Rifaximin in treatment of patients with Irritable bowel syndrome

Lembo A, Pimentel M, Rao SS, Schoenfeld P, Cash B, Weinstock LB, Paterson C, Bortey E, Forbes WP. Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome. Gastroenterology 2016;151(6):1113-1121.

Irritable bowel syndrome (IBS) is a syndrome characterized by chronic recurring abdominal pain or discomfort and altered bowel habits over a period of at least 3 months without any underlying structural or biochemical abnormalities. IBS can be diagnosed by using Rome III criteria and is sub-classified using patients' predominant symptoms either as constipation (IBS-C) or diarrhea predominant (IBS-D), mixed (IBS-M) or unclassified (1). Prevalence of IBS ranges from 1% to 20%. IBS is more common in women than in men, in lower socioeconomic groups and is most commonly diagnosed in patients younger than 50 years of age. Patients with IBS consume a disproportionate amount of resources both in direct and indirect expenditures (2). A recent U.S. based study showed that IBS-D is associated with higher costs than their matched controls (3). Pathophysiology of IBS appears to involve genetics, gut microbiome, immune dysregulation, altered gut permeability and gut-brain interaction (4). Rifaximin is a gut-selective antibiotic with negligible systemic absorption and a broad spectrum of activity against gram positive and gram negative aerobes and anaerobes.

In a 2006 study involving 87 patients with IBS, rifaximin 400 mg was given TID for 10 days (5). The rifaximin group showed greater improvement of IBS symptoms of diarrhea, constipation, bloating and abdominal pain (p=0.002). They also had lower bloating score after the treatment. In a subsequent study in 2006, 124 patients were randomized to receive rifaximin 400 mg BID vs Placebo for 10 days. There was significant global symptom relief of abdominal bloating, distension and flatulence in the rifaximin group (41.3% vs. 22.9%, p=0.03). This improvement was maintained at the end of phase 3 of study (6). Later in 2011, two randomized double-blind placebo-controlled phase 3 trials (TARGET 1 and TARGET 2) enrolled the patients who had IBS without constipation to receive rifaximin 550 mg three times a day for 2 weeks (7). Patients were followed for additional 10 weeks. Significantly more patients in the rifaximin group than in the placebo group had adequate relief of global IBS symptoms (40.7% vs. 31.7%, p<0.001) and adequate relief of bloating (40.2% vs. 30.3%, p<0.001). A greater proportion of patients in rifaximin group had improvement in abdominal pain and stool consistency. The rate of adverse effects was similar to placebo.

A retrospective study in 2011 by Weinstock showed 74% of patients with non-constipation IBS in a community had relief of IBS symptoms with initial and repeat treatment of rifaximin (8). Another retrospective study showed retreatment with rifaximin for IBS was successful up to 5 times in more than 75% of subjects irrespective of initial treatment (9). There was no shortening of benefit duration suggesting a lack of development of clinical resistance to the antibiotic.

A recently published study in 2016, further evaluated the safety and efficacy of repeat treatment of rifaximin in IBS-D. This phase 3, randomized, double-blind, placebo-controlled trial included patients from 270 centers across the United States and Europe (10). Eligible patients were of age ≥18 years, received colonoscopy or flexible sigmoidoscopy with biopsy within last 10 years and had a diagnosis of IBS based on Rome III criteria. Patients with renal, thyroid or hepatic disease, HIV, IBD, DM or previous abdominal surgery were excluded. Furthermore, the patients with use of oral antibiotic or rifaximin within previous 14 days, those using antidiarrheals, antispasmodics, narcotics or other drugs approved for IBS were excluded. Patients were allowed to continue antidepressants if they had been on stable dose for at least 6 weeks.

