Underdiagnosis of Celiac Disease Continues

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Celiac disease affects an estimated 1% of people in the United States, yet only about 3% of people with the disease are being diagnosed, Dr. Peter H.R. Green said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Reasons for the poor rate of diagnosis are multifactorial, said Dr. Green, who directs Columbia University's Celiac Disease Center in New York. They include:

► **A shift to the silent form of celiac disease.** "The patients and the doctors are on the wrong pages in the [medical] textbooks," he said. "The patients got it wrong in that they forgot to get diarrhea, and the doctors got it wrong in that they thought that all patients with celiac disease had to have diarrhea." In fact, he explained, only about half of celiac disease patients present with diarrhea.

So-called silent modes of presentation include bone disease, weight loss, dermatitis herpetiformis, psoriasis, chronic urticaria, and anemia, including iron-deficiency anemia.

"There are increased rates of atopy and there are oral manifestations [in the form of] dental enamel defects such as yellow spots, white spots, and brown spots," he added.

High-risk groups that Dr. Green screens include patients with a family history of celiac disease, patients with type 1 diabetes, and those with primary biliary sclerosis and Sjögren's syndrome.

► **Physicians' failure to recognize celiac disease.** Physicians "are taught that it's a rare condition," he said, when in fact it is not and the clinical manifestations vary widely. "That's one of the reasons why there is such a low rate of diagnosis, because no one set of doctors [is] looking at all of those patients."

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DR. GREEN

► **Lack of support from the pharmaceutical industry.** "We know that over 80% of medical research is financed by the pharmaceutical industry, and by far the bulk of postgraduate education is financed by the pharmaceutical industry," said Dr. Green, who is also a professor of medicine at Columbia.

The major sources of referrals to Columbia's Celiac Disease Center are neurologists. Other common sources of referral include gynecologists, endocrinologists, and rheumatologists.

In patients with suspected celiac disease, Dr. Green and his associates consider a panel of tests that include the tissue transglutaminase 2 (tTG)-IgA, the tTG-IgG, the IgA endomysial antibody (EMA), and total IgA level. "The best test is probably tTG-IgA, and throw in the tTG-IgG," he said. "The IgA endomysial antibody need not be done routinely, but it's of value in difficult cases."

The accepted standard for diagnosis is a biopsy of the descending duodenum. Most celiac disease patients (90%) will have a Marsh III lesion on biopsy, which includes partial, subtotal, and total villous atrophy.

Patients with celiac disease face a 10-fold increased risk of having at least one other autoimmune disease.

Various malignancies have also been linked to having celiac disease, including esophageal and head and neck squamous cell carcinoma, small intestinal carcinoma, and non-Hodgkin's lymphomas.

The management of celiac disease is a lifelong gluten-free diet, which Dr. Green said is difficult to follow in the United States. He recalled seeing gluten-free options on the menu at an ice cream store in Buenos Aires. In Argentina, he said, "there's a lot of celiac disease, and people have very good services."

Dr. Green predicted that more people will be diagnosed with celiac disease as physicians learn about the wide variability of clinical presentation and the availability of sensitive and specific tests. "As more people become diagnosed, there will be greater awareness, and then people with celiac disease will get a better deal in this country." ■

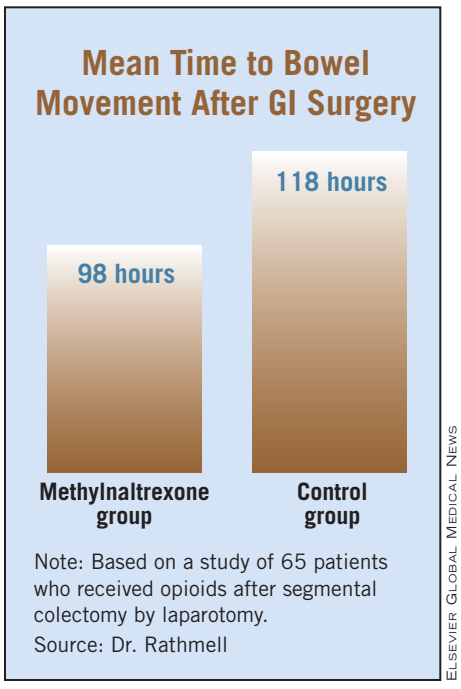
Methylnaltrexone Relieves Opioid-Induced Constipation Without Tachyphylaxis

BY BRUCE JANCIN
Denver Bureau

DALLAS — Backed by two positive phase III randomized trials, methylnaltrexone is now under Food and Drug Administration review for treatment of opioid-induced constipation in patients with advanced illness.

