Fructooligosaccharides Promising As 'Prebiotic' in Crohn's Therapy

It may provide a substrate upon which healthy bacteria can grow.

BY ANN C. LOGUE
Contributing Writer

CHICAGO — Ten patients with moderate Crohn's disease took supplements of fructooligosaccharide, a substance found in artichokes and asparagus, and showed an increase in fecal *Bifidobacteria* and production of mucosal dendritic cells, James Lindsay, Ph.D. said at the annual Digestive Disease Week.

Although the findings are preliminary, this is the first known study of "prebiotic" dietary therapies for Crohn's, and the strategy may offer a way to supplement traditional treatments or to manage patients who do not respond to them, he said.

Fructooligosaccharide is a carbohydrate that selectively alters the colonic microbiota, Dr. Lindsay explained. It is a prebiotic that may provide a substrate upon which healthy bacteria can grow, as opposed to probiotics, which are the healthy bacteria themselves.

The supplement given to the 10 patients in the open-label study was prepared by Nestlé UK, which provided financial support for the research. The patients took 15 g per day for 3 weeks.

Patients and doctors noted an improvement on the Harvey Bradshaw index, with the mean falling from 9.8 at the start of the study to 6.9 at the end. Remission of Crohn's disease was achieved by 40% of the patients. There was a 6.8% increase in the volume of *Bifidobacteria* found in dried fecal samples between the start and end of the study. In addition, the number of interleukin-10 dentridic cells increased, as did the number of cells expressing Toll-like receptors.

Patients in the study, 60% of whom were completely compliant with the study regimen, tolerated the supplement well. The most common complaints were rumbling and flatulence.

"Traditional therapies tend to increase effector pathways. The alternative is to increase regulatory pathways," said Dr. Lindsay, consultant gastroenterologist at St Bartholomew's Hospital and the Royal London Hospital.

Balfour Sartor, M.D., a professor of medicine, microbiology, and immunology at the University of North Carolina at Chapel Hill, is familiar with the work of Dr. Lindsay and his colleagues because it overlaps with his own.

He said that Dr. Lindsay's study is not in the mainstream of Crohn's research, but that it is a legitimate area of investigation.

"The normal bacteria in the gut are probably the dominant antigenic stimulus driving immune mediation," he said. "Altering the diet is a natural way of doing things that is presumed to have less toxicity and be less costly," he said.

Dr. Lindsay emphasized the preliminary nature of the findings. ■

Genetic Variants May Predict Risk for Upper GI Disease in Crohn's

ORLANDO, FLA. — Crohn's disease patients with two allelic variants of the *NOD2/CARD15* gene have an increased risk of upper GI disease involvement, Houssam E. Mardini, M.D., reported at the annual meeting of the American College of Gastroenterology.

Genetic testing of patients in an inflammatory bowel disease database revealed that six of nine patients with Crohn's disease in the upper GI tract had two allelic variants of the *NOD2/CARD15* gene.

In comparison, a significantly lower percentage of patients without upper GI disease had two allelic variants of the gene (4% of 169). "Our data suggest that patients with two *NOD2/CARD15* allelic variants should be carefully evaluated for upper GI involvement," Dr. Mardini and his associates said in a poster presentation.

NOD2/CARD15 is so far the only gene that is highly associated with Crohn's disease. Four of the patients with upper GI disease had homozygous allelic variants, whereas none of the patients without upper GI disease were homozygous for an allelic variant. Wild type alleles of *NOD2/CARD15* occurred in 68% of the patients without upper GI disease; another 28% of those without upper GI disease had one allelic variant.

Compared with patients who did not have upper GI disease, significantly more of the patients with upper GI involvement had a family history of inflammatory bowel disease (19% vs. 44%), were male (41% vs. 78%), and were younger at diagnosis (25 years vs. 17 years). Osteopenia or osteoporosis developed significantly more often in patients with upper GI disease than in those without (33% vs. 9%).

—Jeff Evans

Lower Rice Consumption May Be Tied to Crohn's

CHICAGO — The increasing prevalence of Crohn's disease in Japan correlates closely with decreased consumption of rice, Ryosuke Shoda, M.D., said at the annual Digestive Disease Week.

Crohn's disease was once almost unknown in Japan, Dr. Shoda said in a poster presentation that reviewed the epidemiology of Crohn's disease and trends in the consumption of fiber from rice and other sources in the Japanese diet. In the early 1960s and before, rice was the main source of dietary fiber in Japan, providing the average citizen with about 28 g of fiber per day. Today, the average intake of fiber from rice is 12-15 g/day.