After the screening phase, eligible patients received open-label treatment with rifaximin 550 mg TID for 2 weeks and were observed for 4 weeks to assess the response to treatment. The patients who showed simultaneous improvement of abdominal pain and stool consistency for greater than 2 weeks were called

responders. They were monitored for another 18 weeks while non-responders were withdrawn from the study. During this 18 week observation period among responders (1074 patients), the patients who had a relapse of IBD-D symptoms (692 patients, 64.4%) were randomized to receive 2 repeat treatment courses of rifaximin 550 mg TID (n=328) or Placebo (n=308) for 2 weeks. Response to treatment was assessed during the 4 weeks immediately after treatment. The patients were observed for another 6 weeks and then received the repeat course of rifaximin or placebo irrespective of their symptoms recurrence.

Evaluation of individual endpoint components showed a statistically significant difference for responders of abdominal pain (50.6% vs. 42.2%; p=0.018) in rifaximin group than placebo but not for responders of stool consistency (51.8% vs. 50.0%; p=0.42). No significant difference was noted for bloating. The number of adverse effects apart from nausea was similar in both of the groups. Only one case of clinical C difficile infection was identified.

The results of this most recent study strongly supported beneficial effects of rifaximin in IBS. There is growing evidence that gut microbiota is altered in IBS but the precise mechanism which alters pathophysiology of IBS remains to be elucidated. Most studies have focused on the use of rifaximin in IBS-D, however, it also has been found to be effective among other sub-classes of IBS (11). These studies were restricted to a maximum of two or three treatment courses of rifaximin, however, patients with continuous symptoms or relapse of the disease might need a more frequent use of the antibiotic. Ongoing randomized placebo-controlled studies on intestinal microbiota on the pathogenesis would recommend fecal transplantation as a new therapeutic option for IBS patients due to their disturbed gut ecosystem.

Bhupinder Romana, Veysel Tahan

Division of Gastroenterology and Hepatology, University of Missouri-Columbia
1 Hospital Drive, Columbia, Missouri, USA

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD. Functional bowel disorders. Gastroenterology 2006; 130: 1480-91. **[CrossRef]**
2. Brandt LJ, Chey WD, Foxx-Orenstein AE. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol 2009; 104(Suppl 1): S1-35. **[CrossRef]**
3. Doshi JA, Cai Q, Buono JL. Economic burden of irritable bowel syndrome with constipation: a retrospective analysis of health care costs in a commercially insured population. J Manag Care Spec Pharm 2014; 20: 382-90. **[CrossRef]**
4. Lacy BE, Chey WD, Lembo AJ. New and Emerging Treatment Options for Irritable Bowel Syndrome. Gastroenterol Hepatol (N Y) 2015; 11: 1-19.
5. Pimentel M, Park S, Mirocha J. 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. **[CrossRef]**
6. Sharara AI, Aoun E, Abdul-Baki H. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. Am J Gastroenterol 2006; 101: 326-33. **[CrossRef]**
7. Pimentel M, Lembo A, Chey WD. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011; 364: 22-32. **[CrossRef]**
8. Weinstock LB. Long-term outcome of rifaximin therapy in nonconstipation irritable bowel syndrome. Dig Dis Sci 2011; 56: 3389-90. **[CrossRef]**
9. Pimentel M, Morales W, Chua K. Effects of rifaximin treatment and retreatment in nonconstipated IBS subjects. Dig Dis Sci 2011; 56: 2067-72. **[CrossRef]**
10. Lembo A, Pimentel M, Rao SS. Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome. Gastroenterology 2016; 151: 1113-21. **[CrossRef]**
11. Zeber-Lubecka N, Kulecka M, Ambrozkiewicz F. Limited prolonged effects of rifaximin treatment on irritable bowel syndrome-related differences in the fecal microbiome and metabolome. Gut Microbes 2016; 7: 397-413. **[CrossRef]**

Address for Correspondence: Veysel Tahan
E-mail: tahanv@health.missouri.edu
Received: 12.12.2016 **Accepted:** 20.12.2016
© Copyright 2017 by The Turkish Society of Gastroenterology
• Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2016.25122016