Antibiotic Therapy for the Irritable Bowel Syndrome

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The irritable bowel syndrome (IBS) is one of the most common conditions seen in clinical practice. The number of effective pharmacologic agents for IBS is limited, and therapeutic innovation is hampered by a lack of complete understanding of the pathophysiology of the syndrome, which is probably heterogeneous.[1] Alterations in the bacterial flora are increasingly considered to be a relevant pathogenetic factor.[2] Consequently, probiotics are being studied as treatment for IBS, but the magnitude of improvement in symptoms with probiotics is limited.[2] Some studies have suggested that there are beneficial effects with poorly absorbed antibiotics, but the results of the studies have been questioned because of issues with patient selection, the choice of end point, and the statistical analysis, and, most of all, because lactulose breath test results were interpreted as indicative of small-intestine bacterial overgrowth.[3-6]

In this issue of the *Journal*, Pimentel et al. report the results of two identically designed, large, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2) of rifaximin, a poorly absorbed antibiotic, in patients with IBS without constipation.[7] A total of 1260 patients were randomly assigned to receive rifaximin, at a dose of 550 mg three times daily, or placebo for 2 weeks, followed by a 10-week posttreatment follow-up period. The primary end point was the proportion of patients who reported adequate relief of IBS symptoms, as assessed by responses (yes or no) to a question about relief of symptoms that was asked weekly during the first 4 weeks after treatment. The key secondary end point was the proportion of patients reporting adequate relief of bloating during the same period.

In both studies, patients consistently met the criteria for relief of global IBS symptoms and IBS-related bloating. In the rifaximin groups, as compared with the placebo groups, a significantly higher proportion of patients reported adequate relief of IBS symptoms (41% vs. 32% in the two trials combined, $P<0.001$) or bloating (40% vs. 30%, $P<0.001$) for at least 2 of the first 4 weeks. Similarly significant results were obtained in an analysis of relief of symptoms during the 10-week period after the end of the double-blind treatment phase.

These large, high-quality, multicenter studies confirm that, as a group, patients who have IBS without constipation have a significantly better response to rifaximin than to placebo. Rifaximin is a poorly absorbed antibiotic with broad-spectrum activity against gram-negative bacteria, gram-positive bacteria, and anaerobes, including *Clostridium difficile*. It has been extensively used in the treatment and prevention of travelers' diarrhea, for which it has shown a favorable side-effect and safety profile, with low risk for the development of resistance.[8]

The TARGET studies have some attractive findings. First, the sustained benefit over at least 10 weeks, after a short treatment course, is appealing. Second, the beneficial effects of rifaximin include its effects on bloating, which is one of the most challenging symptoms of IBS. Third, the similarity of the results in both studies confirms the reproducibility of the therapeutic effect. On the other hand, the therapeutic gain, with the rates of response to treatment (i.e., adequate relief) ranging between 9 and 12% more with rifaximin than with placebo, is in the lower spectrum of what is considered to be clinically relevant.[9] Although it is clear that not all patients have a response with rifaximin, the available data suggest that a subgroup of patients may have a substantial response.[5,7] It is unclear whether this group can be identified by demographic characteristics, symptoms, or results of lactulose breath testing. Most important, IBS is a chronic disorder, and although the therapeutic effect persists after the 2-week treatment period, the response over time suggests that there is some loss of efficacy, as compared with placebo, with respect to certain symptoms toward the end of the 10-week follow-up period. It is unknown whether patients would have a favorable response again with retreatment.

The mechanism underlying the beneficial effect of rifaximin with respect to symptoms of IBS is a matter of controversy. Initial studies of poorly absorbed antibiotics for the treatment of patients with IBS were based on the hypothesis

that a large proportion of these patients had small-intestine bacterial overgrowth, a disorder characterized by the presence of abnormally high numbers of bacteria in the small intestine.[7] Initial studies reported the presence of small-intestine bacterial overgrowth in up to 80% of patients, on the basis of a rapid rise in breath hydrogen during lactulose breath testing. However, this test is prone to false positive results, and several other investigators failed to reproduce these high incidences.[10] When the standard method of jejunal aspiration and bacterial culturing was used, small-intestine bacterial overgrowth was found in only 4% of patients with IBS.[10] More recently, it was suggested that the use of proton-pump inhibitors conferred a predisposition to enhanced bacterial colonization of the small intestine.[10] Most studies assessing poorly absorbed antibiotics in the treatment of patients with IBS, including the present study, do not report or adjust for the concomitant use of proton-pump inhibitors, so this remains an area of controversy. The most likely mode of action of rifaximin is a reduction in overall bacterial load, especially in the large bowel.[8] This may lead to decreased bacterial fermentation and less bloating, possibly in combination with decreased secretion of bacterial products or host responses to bacterial products that contribute to the generation of symptoms.

Neither rifaximin nor any other antibiotic has been approved for the treatment of IBS, and the Food and Drug Administration is currently reviewing the new-drug application for rifaximin for the treatment of patients who have IBS without constipation and IBS-related bloating. With three studies confirming the efficacy of the drug after a short-term regimen and a relatively short follow-up period,[5,7] rifaximin has the potential to provide a welcome addition to the limited armamentarium of agents that are available to treat IBS. Moreover, rifaximin had a favorable safety profile in these studies, with no treatment-associated major adverse events and no cases of *C. difficile* colitis. At the current stage of knowledge, however, clinicians should proceed with caution. IBS is a chronic condition, and some regulatory authorities recommend that studies be conducted that will address the efficacy of rifaximin when it is used for continued or intermittent treatment of IBS (see www.tga.gov.au/docs/pdf/euguide/ewp/078597en.pdf), and this seems to be even more appropriate in the case of antibiotic therapy that may have a risk of inducing resistance over time. Furthermore, taking into account the high prevalence of IBS in the general population, the effect that larger-scale use of poorly absorbed antibiotics may have on antibiotic-resistance profiles should be taken into account.[6] Studies aimed at better identifying the patients with IBS who may have a response to rifaximin and, especially, studies that will assess the longer-term effect of rifaximin treatment are eagerly awaited. Until this information becomes available, it seems prudent to restrict the use of nonabsorbable antibiotics to patients in whom small-intestine bacterial overgrowth has been confirmed, or to single-treatment cycles in patients who have IBS without constipation and who have not had a response to currently available symptom-directed therapies.[1]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130:1480-91. [Erratum, Gastroenterology 2006;131:688.]
2. Lee KJ, Tack J. Altered intestinal microbiota in irritable bowel syndrome. Neurogastroenterol Motil 2010;22:493-8.
3. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 2000;95:3503-6.
4. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2003;98:412-9.
5. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. Ann Intern Med 2006;145:557-63.
6. Drossman DA. Treatment for bacterial overgrowth in the irritable bowel syndrome. Ann Intern Med 2006;145:626-8.
7. Pimentel M, Lembo T, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22-32.
8. Layer P, Andresen V. Review article: rifaximin, a minimally absorbed oral antibacterial, for the treatment of travellers' diarrhoea. Aliment Pharmacol Ther 2010;31:1155-64.
9. Corazziari E, Bytzer P, Delvaux M, et al. Clinical trial guidelines for pharmacological treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2003;18:569-80.
10. Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2009;7:1279-86.