IBS Drug Pipeline Offers Some Promise

BY PATRICE WENDLING
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MILWAUKEE — There are a number of drugs in the developmental pipeline that likely will offer benefits to different categories of patients with irritable bowel syndrome, Dr. William D. Chey reported at an international symposium sponsored by the International Foundation for Functional Gastrointestinal Disorders.

New drugs would be welcome, given the scarcity of approved agents for irritable bowel syndrome (IBS), particularly since tegaserod maleate (Zelnorm) was withdrawn from the market on March 30 because of a possible increased risk of serious cardiovascular adverse events. But Dr. Chey cautioned that these new drugs won't be a panacea.

"The one thing that's fair to say is that until we get some biomarkers that stratify patients on the basis of pathophysiology, it's unlikely that you're going to see anything better than what I've shown you repeatedly … and that is these statistically significant benefits that are not overwhelmingly impressive," he said.

Drugs for Constipation-Predominant IBS

Renzapride, a mixed 5-hydroxytryptamine (HT) type 4 receptor agonist and 5-HT type 3 receptor antagonist, is currently in phase III clinical trials in the United States for patients with constipation-predominant IBS. In a small phase II trial, renzapride was shown to improve stool consistency and ease of stool passage (Clin. Gastroenterol. Hepatol. 2004;2:895-904). But the study was underpowered and did not reach a secondary outcome of satisfactory relief, said Dr. Chey, associate professor of medicine and director of the GI Physiology Laboratory, division of gastroenterology, University of Michigan Medical Center, Ann Arbor.

Lubiprostone, a chloride channel activator, has just recently been assessed in two phase III trials. Preliminary data suggest that 8 mcg of lubiprostone b.i.d. provided a greater overall response among patients with IBS with constipation than did placebo (17.9% responders vs. 10.1%), Dr. Chey said.

MD-1100 or linaclotide, a potent guanylate cyclase-C agonist that acts luminally to increase the production of cyclic guanosine monophosphate in human colon cells, is heading into phase II trials for both IBS with constipation and chronic constipation. A recent 7-day, multidose phase I study in 48 healthy volunteers reported significant changes in stool consistency, ease of stool passage, stool frequency, and stool weight with MD-1100 (Gastroenterology 2006;130[suppl. 2]:A26).

Asimadoline, a kappa-opioid agonist, was originally developed to treat peripheral pain such as arthritis, and is now in clinical development for the treatment of IBS and postoperative ileus. Early results show decreased sensitivity to balloon distention in a barostat study.

Drugs for Diarrhea-Predominant IBS

Phase II trials were recently completed in the United States for crofelemer, a derivative obtained from the sap of the South American *Croton lechleri* tree. Data from a 12-week dose-ranging study in 246 patients with diarrhea-predominant IBS show significant improvement in pain and a trend toward improvement in stool frequency, said Dr. Chey at the meeting, cosponsored by the University of Wisconsin.

R-verapamil, a calcium channel antagonist, is expected to go into phase II clinical study in the United States sometime in 2007. In one small unpublished eastern European study, R-verapamil was shown to be of benefit for patients with IBS and diarrhea, Dr. Chey said.

There is also very elegant and interesting basic science work and supportive preliminary clinical data suggesting that corticotropin-releasing factor antagonists might offer benefits to patients with IBS and diarrhea. Also being studied are α-agonists, including the compound AGN 203818, in later-stage development, and clonidine as well as the benzodiazepine derivatives, tofisopam and dextofisopam, Dr. Chey said. ■

Hotline Focuses on Colorectal Ca

The Patient Advocate Foundation is offering the Colorectal CareLine, a hotline designed to assist people who have been diagnosed with colorectal cancer and are seeking education and access to care.

The CareLine is staffed by case managers with both nursing and social work backgrounds. Financial aid is available.

To contact the CareLine, which is sponsored by Amgen Inc., call 866-657-8634. ■

ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

Probiotics for Irritable Bowel Syndrome

History and Rationale for Use

The concept of probiotics as beneficial for intestinal health began with Nobel Prize–winning Russian scientist Ilya Ilyich Mechnikov. He viewed the large intestine as a vestigial organ that harbored dangerous, putrefaction-inducing bacteria, and believed that introducing lactobacilli into the body would promote health. The longevity of Balkan peasants, he wrote in "The Prolongation of Life: Optimistic Studies" in 1907, was likely a result of their consumption of fermented milk products.