The investigational drug, a quaternary derivative of naltrexone, offers significant advantages over conventional laxatives for this tough-to-treat condition, Dr. Jay Thomas said at the annual meeting of the Society of Hospital Medicine.

The response to subcutaneous methylnaltrexone is rapid, with most responders in the two double-blind, randomized, placebo-controlled phase III trials having a bowel movement within 1 hour—and many within 30 minutes, he said.



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Moreover, efficacy persists without tachyphylaxis when methylnaltrexone is administered every other day over a 2-week period, added Dr. Thomas, medical director of San Diego Hospice.

There is also interest in pursuing a second indication for methylnaltrexone. The results of a phase II study presented at the meeting indicated that methylnaltrexone—this time given intravenously—accelerated GI recovery and hospital discharge eligibility without affecting opioid analgesia in patients who underwent bowel resection, reported Dr. James Rathmell of Harvard Medical School, Boston.

Dr. Thomas, principal investigator in the two phase III trials that included a total of 288 frail hospice patients with opioid-induced constipation, said about 60% of methylnaltrexone-treated patients had a bowel movement within 4 hours, compared with 13%-15% who got a placebo.

In an interview, he said he sees two major advantages for methylnaltrexone: reduced pill burden, and the speed and smoothness of the drug's effect.

"Sometimes with these patients you have to titrate up the traditional laxatives such that the number of pills they're taking becomes a burden. And there can be an unpredictable response to them. For example, with an oral osmotic like magnesium citrate, sometimes the bowel movement can happen unpredictably—and in some cases explosively and uncontrollably," he explained.

"The people in these studies who responded to methylnaltrexone did so within 30 minutes," Dr. Thomas observed. "Let's say you want to go to the park with your grandkids. You can potentially do a subQ injection with methylnaltrexone and have a response within 30 minutes. If you need help from a caregiver, the caregiver can schedule [his or her] day. So it gives you some control back, especially for very sick advanced-illness patients, like hospice patients.

"Whereas if you do an oral medication," he continued, "it may be hours before you have a response, and you don't know when that response is going to happen. If you're in the park with your grandkids, you may have a hard time dealing with it."

Methylnaltrexone reverses the slowing of GI transit caused by opioids. Importantly, there was no sign of central opioid withdrawal or loss of analgesic effect in the 2-week study.

The most common methylnaltrexone-related side effect was mild to moderate abdominal pain in 29% of patients. There was also an increase in flatulence and nausea and vomiting. No patients dropped out because of these adverse events, he said.

In a separate presentation, Dr. Rathmell reported on 65 patients who received opioids after undergoing segmental colectomy by laparotomy who were randomized in a double-blind manner to methylnaltrexone or placebo.

Mean time to first bowel movement was 98 hours in the methylnaltrexone group, 20 hours faster than in controls. The methylnaltrexone group was eligible for hospital discharge in a mean of 116 hours, 33 hours sooner than controls. These are clinically meaningful improvements, Dr. Rathmell noted.

All three clinical trials were sponsored by Progenics Pharmaceuticals Inc. ■

FDA to Allow Tegaserod Use in Certain Patients

The Food and Drug Administration will allow limited use of the irritable bowel syndrome drug tegaserod.

The agent, marketed by Novartis Pharmaceuticals as Zelnorm, will now be available under a treatment investigational new drug (IND) protocol to treat IBS with constipation and chronic idiopathic constipation in women under age 55 who meet specific guidelines, according to the FDA.

"These patients must meet strict criteria and have no known or preexisting heart problems and be in critical need of this drug," Dr. Steven Galson, director of the FDA's Center for Drug Evaluation and Research, said in a written statement. "Zelnorm will remain off the market for general use," he added.

The drug was pulled off the U.S. market in late March in response to an FDA request. At the time, the FDA said that patients taking Zelnorm had a higher risk of adverse cardiovascular events. The relative risk of serious and life-threatening events was 0.1% for Zelnorm and 0.01% for those taking placebo. However, the agency also said it would work with Novartis to find a way to make the drug available to patients who had no other alternatives.

Zelnorm was approved in the United States in 2002 for short-term treatment of women with irritable bowel syndrome with constipation. A supplemental approval was granted in 2004 for chronic constipation in men and women under age 65.

Physicians who think their patients meet the IND criteria should call Novartis at 888-669-6682. Patients or physicians can also contact the FDA's Division of Drug Information at 888-463-6332 for other options.

—Alicia Ault