Functional Disease, Dysbiosis, and Dyspepsia: How Helpful Is Rifaximin?

Sridhar Sundaram¹ · Harish Darak²

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Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are functional gastrointestinal disorders abnormal gut-brain interactions. FD is defined as foregut symptoms such as heartburn, dyspepsia, and nausea whereas IBS is defined as altered bowel habits related to abdominal pain, with both conditions diagnosed in the absence of demonstratable pathology. These disorders may occur either in isolation or may overlap with other functional gastrointestinal disorders (FGID), usually on a background of anxiety and depression. When FD and IBS overlap, the severity of symptoms of both disorders increases [1]. Interestingly, both share similar pathophysiological mechanisms including altered gastrointestinal motility and sensory function, increased intestinal paracellular permeability, low-grade mucosal inflammation, microbial dysbiosis, and dysfunction of the brain-gut axis with psychiatric comorbidities [2]. Microbial dysbiosis and small intestinal bacterial overgrowth (SIBO) are associated with both FD and IBS. Wide variations in prevalence rates of SIBO have been reported in patients with FGID. In IBS, over 20 studies have reported the frequency of SIBO in affected patients of 2%–84% [3]. A recent meta-analysis showed the prevalence of SIBO in FD was 2.8 times higher than in controls [4]. The prevalence of SIBO is higher in patients with overlap compared to isolated FD and IBS. The conventional diagnosis of SIBO is based on jejunal aspirate culture, with colony count $\geq 10^5$ CFU/ml diagnostic of SIBO. Non-invasive tests for diagnosis of SIBO used primarily in clinical practice are the glucose hydrogen breath test (GHBT) and

lactulose hydrogen breath test (LHBT) [5]. Though popular, their accuracy is doubtful, with a recent meta-analysis showing both tests to have low sensitivity with high specificity. Rifaximin is the one of first-choice therapies in SIBO, where it acts as a poorly absorbed oral antibiotic that alters the composition of the gut microbiota. This effect is also useful in patients with IBS and FD where disturbances in gut microbial composition are common. A recent network meta-analysis showed significant benefit of rifaximin over placebo in patients with IBS. Rifaximin was also the safest drug in patients with IBS [6]. On the other hand, data on the efficacy of rifaximin in FD remains sparse. The benefits of rifaximin in the patients with overlap of FD and IBS remain elusive.

In this issue of *Digestive Diseases and Sciences*, Shah et al. [7] presented the findings of their single-center prospective study using rifaximin in patients with FD with or without associated overlapping IBS, determining its effects on visceral sensory function. In this study of 21 patients with FD of which 14 had FD and IBS overlap received rifaximin after the failure of standard treatment with proton pump inhibitors, prokinetics, and low-dose psychotropic drugs. After a 2-week run-in period, all patients underwent a baseline standardized nutrient challenge test (marker for visceral hypersensitivity), glucose hydrogen breath test, and SAGIS (structured assessment of gastrointestinal symptoms scale) questionnaire assessment. Rifaximin treatment was associated with significant improvement in total SAGIS score, SAGIS dyspepsia, and SAGIS diarrhea sub-score at 2 and 6 weeks in FD patients with or without IBS. Treatment also significantly improved the nutrient challenge test in FD patients irrespective of IBS status, suggesting an improvement in visceral sensory function. While the primary mode of action of rifaximin thought to be related to alteration of the composition of the gut microbiota, the study also established additional mechanisms of action which include reducing gut inflammation and ameliorating visceral hyperalgesia.

One of the strengths of the study is a simultaneous assessment of symptoms and visceral sensory function. The tool

✉ Sridhar Sundaram
drsridharsundaram@gmail.com

Harish Darak
harishdarak007@gmail.com

¹ Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Homi Bhabha National Institute, Parel, Mumbai 400012, India

² Department of Gastroenterology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai, India

used to measure symptoms of FGID was the SAGIS questionnaire, which simultaneously assesses psychological effects on gastrointestinal symptoms. This score, validated by Koloski et al., has excellent psychometric properties, supporting clinical assessment, and symptom-based categorization of patients with a broad spectrum of gastrointestinal symptoms [8].

Despite these strengths, the study had few weaknesses such as the small sample size that limits its generalisability. Of all included patients with overlap, improvement in the SAGIS score after treatment was not significant in the 2 with IBS-C. As rifaximin is currently only approved for non-constipated IBS [6], the benefits of rifaximin in FD patients with IBS overlap irrespective of subtype remains unproven. von Woffen et al. showed that in patients with severe FD/IBS, there is a higher probability of overlap. Furthermore, as compared with routine clinical documentation, standard questionnaires increase the probability of diagnosing overlap [9]. Since in the study by Shah et al. the criteria included patients with moderate–severe symptoms, the probability of enrolling patients with overlap was likely to be increased.

While there is improvement in the overall symptom score at 2 and 6 weeks after rifaximin in patients with FD, the sustainability of the benefit remains a topic of interest. In a previous study of 1094 patients with IBS-D, though the symptom relapse of after rifaximin occurred in 64% patients, there was a greater likelihood of response after repeat treatment with rifaximin [10]. The present study by Shah et al. had a short follow-up of ≤ 6 weeks. As FD is a chronic disorder, it will be useful to design a study with a longer follow-up. Though the recommended dose of rifaximin in non-constipated IBS is 550 mg t.i.d., the 550 mg b.i.d. dose used in the study by Shah et al. was adequate for positive results. Further studies for optimizing dosage of rifaximin in FD may be required.

The authors need to be congratulated on one of the first studies of the impact of presence of overlap syndrome on therapeutic outcomes with antimicrobial treatment. Despite a small number of patients, the study has shown significant benefit in FD patients with or without overlap. These findings need to be confirmed in larger studies and RCTs.

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