► *Theoretical reasons why probiotics could be beneficial in irritable bowel syndrome include anti-inflammatory effects and immune modulation in the gut.*
► *Clinical trial data remain sparse, and quality control is problematic.*

A century later much is known about gut function, the 400 species of bacteria that reside in the colon, and host-flora interactions, including communication between intestinal microbes and the immune system. For instance, the host's immune system can differentiate between pathogenic bacteria and commensals through pattern recognition receptors and Toll-like receptors (TLRs). TLR2 triggers an immune response to gram-positive bacteria and yeasts, TLR4 mediates responses to lipopolysaccharides from gram-negative bacteria, and TLR9 recognizes certain sequences of bacterial DNA (Dig. Dis. 2006;24:137-47).

The currently accepted definition of probiotics is "nonpathogenic microorganisms, which, when ingested as living cells, exert a positive influence on host health or physiology" (Dig. Dis. 2006;24:137-47). The *Lactobacillus* and *Bifidobacterium* genera of bacteria are the most widely tested and commonly used probiotics.

There are several reasons why certain probiotic organisms could have beneficial effects in irritable bowel syndrome (IBS). Many have antiviral and antibacterial effects, which could be important in the 15%-25% of patients whose IBS dates from an episode of infectious gastroenteritis. Also, probiotics have anti-inflammatory effects on mucosal surfaces. By reducing gut mucosal inflammation, these organisms could decrease immune-mediated activation of enteric neurons and thus alter neural traffic between the gastrointestinal tract and the central nervous system. Moreover, probiotics could quantitatively and qualitatively alter the gut flora, change the volume and composition of stool and gas, and increase secretion of intestinal mucus (Gastroenterology 2005;128:541-51).

Clinical Trials

Two studies done at the Mayo Clinic, Rochester, Minn., used a composite probiotic (VSL#3, manufactured by VSL Pharmaceuticals). The first study included 25 patients with diarrhea-predominant IBS who received VSL#3 powder (450 billion lyophilized bacteria per day) or placebo twice daily for 8 weeks. There was a borderline significant difference between the active and placebo groups on abdominal bloating, but no differences in gastrointestinal transit time, bowel function scores, or global symptom relief (Aliment. Pharmacol. Ther. 2003;17:895-904).

In the second trial, 48 patients were randomized to receive either the active treatment or placebo for up to 8 weeks. Mean posttreatment scores for symptoms including abdominal pain, flatulence, and bloating were numerically lower in the active treatment group, but only the score for flatulence achieved statistical significance. A total of 46% of patients in the active treatment group and 33% of patients in the placebo group had satisfactory relief for half of the weeks (J. Clin. Gastroenterol. 2006; 40:264-9).

Another research group, led by Dr. Eamonn Quigley, professor of medicine at University College Cork (Ireland), randomized 362 women with IBS of any subtype to receive either placebo or one of three doses of encapsulated *B. infantis* (1×10^6, 1×10^8, or 1×10^{10} colony-forming units per milliliter) each day for 4 weeks.

On the primary end point, abdominal pain/discomfort at week 4, only the 1×10^8 group had significant improvements, compared with baseline. Patients in this group also had significant improvements on the secondary outcomes of bloating/distention, sense of incomplete evacuation, passage of gas, straining, and bowel habit satisfaction (Am. J. Gastroenterol. 2006;101:1581-90).

A Role for Inflammation

In another study, 75 patients were randomized to receive either 1×10^{10} of *L. salivarius* or *B. infantis* in a malted milk drink or a malted milk placebo for 8 weeks. On the three cardinal symptoms of IBS—abdominal pain/discomfort, bloating or distention, and bowel movement difficulty, the *Bifidobacterium* was superior to the *Lactobacillus,* and the therapeutic gain of 20%-25% over placebo was equivalent to that reported for tegaserod (Gastroenterology 2005; 128:541-51).

In this study, the investigators also measured peripheral blood cytokine levels and reported that, compared with normal controls, baseline levels of interleukin (IL)-10 were low and levels of IL-12 were increased, a ratio that is skewed toward a proinflammatory cytokine profile. This ratio returned to normal among patients in the *B. infantis* group, but not in the *L. salivarius* group or the normal controls.

The authors wrote that in this study, "by demonstrating a normalization of the IL-10/IL-12 ratio in the bifidobacteria-fed subjects alone, and in parallel with symptomatic improvement, we provide the first evidence for efficacy for an anti-inflammatory approach in IBS."

Advice From an Expert

Much confusion exists regarding the use of probiotics for IBS, with many substandard studies and exaggerated claims, according to Dr. Quigley, who is also vice president of the World Gastroenterology Organisation. In an interview, he noted that few probiotics have been subjected to high-quality clinical trials. He also pointed out that quality control is a real issue.

"Many of the probiotics on the shelf cannot be validated in terms of constituents, dose, viability, properties, efficacy, lack of contamination, and shelf-life," he noted. Finally, he cautioned that probiotics differ: "No two are exactly the same. Extrapolations from one, even if closely related, cannot and should not be made."

—Nancy Walsh