remained on PPIs. However, each group had a similar drop in the percentage of time spent at a pH less than 4.

At 3 years, satisfaction with symptom control was 15% higher in surgical patients than it was in patients on medical therapy. Although both treatments helped patients maintain a high quality of life as measured on the Short Form-36 questionnaire, surgery was superior to medical therapy in improving quality of life, said Dr. Anvari, professor of general surgery at the university.

Treatment failures occurred in 18% of surgical patients (three required revisions because of persistent dysphagia, and six needed PPI therapy) and in 16% of patients on medical therapy (eight required surgery).

"Laparoscopic Nissen fundoplication should be offered to patients requiring more than 2 years of PPI therapy who are seeking alternatives. And it should be a standard for comparison [against] all endoscopic antireflux procedures that are being devised," Dr. Anvari advised.

He reported no relevant conflicts of interest and said there was no industry involvement in the conduct of the study. ■

## 'Optical Biopsy' May Ease Barrett's Diagnosis, Treatment

BY ROBERT FINN

San Francisco Bureau

SAN DIEGO — Two studies presented at the annual Digestive Disease Week indicate that confocal laser endoscopy increases diagnostic yield and is both accurate and safe.

The studies suggest that one day it may be possible to skip a step in the diagnosis and treatment of Barrett's esophagus, Dr. Kerry B. Dunbar said in a news conference. Dr. Dunbar was the senior author of the randomized study and a coauthor of the retrospective study.

In confocal laser endoscopy (CLE), an endoscope is equipped with a microscope that magnifies living cells close to the surface of the GI tract 1,000 times. When used in conjunction with intravenous contrast agents such as fluorescein, acriflavine, and cresyl violet, the microscope allows endoscopists to visualize the abnormal cell growth that is characteristic of cancerous lesions.

In one study, investigators retrospectively combined the results of 2,102 CLE examinations on 1,771 patients at three academic medical centers. They found the "optical biopsy" technique to be 91% accurate compared with standard biopsy. Moreover, the technique changed the initial diagnosis in 32% of the upper GI examinations and 22% of examinations of the lower GI tract.

Complications occurred in only 1% of patients. There were four perforations and four bleeding episodes, which are typical of any endoscopic procedure and not specifically related to CLE. The only CLE-specific complications—five cases of nausea and nine cases of decreased blood pressure—were related to

the intravenous fluorescein.

The other study was a prospective, controlled, crossover trial in which 36 patients underwent both CLE and standard endoscopy (in random order and separated by 2-6 weeks) to identify areas of dysplasia in Barrett's esophagus. The two techniques uncovered about the same number of sites with high-grade dysplasia, but CLE required 60% fewer mucosal biopsies to do so.

Furthermore, 9 of 15 patients (60%) at high risk of high-grade dysplasia and 14 of 21 patients (67%) undergoing surveillance endoscopy following a Barrett's diagnosis required no mucosal biopsies at all during their CLE procedures, because the investigators detected no suspicious sites.

There were no fluorescein-related complications, but pneumonia developed in one patient who underwent CLE.

"Currently the biopsies go out to the pathologist [and] a week later I have to call the patient, discuss the results, do another invasive procedure, and then do a mucosal resection of the areas of dysplasia," said Dr. Dunbar of Johns Hopkins University, Baltimore. "One of the great promises of confocal microscopy is that we instantly get a diagnosis."

Dr. Dunbar said she had no relevant conflicts of interest, but disclosed that one of the investigators in the retrospective study received unrestricted research funding from Pentax, which manufactures a CLE system. The randomized study was funded by the National Institutes of Health and by a research award from the American Society of Gastrointestinal Endoscopy. ■