Celiac Disease Therapies Show Early Promise

BY ALICIA AULT
Associate Editor, Practice Trends

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 small trial indicated that the diagnostic criteria for celiac disease may be too strict, leaving many patients with early-stage disease undiagnosed and untreated.

Celiac disease is a T-cell–mediated autoimmune disorder characterized by small intestinal inflammation, injury, and intolerance to gluten found in wheat, rye, and barley products. Celiac disease affects about 6.5 million people worldwide and 3 million people in the United States. The small intestine primarily is affected, but the disorder is associated with a wide range of other systemic effects including 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 and is being developed by Baltimore-based Alba Therapeutics Corp. Dr. Daniel Leffler and his colleagues—from the 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. Subjects 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 with meals.

The primary end point was intestinal permeability, as measured by the urinary lactulose/mannitol ratio. Among the 69 patients who completed the study, the primary outcome was not met in the 14-day study period. In ad hoc analyses, however, permeability was significantly improved by day 21, reported 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, said Dr. Leffler.

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DR. GREEN

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 digestion.

For the study, 20 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 thus avoid inflammation and symptoms, said Dr. Watson.

After treatment, there was no significant difference in symptom profiles, but 10 patients had a decrease in fecal fat levels, indicating increased gluten tolerance.

Dr. Peter H. Green, director of the celiac disease center at Columbia University, New York, hailed the two studies, saying that they indicated a potential for patients to have a treatment besides diet, which is notoriously difficult to follow. "It's very exciting for [researchers] and patients that the pharmaceutical industry has started to study this," he said.

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 that indicate damage from celiac disease occurs gradually, with clinical symptoms

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'Optical Biopsy' Safe and Effective for Endoscopy

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.

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DR. DUNBAR

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 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.

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.

"One of the great promises of confocal microscopy is that we instantly get a diagnosis: 'Aha, here's the area of dysplasia. I'm going to do a mucosal resection now.' And the patient only gets one sedated procedure," said Dr. Dunbar of Johns Hopkins University, Baltimore.

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. ■

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appearing well before histologic damage.

Dr. Mäki 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. These 23 patients were randomized 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.

Symptoms, antigluten antibodies, and mucosal inflammation were all significantly reduced in those who restricted gluten, Dr. Mäki said.

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

Dr. Green said that until a serum-based diagnostic test was available, intestinal biopsies were likely to remain the diagnostic standard.

Fewer than 5% of Americans with celiac disease have been diagnosed, Dr. Green estimated. "We're all looking for an easier way [than biopsy] to diagnose this disorder." ■