Rifaximin Effective in FD, Suggesting Intestinal Microbiota Involvement

Written by Lynne Lederman, PhD

Functional dyspepsia (FD) is a common gastrointestinal disorder for which effective treatments are not available. FD and the related irritable bowel syndrome (IBS) often coexist and share symptoms of bloating, abdominal discomfort, and pain. Dysbiosis of the intestinal microbiota may be involved in the pathogenesis of functional gastrointestinal disorders, including FD. The nonabsorbable antibiotic rifaximin has shown efficacy in relieving IBS symptoms [Pimentel M et al. *N Engl J Med*. 2011].

Victoria P. Tan, MBBS, University of Hong Kong, Hong Kong, China, discussed a double-blinded placebo-controlled pilot study [NCT01643083] to test the ability of rifaximin in patients with FD to improve global dyspepsia symptoms, belching, and bloating. This trial enrolled adults with FD per Rome III criteria, with normal gastroscopy results within the last 2 years, and with active symptoms in the prior month. Patients who had IBS and other chronic conditions or who had taken proton pump inhibitors or antibiotics within the last 8 weeks were excluded.

During screening, a 3-hour hydrogen breath test (HBT) was performed. Baseline characteristics were similar between the 2 arms; however, Prof Tan noted a slight excess of patients with belching in the placebo group (73.9%) as compared with the rifaximin group (55%), which could affect how results are interpreted.

Patients were randomly assigned 1:1 to rifaximin (n = 40) 400 mg TID or placebo (n = 46) TID for 2 weeks. Follow-up assessments were performed at weeks 2, 4, and 8. Patients who took ≥ 75% of their treatment medication included 33 in the rifaximin group and 39 in the placebo group.

Global dyspeptic symptoms, the primary outcome, improved with rifaximin at week 2; at week 8, 23.5% in the rifaximin group vs 47.4% in the placebo group had moderate to severe global dyspeptic symptoms.

Secondary outcomes included belching and bloating. At week 4, moderate to severe belching occurred in 14.3% of patients in the rifaximin group vs 35.7% of the placebo group ($P = .03$); however, by week 8 of follow-up, there was no significance between groups.

Moderate to severe bloating decreased in both groups: at week 4, it occurred in 20% of the rifaximin group and 42.9% of the placebo group ($P = .03$); at week 8, it increased in the rifaximin group and decreased in the placebo group, until the difference was no longer significant.

A subgroup analysis of female patients with FD showed a decrease in moderate to severe global dyspeptic symptoms in both treatment groups during the study: at week 4, symptoms were reported in 20.8% of the rifaximin group vs 59.4% in the placebo group ($P = .006$); at week 8, the differences were still significant (20% for rifaximin vs 48.4% for placebo; $P = .048$).

Table 1. Secondary Outcome: Hydrogen Breath Test Results

	Rifaximin	Placebo	*P* Value
H_2 peak above baseline	2.94 (11.1)	0.11 (12.22)	.29
H_2 AUC, ppm	+43.64 (1033.07)	−49.71 (1360.78)	.76
OCTT, min	+24.23 (38.50)	+16.50 (49.72)	.68

Values presented in mean (SD).

AUC, area under the curve; OCTT, oral-cecal transit time; ppm, parts per million.

HBT results at week 8 vs baseline are presented in Table 1.

There were no significant differences between treatment groups for major or minor adverse events at week 2, 4, or 8.

One limitation of this study is that it was a 2-institution pilot study with a small sample size. In addition, the durability of the rifaximin effect was unclear, and response was associated with changes in HBT.

To conclude, the efficacy of rifaximin in FD—particularly for global dyspeptic symptoms, belching, and bloating—suggests a role for the gut microbiota in the pathogenesis of FD. These results should be confirmed in a large multicenter study.

Ramosetron Is Effective in Women With IBS-D

Written by Lynne Lederman, PhD

Controlling symptoms in irritable bowel syndrome with diarrhea (IBS-D) can be challenging. Studies have suggested a role for serotonin 5-hydroxytryptamine ($5\text{-}HT_3$) receptors and antagonists in the gastrointestinal tract in the pathogenesis of IBS-D. In one study, ramosetron, a $5\text{-}HT_3$ antagonist, significantly improved stool consistency when compared with placebo in Japanese men ($P < .001$) [Fukudo S et al. *Clin Gastroenterol Hepatol.* 2014]. Of note, ramosetron is not FDA approved.

