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Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome

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BACKGROUND & AIMS: Few treatments have demonstrated efficacy and safety for diarrhea-predominant irritable bowel syndrome (IBS-D). A phase 3, randomized, double-blind, placebo-controlled trial was performed to evaluate the safety and efficacy of repeat treatment with the nonsystemic antibiotic rifaximin. **METHODS:** The trial included adults with IBS-D, mean abdominal pain and bloating scores of 3 or more, and loose stool, located at 270 centers in the United States and Europe from February 2012 through June 2014. Those responding to a 2-week course of open-label rifaximin 550 mg 3 times daily, who then relapsed during an observation phase (up to 18 weeks), were randomly assigned to groups given repeat treatments of rifaximin 550 mg or placebo 3 times daily for 2 weeks. The primary end point was percentage of responders after first repeat treatment, defined as a decrease in abdominal pain of ≥30% from baseline and a decrease in frequency of loose stools of ≥50% from baseline, for 2 or more weeks during a 4-week post-treatment period. **RESULTS:** Of 1074 patients (44.1%) who responded to open-label rifaximin, 382 (35.6%) did not relapse and 692 (64.4%) did; of these, 636 were randomly assigned to receive repeat treatment with rifaximin (n = 328) or placebo (n = 308). The percentage of responders was significantly greater with rifaximin than placebo (38.1% vs 31.5%; $P = .03$). The percentage of responders for abdominal pain (50.6% vs 42.2%; $P = .018$) was significantly greater with rifaximin than placebo, but not stool consistency (51.8% vs 50.0%; $P = .42$). Significant improvements were also noted for prevention of recurrence, durable response, and bowel movement urgency. Adverse event rates were low and similar between groups. **CONCLUSIONS:** In a phase 3 study of patients with relapsing symptoms of IBS-D, repeat rifaximin treatment was efficacious and well tolerated. ClinicalTrials.gov ID: NCT01543178.

Keywords: Bloating; Functional Bowel Disease; Nonabsorbed; Xifaxan.

Diarrhea-predominant irritable bowel syndrome (IBS-D) is a common gastrointestinal disorder characterized by recurring abdominal pain, bloating, and loose stools in the absence of structural or biochemical abnormalities.[1] Nonpharmacologic options for the treatment of IBS-D include psychological approaches, dietary and lifestyle modifications, probiotics, and fiber supplementation, although each has shown variable and less than optimal relief of IBS-D symptoms.[2–4] Pharmacologic therapies, such as anti-diarrheals (eg, loperamide),[3] have limited beneficial effects on global IBS symptoms (eg, abdominal pain), and the $5HT_3$ antagonist alosetron is approved only for women with severe, treatment-refractory IBS-D,[3] with substantial restrictions on its use. Antidepressants, such as tricyclic agents, although not approved for the treatment of IBS-D, have been considered efficacious for reducing abdominal pain and global IBS symptoms in patients with IBS.[2] However, data on the efficacy of these agents specifically for treatment of IBS-D are limited.[2] Eluxadoline, a twice-daily μ-opioid receptor agonist and δ-opioid receptor antagonist,[5] was approved in 2015 for the treatment of IBS-D.

Patients with IBS have alterations in the intestinal microbiota compared with healthy individuals[6–14]; therefore, the intestinal microbiota may be an effective target for treatment of IBS-D. Rifaximin is an oral, minimally absorbed, broad-spectrum antimicrobial agent that targets the gastrointestinal tract and is associated with a low risk of clinically relevant bacterial antibiotic resistance.[15–18] Rifaximin was approved by the US Food and Drug Administration in May 2015 for the treatment of IBS-D in adults. In 2 large, multicenter, phase 3 trials of patients with IBS-D (Targeted, Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for IBS-D [TARGET] 1 and 2), 40.7% of patients treated with rifaximin 550 mg 3 times daily (TID) for 2 weeks experienced adequate relief of global IBS symptoms for ≥2 of the first 4 weeks post-treatment compared with 31.7% of patients treated with placebo (Δ 9%; $P < .001$, pooled data).[15] In addition, a greater percentage of rifaximin-treated than placebo-treated patients reported durable improvement in IBS-D symptoms for at least 10 weeks post-treatment ($P = .001$, pooled data). However, the persistence of this treatment effect beyond the 10-week follow-up period, assessed in TARGET 1 and 2, and the efficacy and safety of

Abbreviations used in this paper: **AE, adverse event; IBS-D, diarrhea-predominant irritable bowel syndrome; TARGET, targeted, nonsystemic antibiotic rifaximin gut-selective evaluation of treatment for IBS-D; TID, three times daily.**

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repeated treatment after clinical response and subsequent symptom relapse, had only been evaluated in open-label, retrospective studies.[19,20]

The aim of this trial, which included an open-label enrichment phase followed by a randomized, placebo-controlled phase, was to determine the efficacy and safety of repeat treatment with rifaximin in patients with IBS-D who had responded to a 2-week course of rifaximin and subsequently experienced IBS symptom recurrence. Specifically, the primary efficacy assessment compared the percentage of patients who were repeat responders for both abdominal pain and stool consistency during the first 4 weeks after a second course of treatment (repeat treatment with rifaximin or treatment with placebo).

