Two Strategies Aim to Modify Gut Flora in IBS

BY BRUCE JANCIN
Denver Bureau

HONOLULU — Modification of the gut flora is emerging as a promising new treatment approach for the common and vexing problem of irritable bowel syndrome.

Two therapeutic strategies are being pursued. One entails adding bacteria to the gut in the form of oral probiotics. The other involves selectively subtracting bacteria from the gut flora with a non–systemically absorbable antibiotic. Evidence that both approaches alter irritable bowel syndrome (IBS) pathology and modulate symptoms was presented at the annual meeting of the American College of Gastroenterology.

The gut flora has been called "the forgotten organ," but that's changing, said Dr. Eamonn M.M. Quigley, professor of medicine at the National University of Ireland, Cork.

He presented a full IBS spectrum from diarrhea to the constipation-predominant subtype.

The probiotic resulted in a double-blind trial involving 165 women with IBS randomized to 4 weeks of daily capsules containing the novel probiotic bacterium *Bifidobacteria infantis* 35624 or placebo. Baseline bowel movement (BM) frequency ranged across the significant improvement in BM frequency, concentrated among patients at either end of the frequency distribution.

Women with constipation—those in the bottom 15th percentile in terms of baseline BM frequency—experienced a significant increase in frequency that brought them within the 1-2 movements per day range defined by investigators as normal. In contrast, patients with diarrhea as defined by a BM frequency in the 81st percentile or above experienced a significant decrease in frequency to within normal range.

The probiotic resulted in a net 23% improvement over placebo in terms of IBS symptom scores across the entire study population. Patients in the middle range of baseline BM frequency experienced no significant change with the probiotic compared with placebo.

A composite score based on abdominal pain, bloating, and bowel habit satisfaction was significantly improved with probiotic therapy over placebo in patients with diarrhea-predominant IBS, showed a strong but not statistically significant favorable trend in the smaller group of women with constipation-predominant IBS, and no change in alternator-type patients. There were no probiotic-related side effects. The improved stool function and other benefits of *B. infantis* 35624 lasted 1-3 weeks after treatment discontinuation, the gastroenterologist added.

Dr. Quigley stressed that not all probiotics are alike. They're not classified as drugs, so they're prone to the same quality-control issues that arise with other health food–type products. The most clinically effective of them—as he and others have shown true for *B. infantis* 35624 in animal studies—have the ability to not only modify the gut flora, but more importantly to modulate immune activity between the flora and gut mucosa.

Dr. Mark Pimentel presented a double-blind trial in which 87 patients with all types of IBS were randomized to the nonabsorbable antibiotic rifaximin (Xifaxan) at 400 mg t.i.d. or placebo for 10 days. Of patients in the rifaximin group, 38% were deemed clinical responders based upon a greater than 50% improvement in global symptom scores, compared with 16% of those on placebo. The improvement was durable, lasting for roughly 2 months following just 10 days of treatment.

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DR. PIMENTEL

The clinical response rate was greater in patients with diarrhea-predominant IBS: 49%, compared with 23% with placebo. Bloating was also significantly improved. Constipation was not, although the number of affected patients was too small to draw definitive conclusions, according to Dr. Pimentel, director of the gastrointestinal motility program at Cedars-Sinai Medical Center, Los Angeles.

Prior studies suggest that many IBS patients have small bowel overgrowth of hydrogen- or methane-producing bacteria. In the current study, the presence and extent of methane production on a lactulose breath test correlated strongly with constipation severity. This suggests that knocking out methane-producing bacteria in the small bowel may be a good therapeutic strategy in patients with constipation-predominant IBS, he added.

Session cochair Dr. Nicholas J. Talley said he doesn't think that probiotics or antibiotics are ready for prime-time use in IBS.

First, it's still unclear how common small bowel bacterial overgrowth is in IBS. Also, the gut flora is very well adjusted. "It's there with you for life. It doesn't want to go. If you change it, you have to keep changing it. So this is going to be maintenance therapy, not on-off antibiotic therapy. And I'm never going to be able to recommend antibiotics every 2 weeks to my patients for the rest of their lives," said Dr. Talley, professor of medicine at the Mayo Medical School, Rochester, Minn.

In contrast, there is now general agreement that probiotic therapy is safe for the patient and community. It is being successfully used in clinical practice for two conditions—infectious diarrhea and pouchitis secondary to ulcerative colitis surgery—backed by solid clinical trials data. But key questions remain regarding its use in IBS.

