

ADVANCES IN IBS

Current Developments in the Management of Motility Disorders and Irritable Bowel Syndrome

Rifaximin for Treatment of Irritable Bowel Syndrome

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G&H What is the rationale for using rifaximin to treat irritable bowel syndrome?

DD Antibiotics have been used to treat irritable bowel syndrome (IBS) for a very long time; broad-spectrum antibiotics were used for years prior to the development of rifaximin (Xifaxan, Salix). Our initial understanding of this condition was based on the concept of bacterial overgrowth, so antibiotics were a logical treatment. IBS was thought to be complicated by bacterial overgrowth in the small bowel, perhaps as a result of delayed motility, which would lead to postprandial production of gas. However, bacterial overgrowth is no longer thought to play as large a role in IBS, as most investigators see bacterial overgrowth in only approximately 5–10% of these patients.

While only a subgroup of patients will benefit from rifaximin because of its ability to treat bacterial overgrowth, clinicians are learning that this drug may also provide a benefit in patients who do not have bacterial overgrowth. We do not yet have a clear understanding of why antibiotics can work in the absence of bacterial overgrowth; one possibility is that antibiotics reduce overall bacterial content in the colon.

G&H Which other antibiotics might prove beneficial for treating IBS?

DD Ciprofloxacin, levofloxacin, neomycin, and metronidazole can all be effective for the treatment of bacterial overgrowth associated with IBS, but they have not been fully tested for IBS per se. One advantage of rifaximin is that it has no systemic effects; other antibiotics are

absorbed systemically, but rifaximin works only within the gastrointestinal tract.

G&H Aside from antibiotics, what other drugs are used to treat IBS?

DD IBS is a very heterogeneous condition in which different subsets of patients have different treatment requirements. Antimotility agents (eg, anticholinergic agents or loperamide) can be beneficial in patients whose symptoms are primarily related to rapid transit, as with milder types of IBS with diarrhea, while antidepressants are often used to treat patients who have more painful symptoms. We also have specific drugs that are targeted toward the bowel: lubiprostone (Amitiza, Takeda) is approved for IBS with constipation in adult women and alosetron (Lotronex, Prometheus) is on the market for patients with severe IBS with diarrhea. Probiotics may also have a role in reducing bloating-related discomfort and general symptoms. Given these options, clinicians need to determine the best agent for each patient based on his or her specific clinical profile. In general, treatment of IBS involves selecting which patients will respond to each of the available treatment options; often, combinations of treatments are used.

One problem with using antibiotics to treat IBS is that we do not know which patients would most benefit from their use, and we do not have any biomarkers that could help to inform this decision. Previously, clinicians thought that breath testing would help to guide treatment of IBS by detecting patients with bacterial overgrowth. However, we now know that antibiotics work even in patients who do not have bacterial overgrowth, and available tests to detect bacterial overgrowth are not very accurate, so breath testing is starting to fall out of general interest.

G&H What are the advantages and disadvantages of using antibiotics to treat IBS?

DD The advantage to using antibiotics is that they can work quickly and the effect is sustained even when patients go off treatment. If an antibiotic is effective, then clinicians only need to treat patients for a couple of weeks to get lasting benefit, as opposed to keeping a patient on medication longterm. After the antibiotic is

stopped, the patient's IBS symptoms may not return for several months.

The disadvantage to using antibiotics is that these drugs could potentially change the bacterial flora in a way that might lead to the development of resistant organisms. There is a great deal of concern in the general medical community about using antibiotics for long periods of time because of the risk of resistance, so physicians generally try to be very careful when using these drugs. Due to concerns about resistance, I think clinicians will need to use good clinical judgement about when to re-treat with rifaximin or any other antibiotic used for IBS.

Another disadvantage of using antibiotics to treat IBS is that we do not know when to re-treat patients with these drugs. Ideally, I would want to treat a patient and then wait 4–6 months before re-treating him or her; if a patient's symptoms return 2 weeks later, however, the clinician is faced with a dilemma. Since IBS patients may have a placebo response following initial treatment, it is difficult to determine whether a positive response is necessarily due to the drug.

G&H Can you briefly describe the design of the TARGET trials?

DD TARGET 1 and TARGET 2 were multicenter, randomized, double-blind, placebo-controlled trials. Patients were given 550 mg rifaximin 2–3 times per day for 2 weeks and then were followed for another 10 weeks. Approximately 1,200–1,300 patients were enrolled in the 2 studies. Rome II criteria were used to ensure that all patients had IBS, and patients with constipation were excluded from these studies. The studies' primary endpoints were bloating and global assessment of IBS symptoms; secondary endpoints included abdominal pain and stool frequency. Response to treatment was defined as relief of symptoms during 2 of the first 4 weeks of treatment. TARGET 1 and TARGET 2 were identically designed, and results of both studies were reported in a recent paper by Pimentel and colleagues.

G&H What were the results of these trials?

DD These studies met both primary and some secondary endpoints: abdominal pain, bloating, and stool symptoms were all significantly better following rifaximin treatment. In a combined analysis of data from both studies, the responder rate in the rifaximin-treated group was approximately 41% compared to 32% in the placebo group; this difference was significant ($P=.001$). Results for bloating showed a similar difference; there was a 40% responder rate among patients treated with rifaximin compared to a 30% responder rate among patients treated with

placebo ($P<.001$). Abdominal pain, a secondary endpoint, was also significant, although at a lower level ($P=.03$ in TARGET 1 and $P=.02$ in TARGET 2). The authors noted that the benefit of treatment declined slightly over the post-treatment observation period, but daily assessment of global IBS symptoms nonetheless showed a significant effect over the entire 3-month study period.

Some commentators have argued that the studies' findings may not reflect a significant clinical benefit, despite the fact that they were statistically significant; indeed, the difference between the treatment and control groups was approximately 10% for most endpoints. While this difference may not be dramatic, it is consistent with other treatment studies in IBS.

G&H What are the clinical implications of these findings?

DD These studies support the use of rifaximin for treatment of patients with IBS. However, we do not know which patients will show the greatest benefit from such treatment; it would be helpful if we had some clinical or biological markers that could predict treatment response. In addition to learning how to predict which patients are likely to benefit from rifaximin treatment, we also need to determine when we should re-treat patients. Unlike acute infections, for which an antibiotic is often curative, IBS symptoms are likely to recur. If symptoms keep returning within a few weeks, repeated re-treatments with an antibiotic may not be appropriate.

G&H What further research is needed regarding the use of rifaximin in IBS?

DD It would be valuable if studies were performed either pre- or postapproval to determine how quickly patients' symptoms return following rifaximin treatment; such data could help us to better predict when re-treatment might be necessary. We also need studies that can help to determine if any particular biomarkers can predict which patients are most likely to benefit from rifaximin treatment.

Suggested Reading

Pimentel M, Lembo A, Chey WD, et al; TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* 2011;364:22-32.

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Yang J, Lee HR, Low K, Chatterjee S, Pimentel M. Rifaximin versus other antibiotics in the primary treatment and retreatment of bacterial overgrowth in IBS. *Dig Dis Sci.* 2008;53:169-174.