Efficacy of IBS Drug Reflects Gene Variation

Screening for common polymorphisms may help predict patients' response to chenodeoxycholate.

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Major Finding: In women with constipation-predominant IBS (IBS-C), genetic variations in bile acid regulatory genes may determine the therapeutic response to the drug sodium chenodeoxycholate.

Data Source: Two double-blind, randomized studies of chenodeoxycholate 500 mg and 1,000 mg in 36 female IBS-C patients and 60 healthy volunteers.

Disclosures: No disclosures were reported.

BOSTON – The therapeutic response of a patient with constipation-predominant irritable bowel syndrome to sodium chenodeoxycholate may reflect particular variations in genes that control bile acid homeostasis, according to Dr. Banny S. Wong.

"Common single-nucleotide polymorphisms in genes regulating the feedback inhibition of bile acid synthesis, specifically the FGF19-mediated feedback pathway, affect chenodeoxycholate-mediated acceleration of colonic transit in IBS-C [constipation-predominant irritable bowel syndrome], and perhaps less so in health," Dr. Wong said at the meeting, hosted by the American Neurogastroenterology and Motility Society.

In this study, 15 single-nucleotide polymorphisms (SNPs) from seven genes (SHP, ASBT, Klotho-beta, FGFR4, OST-alpha, OST-beta, and CYP7A1) were analyzed. The chosen genes are thought to play critical roles in bile acid synthesis, ileal absorption, and hepatic uptake. Genomic DNA was isolated from blood using standard methods.

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Genotyping was carried out in 36 female IBS-C patients and 60 healthy volunteers who were enrolled in two double-blind, randomized, placebo-controlled trials. Chenodeoxycholate was administered in a pH-sensitive methacrylate coating to maximize delivery to the colon. Participants received either placebo, low-dose chenodeoxycholate (500 mg), or high-dose chenodeoxycholate (1,000 mg) for 4 consecutive days, after which colonic transit was assessed by using a validated scintigraphic method.

Chenodeoxycholate is currently not FDA approved for the treatment of IBS-C, reported Dr. Wong of the Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER) program at the Mayo Medical School, Rochester, Minn.

"We found interesting results for genetic variations in two genes, FGFR4 and Klotho-beta, both of which are crucial in allowing the hormone FGF19, secreted by the enterocytes in the ileum, to signal the liver and its hepatocytes to shut off further bile acid production," said Dr. Wong.

For the FGFR4 SNP rs376618, participants with the TT genotype showed significantly accelerated transit, compared with placebo, in response to both doses of chenodeoxycholate, while only the high dose produced a significant response in those with the TC/CC genotype. Analysis of the Klotho-beta SNP rs17618244 by the GG or GA/AA genotypes showed that the drug accelerated transit only for those with the GG subtype receiving high-dose chenodeoxycholate.

Further analysis focused on chenodeoxycholate's effect on ascending colonic emptying time (a surrogate for colonic transit), taking into consideration both the Klotho-beta rs17618244 genotype and the clinical phenotype (healthy or IBS-C). In this case, differential pharmacogenetic effects were observed only for IBS-C patients with the GG genotype, whose colonic transit was significantly accelerated with both doses of the drug. Therapeutic responses to either dose of chenodeoxycholate were not seen in healthy volunteers, no matter what their rs17618244 genotype, nor in IBS-C patients with the GA/AA genotypes.

In previous studies, chenodeoxycholate accelerated colonic transit, increased stool frequency, and loosened stool consistency in both healthy volunteers and patients with IBS-C. "Our studies strongly support the theory that bile acids are natural laxatives and that derangements of bile acid homeostasis, including those predisposed by certain genetic variants, may play a significant role in constipating or diarrheal disorders such as IBS," said Dr. Wong.

The current results suggest that screening IBS-C patients for common polymorphisms in the FGFR4 and Klotho-beta genes may help preselect the subset of patients who will achieve the best clinical response to chenodeoxycholate pharmacotherapy. ■