Shin Fukudo, MD, PhD, Tohoku University Graduate School of Medicine, Sendai, Japan, presented the results of a double-blind placebo-controlled phase 3 trial designed to determine the effects of ramosetron vs placebo in women with IBS-D and to assess adverse events (AEs) [NCT01736423]. Women with IBS-D were randomly assigned to oral ramosetron 2.5 μg (n = 292)

Table 1. Co–primary End Point Results: Global Improvement

Treatment	Responder Rate, %			
	Month 1	Month 2	Month 3	Last Point
Placebo	19.4	28.5	31.7	32.0
Ramosetron 2.5 μg	31.5*	41.8*	49.3**	50.7**

*$P = .001$.

**$P < .001$.

or placebo (n = 284) once a day before breakfast for 12 weeks. Co–primary end points included responder rates assessed by global improvement of irritable bowel syndrome symptoms and the Bristol Stool Scale. Secondary end points included abdominal pain or discomfort, abnormal bowel habit, stool frequency, and Japanese version of IBS-Quality of Life (IBS-QOL-J).

There were no significant differences between groups in baseline characteristics, including mean age (41 years), duration of disease (156 months), and symptoms. The co–primary end point results are shown in Table 1.

Ramosetron rapidly improved symptoms, with significant relief occurring by week 2. Stool consistency improved significantly with ramosetron treatment vs placebo at monthly assessments throughout the trial ($P < .001$). At the last point, 40.8% of the ramosetron group vs 24.3% of the placebo group showed significant improvement in stool consistency ($P < .001$). By day 2, patients in the ramosetron group showed an improved Bristol Stool Scale ($P = .018$ vs placebo). In addition, ramosetron significantly reduced daily stool frequency ($P < .001$). At study end, ramosetron also significantly improved abdominal pain and discomfort vs placebo (51.4% vs 37.7%; $P = .001$) and abnormal bowel habits during the study (50.3% vs 31.0%; $P < .001$). Ramosetron significantly improved some measures of IBS-QOL at study end, including overall quality of life, dysphoria, and food avoidance ($P < .01$ for all), as well as interference with activity ($P < .001$).

Ramosetron was associated with significantly more AEs than placebo, including gastrointestinal disorders ($P < .001$); however, there were no differences between treatment groups in infections and infestations. No ischemic colitis was observed, but the number of patients in the study may be too small to see this AE.

To conclude, ramosetron is effective in women with IBS-D at a dose half of that indicated for men, for reasons that are currently unclear. Improvements in IBS-QOL exceeded the minimal clinically important difference, further supporting ramosetron as therapeutic option for women as well as men.

High-Definition Chromoendoscopy Improves Dysplasia Detection in Ulcerative Colitis

Written by Lynne Lederman, PhD

Individuals with ulcerative colitis (UC) have an increased risk for colorectal cancer when compared with the general population [Jess T et al. *Clin Gastroenterol Hepatol*. 2012]. Surveillance endoscopy to detect dysplastic lesions is critical in reducing this risk. Image-enhanced endoscopy offers improved resolution and lesion detection during surveillance endoscopy [Subramanian V, Ragunath K. *Clin Gastroenterol Hepatol*. 2014]. Advances in image enhancement include improving contrast using dye-based chromoendoscopy (CE), using virtual CE that relies on filters or software manipulation, or using autofluorescence endoscopy based on filter technology with software manipulation.

CE increased the detection of dysplasia during surveillance endoscopy as compared with standard-definition white light endoscopy (SDWLE) in a pooled analysis [Soetikno R et al. *Gastroenterology*. 2013]. High-definition white light endoscopy (HDWLE) improved detection rates for dysplasia about 2.5-fold when compared with SDWLE [Subramanian V et al. *Inflamm Bowel Dis*. 2013]. HDWLE detected dysplasia in 24 (11.5%) of 209 patients, whereas SDWLE detected dysplasia in 8 (5.0%) of 160 patients (prevalence ratio, 2.3; 95% CI, 1.03 to 5.11).

Venkat Subramanian, MD, St James University Hospital, Leeds, United Kingdom, presented the results of a randomized trial [NCT02138318] to compare the rate of detection of dysplasia in patients with long-standing (> 8 years of disease) UC using HDWLE compared with high-definition chromoendoscopy (HDCE).

Adults were included if they had long-standing extensive UC (extending proximal to splenic flexure) and a surveillance colonoscopy. Exclusion criteria were pregnancy, unwillingness or inability to give informed consent, or severe active colitis as assessed by the endoscopist at the time of the procedure.

For HDCE, 0.2% indigo carmine dye spray was used on withdrawal. Targeted and random biopsies from each colonic segment were taken from all patients. Patients randomly assigned to the HDWLE group (n = 53) were matched with those in the HDCE group (n = 50) for baseline demographics, including age, duration of disease, smoking status, presence of primary sclerosing cholangitis, family history of colorectal cancer, and use of 5-aminosalicylates or immunomodulators. About two-thirds of patients in the HDWLE group and about half the patients in the HDCE group were women. Results are shown in Table 1.