Meanwhile, the prevalence of Crohn's disease went from virtually nothing in the 1960s to 2.9 per 100,000 persons in the mid-1980s and to about 14 per 100,000 today, said Dr. Shoda, chief of the department of general internal medicine at the International Medical Center of Japan, Tokyo.

Data on fiber consumption and Crohn's disease from the Japanese Ministry of Health, Welfare, and Labor from 1966 to 1993 show that the rising prevalence of Crohn's disease closely paralleled the decreasing intake of fiber and rice and the increasing intake of fiber from wheat and grains, Dr. Shoda said.

Of nine sources of fiber studied, rice was the only one that was independently correlated with the prevalence of Crohn's disease. The other sources were wheat and grain, potatoes, fruit, vegetables, beans, seaweed, sweets, and seeds. When changes in the consumption of animal fat were included in the analysis, rice remained the only independent factor.

Breakfast is the meal that has changed the most in Japan and is probably the most responsible for the decline in rice consumption, Dr. Shoda said in an interview.

Many people in Japan now eat bread rather than rice with breakfast.

—Timothy F. Kirn

Antidepressants, Not Fiber, Help in IBS

BY TIMOTHY F. KIRN
Sacramento Bureau

SAN FRANCISCO — An antidepressant often is better than a high-fiber bulking agent as first-line treatment for irritable bowel syndrome, at least for the diarrhea-predominant form of the disorder, Philip S. Schoenfeld, M.D., said at the annual meeting of the American College of Physicians.

Results from 14 well-designed clinical trials of the use of bulking agents for irritable bowel syndrome (IBS) "consistently show … that they are no better than placebo," said Dr. Schoenfeld, chief of the division of gastroenterology at the Ann Arbor (Mich.) Veterans Affairs Medical Center.

Worse, bulking agents usually cause uncomfortable bloating. In one study of psyllium (Metamucil), placebo patients actually did better than treated patients, said Dr. Schoenfeld, who was a member of the American College of Gastroenterology's task force that reviewed treatment evidence in 2002.

The only time to try a bulking agent is with a patient with constipation-predominant IBS who does not normally have bloating discomfort with the constipation, he said.

Tricyclic antidepressants, on the other hand, are good agents for pain control. Several studies have shown that tricyclics reduce abdominal pain. The most recent study—which met the criteria for good study design spelled out by the International Congress of Gastroenterology's Rome guidelines—showed a significant reduction of symptoms, Dr. Schoenfeld said.

The study used low-dose desipramine, which Dr. Schoenfeld said he prefers to use first. He uses it in patients with diarrhea-predominant IBS because tricyclics can cause constipation.

About one-quarter of patients don't tolerate tricyclic therapy; they can be switched to a selective serotonin-reuptake inhibitor (SSRI), with advice to use loperamide as needed.

Of the three well-designed trials that have tested the use of an SSRI, one showed significant symptom improvement, one showed a trend to improvement, and one showed decreased health care utilization.

Although IBS has been called a diagnosis of exclusion, in practice it does not really need to be. That approach leads to a lot of expensive tests—40% of IBS patients, for example, get endoscopy at the time of initial diagnosis, Dr. Schoenfeld said.

In the absence of specific danger signs, such as fecal blood, the incidence of other serious conditions in patients with IBS-like symptoms is generally about the same as in the general population (less than 1%). The exception is celiac sprue, which occurs about 10 times more often in patients with diarrhea-predominant IBS-like symptoms than it does in the general population.

Dr. Schoenfeld said that he prefers to test for serum celiac sprue using the tissue transglutaminase antibody test, because its sensitivity is almost 100%. There are false positives, but a negative test rules out the disorder.

In clinical trials, tegaserod maleate (Zelnorm) was effective in about 40% of patients. Yet about 30% of placebo patients had improvement, as they often do in IBS trials, so the absolute difference was only about 10%.

Tegaserod is worth a try in constipation-predominant, female patients; when it works, symptoms improve rapidly. But Dr. Schoenfeld does not continue a trial for very long because the drug is expensive. "It's not a miracle drug, and if they haven't improved in about a month they are unlikely to improve," he said.

He usually stops the drug after 8 weeks, as specified on the product label. IBS patients generally have flares and quiescent periods, and studies have shown the average flare lasts 6-8 weeks. Moreover, evidence indicates that response to the drug, when reinitiated, is exactly the same as the initial response.

Dr. Schoenfeld has a consultantship with Novartis Pharmaceuticals Corp., the maker of Zelnorm. ■