"We don't know enough, in my mind, to be saying absolutely everybody with IBS should be on this. … The problem we have currently is what to recommend—what dose, how often, which type," Dr. Talley added.

Nevertheless, these are promising new approaches worthy of thorough exploration at a time when medical understanding of the true nature of IBS has undergone a complete change. IBS is no longer viewed by experts as a psychogenic disorder with no demonstrable physical pathology. It is a mixed motility disorder involving a hyperacute sensation of pain to the gut.

"Yes, psychologic factors are relevant, but IBS is a real disease of the gut. It involves immunologic changes, inflammatory changes, and—based upon limited data so far—flora changes," the gastroenterologist observed.

Dr. Quigley is a consultant to and stock shareholder in Alimentary Health, which is developing *B. infantis* 35624 for commercial applications.

Dr. Pimentel is a consultant to Salix Pharmaceuticals Inc., which markets rifaximin for the indication of traveler's diarrhea. ■

Genetics, Environment Affect Risk for Primary Biliary Cirrhosis

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Two separate studies have produced strong evidence supporting both genetic and environmental risk factors for primary biliary cirrhosis. The findings were presented at the annual meeting of the American Association for the Study of Liver Diseases.

Little is known about the cause of this autoimmune cholestatic liver disease that affects an estimated 100,000 people in the United States. Primary biliary cirrhosis typically strikes women in the prime of their lives, attacking small ducts of the liver and ultimately requiring a liver transplant.

Symptoms include intractable itching, fatigue, and sometimes jaundice, although today many patients are diagnosed while asymptomatic based on abnormal liver function tests.

Detailed telephone surveys of 1,032 patients (93% women) and 1,041 closely matched controls (92% women) in all but two U.S. states found that the risk for primary biliary cirrhosis increased with a family history of the disease or of other autoimmune diseases. Other risk factors were smoking, a history of urinary tract infection (UTI), and high income, plus a slight increase in risk with the use of nail polish, Dr. Carlo Selmi reported.

A family history of primary biliary cirrhosis increased a person's risk for the disease 11-fold.

DR. SELMI

The average age at diagnosis of primary biliary cirrhosis was 58 years in Dr. Selmi's study; the control subjects also averaged 58 years.

Six percent of patients with primary biliary cirrhosis had another family member with the disease—usually a mother or sister. One-third of patients had another autoimmune disease, reported Dr. Selmi of the University of California, Davis, and his associates.

A family history of primary biliary cirrhosis increased a person's risk for the disease 11-fold. The risk doubled with a family history of lupus and increased sixfold with a family history of Sjögren's disease.

Previous UTIs were associated with a 50% increase in risk for primary biliary cirrhosis. The risk increased by 60% with a history of smoking more than 10 cigarettes per day. Use of nail polish increased the risk only slightly, but the difference was significant, he said.

Patients with primary biliary cirrhosis had significantly higher family incomes, compared with controls, a risk factor that's hard to explain, said Dr. M. Eric Gershwin, a coinvestigator in the study and chief of rheumatology, allergy, and clinical immunology at the university.

One "hygiene hypothesis" posits that wealthier people may be "too clean," disrupting the autoimmune system, he said at a press briefing.

Noting the higher rate of UTIs in patients with primary biliary cirrhosis, he hypothesized that certain bacteria resembling the pathogens of UTIs may predispose someone to primary biliary cirrhosis if the body attacks the lookalike bacteria by mistake.

A separate British study comparing 2,576 patients with primary biliary cirrhosis to 2,438 controls produced results that were "extraordinarily similar" to those of the U.S. study, Dr. Oliver James said in a separate presentation.

The cirrhosis group included 318 consecutive patients seen in one region and 2,258 members of the Primary Biliary Cirrhosis Foundation support group living in the United Kingdom.

A family history of primary biliary cirrhosis doubled the risk for disease in the regional patient group and quadrupled risk in the Foundation group, compared with controls. Previous obstetrical pruritus doubled the risk in both patient groups compared with controls, said Dr. James of the University of Newcastle Upon Tyne.

Other factors that increased risk for the disease in both patient groups, compared with controls, included smoking, use of hair dye, recurrent UTIs, thyroid disease, and rheumatoid arthritis. Additional factors increased risk in at least one of the patient groups; these factors were celiac disease, history of shingles, or prior tonsillectomy or appendectomy.

History of pregnancy slightly but significantly reduced risk in women and also in men whose partners became pregnant. ■