Rifaximin May Relieve IBS Symptoms in Some

Broad-spectrum antibiotic may work by controlling bacterial overgrowth in the gut.

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A 2-week course of rifaximin was associated with adequate relief of irritable bowel syndrome symptoms for the first 4 weeks after completion of therapy in 41% of patients who had IBS without constipation.

The results of two identical phase III placebo-controlled studies, TARGET 1 and TARGET 2, were similar overall, Dr. Mark Pimentel and his colleagues wrote (N. Eng. J. Med. 2011;364:22-32).

TARGET 1 found that 41% of patients who were taking rifaximin reported adequate relief of their global IBS symptoms, compared with 31% of those taking placebo ($P = .01$), for at least 2 of the first 4 weeks after treatment ended. In TARGET 2, those numbers were 41% vs. 32% ($P = .03$), and for the two studies combined the results were also 41% vs. 32%, respectively (P less than .001).

Rifaximin, which is a poorly absorbed broad-spectrum antibiotic, may work by controlling bacterial overgrowth in the gut, wrote Dr. Pimentel of the Cedars–Sinai Medical Center, Los Angeles, and his colleagues. However, the authors explained, "some patients in both of our studies did not have a response to treatment, a finding that is consistent with the results of other placebo-controlled clinical trials involving patients with IBS and that may reflect differences in the underlying cause of the symptoms."

Both studies were funded by Salix Pharmaceuticals, the drug's manufacturer. They included a total of 1,260 patients (623 in TARGET 1 and 637 in TARGET 2). All patients were randomized to 14 days of either placebo or 550 mg rifaximin three times daily and were followed weekly for 10 additional weeks. Study retention was high, with 90% completing the entire trial. Last-results carried forward were used in a secondary analysis.

The patients' average age was 46 years in each group. Overall, most of the patients (about 72%) were female, and 91% were white. All had IBS without constipation, with an average duration of 11-12 years.

Patients eligible for the study rated their IBS symptoms of abdominal pain and bloating as a 2-4.5 on a 7-point Likert scale (where 0 = not at all, and 6 = a very great deal). Most patients (82%) reported daily stool urgency.

The primary end point was adequate relief of global IBS symptoms, which patients answered with "yes" or "no." Dr. Pimentel and his associates prospectively determined the threshold of "adequate relief" as a score of 0 or 1 for at least 50% of days in a given week and 1 or 2 for 100% of the days in a given week. Additionally, patients were asked to rate relief of bloating, abdominal pain and discomfort, and daily stool consistency.

Overall, significantly more patients in the active group than the placebo group met the primary end point (41% vs. 32%). The secondary analysis with last observation carried forward yielded similar results.

In the two studies combined, significantly more patients in the active group than the placebo group reported adequate relief of bloating for at least 2 of the first 4 weeks after treatment (40% vs. 30%; P less than .001), the investigators said.

For the composite end point of abdominal pain or discomfort and loose or watery stools during this time period, significantly more patients treated with rifaximin had relief, compared with placebo-group patients (TARGET 1: 47% vs. 39%, $P = .04$; TARGET 2: 47% vs. 36%, $P = .008$).

In an analysis of durability of response based on a weekly assessment, "more patients in the rifaximin group than in the placebo group in both studies had adequate relief of global IBS symptoms within the first month, with continued relief during the first 2 months and during all 3 months in both studies," the authors wrote, noting that the difference was significant at P less than .001 for both studies combined, for relief during all 3 months.

Dr. Pimentel and his associates provided a supplementary appendix containing graphs showing that the percentage of patients with adequate relief of global IBS symptoms declined in both groups, in both studies, during the 10 weeks after treatment.

Two patients in the rifaximin group and five in the placebo group had serious adverse events. The incidence of infections was similar in the two groups. There were no cases of ischemic colitis and no deaths.

Regarding the mechanism of action, the authors noted several possible pathways. Besides altering the balance of the gut flora, the drug might also decrease gas associated with bacterial activity, reduce local inflammatory response to bacteria, or alter both the bacteria and host response.

"Whatever the final pathway, the durable effects suggest that rifaximin is affecting an underlying cause of IBS that is linked to an alteration in the intestinal microbiota," they said.

In an accompanying editorial, Dr. Jan Tack of the University of Leuven, Belgium, noted the declining durability of rifaximin's effect and the relatively small difference between the active and placebo responses.

"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," he wrote. Dr. Tack also noted that since IBS is a chronic disorder, the follow-up period was relatively short (N. Eng. J. Med. 2011;364:81-2).

Despite the studies' positive findings, including the favorable safety profile, he wrote that "clinicians should proceed with caution."

Although "rifaximin has the potential to provide a welcome addition to the limited armamentarium of agents that are available to treat IBS," he also wrote that, "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."

Until researchers are able to identify a subgroup of patients that might respond well to the drug, "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," he wrote.

Dr. Tack reported no financial relationship with Salix. ■

VITALS

Major Finding: In 41% of patients, rifaximin was associated with adequate relief of global IBS symptoms during the first 4 weeks after treatment ended, compared with 32% who took placebo (P less than .001), in two studies combined.

Data Source: Two phase III, double-blind placebo-controlled studies of a 2-week course of rifaximin at a dose of 550 mg three times daily; a total of 1,260 patients were randomized.

Disclosures: Salix Pharmaceuticals sponsored both studies. All of the paper's authors reported financial relationships with Salix, either in the form of grants, payment for producing educational materials, travel expenses, speakers' fees, company stock, or company employment. Cedars–Sinai Medical Center, employer of the primary investigator, holds patents licensed by Salix Pharmaceuticals.