Methods

Study Patients

Eligible patients were 18 years of age or older; had a colonoscopy in the past 10 years or underwent a flexible sigmoidoscopy with biopsies; received a diagnosis of IBS (confirmed by Rome III diagnostic criteria); and did not have adequate relief of global IBS symptoms and bloating during a screening phase. Exclusion criteria included renal or hepatic disease, diabetes, and history of inflammatory bowel disease; previous gastrointestinal surgery; abnormal thyroid function not adequately controlled by thyroid medication; and infection with human immunodeficiency virus or hepatitis B or C.

Based on daily responses to a diary questionnaire (Supplementary Table 1) during the placebo-screening phase, patients must have rated their average abdominal pain $\geq$3 (scale 0–10: 0 = no pain; 10 = worst possible pain) and bloating $\geq$3 (scale 0–6: 0 = not at all; 6 = a very great deal) and have experienced loose stools for $\geq$2 days in a week with a Bristol Stool Scale type 6 (fluffy pieces with ragged edges, a mushy stool) or 7 (watery stool, no solid pieces; entirely liquid stool). These 3 inclusion criteria had to be met for patients to proceed in the study. Furthermore, patients were excluded if (after initiating diary assessments during the placebo-screening phase) they were taking anti-diarrheals, anti-spasmodics, narcotics, prokinetic drugs, warfarin, drugs indicated for IBS (eg, alosetron, lubiprostone), or products marketed as probiotics; patients also were excluded if they were taking rifaximin or any antibiotic within 14 days before providing written informed consent. Patients could continue to take antidepressant agents, provided that they had been taking a stable dose for at least 6 weeks before providing written informed consent. The protocol was approved by all institutional review boards and ethics committees at participating sites, and all patients provided written informed consent. All authors had full access to the study data and reviewed and approved the final manuscript.

Study Design

In total, 270 centers in the United States, Germany, and the United Kingdom participated in the randomized, double-blind, placebo-controlled, 51-week, phase 3 trial (Figure 1*A*) conducted from February 2012 through June 2014 (ClinicalTrials.gov ID: NCT01543178). After a prescreening eligibility phase, patients entered into a single-blind screening (ie, baseline) phase of placebo TID for 10 $\pm$ 3 days. After completion of the screening phase, patients meeting all eligibility criteria entered into the open-label treatment phase, which consisted of open-label treatment with rifaximin 550 mg TID for 2 weeks, followed by a 4-week assessment period to determine response to rifaximin. A responder was defined as a patient simultaneously meeting weekly response criteria for abdominal pain ($\geq$30% decrease from baseline in mean weekly pain score) and stool consistency ($\geq$50% decrease from baseline in number of days/week with Bristol Stool Scale type 6 or 7 stool) during $\geq$2 of the 4 weeks after treatment. Responders to open-label rifaximin were then monitored in an observation phase for up to an additional 18 weeks or until symptom relapse occurred. Patients who failed to meet the prespecified weekly response criteria for both abdominal pain and stool consistency after the initial open-label rifaximin treatment were classified as nonresponders and withdrawn from the trial.

Patients who were classified as responders to the initial open-label rifaximin treatment and who experienced a relapse in IBS-D symptoms (defined as a loss of treatment response for either weekly abdominal pain [<30% decrease from baseline in mean weekly pain score] or stool consistency [<50% decrease from baseline in number of days/week with Bristol Stool Scale type 6 or 7 stool] for $\geq$3 weeks of a consecutive, rolling 4-week period during the 18-week observation phase) entered into the double-blind treatment phase of the trial, in which patients were randomly assigned (1:1) to receive 2 repeat treatment courses of rifaximin 550 mg TID or placebo TID for 14 days. Randomization was stratified by site. Each site used a randomization code generated and maintained by a clinical research organization by a block randomization schema (block size of 2) using a computerized interactive voice or web response system that was independent of other centers' randomization codes. Response to repeat treatment was assessed during the 4 weeks immediately after a repeat treatment course. The prespecified primary evaluation period for the trial was the 4-week follow-up period after the first repeat treatment. However, all patients, regardless of response or relapse status after the first repeat treatment, received a second repeat treatment with the same treatment assigned at randomization (ie, rifaximin 550 mg or placebo TID for 14 days). The second repeat treatment course was initiated 10 weeks after completion of the first repeat treatment course (ie, after the 4-week primary evaluation period and 6-week repeat treatment observation phase) and was included to assess the safety of additional treatment with rifaximin. The overall trial design reflected input from the United States and European health authorities, and is in keeping with the subsequent publication of US Food and Drug Administration and European Medicines Agency guidance for the development of drugs for IBS.[21–23]

Efficacy End Points and Safety Assessments

An interactive voice or web response system was used to collect responses to daily symptom questions and a separate weekly global IBS symptom question (Supplementary Table 1). The primary end point of the trial was the percentage of patients who were responders (as defined here) for both abdominal pain and stool consistency during the 4-week follow-up after the first repeat treatment course (see Figure 1*A*). Three key secondary end points were evaluated: