

Efficacy of Ramosetron in Male Patients With Irritable Bowel Syndrome With Diarrhea

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Summary

Serotonin (5-Hydroxytryptamine [5-HT]) plays an important role in gastrointestinal (GI) motility and sensation, and abnormal levels have been shown in patients with irritable bowel syndrome (IBS).^{1,2} Drugs acting on 5-HT receptors have the potential to reduce the smooth muscle spasm, abdominal pain, and changes in bowel habit in IBS.

Recently, Lee et al³ assessed the efficacy and safety of ramosetron, a 5-HT₃ receptor antagonist, compared with mebeverine in male patients with diarrhea-predominant IBS (IBS-D). This study was performed in a multicenter, randomized, open-label, parallel-group, non-inferiority comparative design. A total of 343 male patients with IBS-D were randomized to either ramosetron 5 µg once daily or mebeverine 135 mg 3 times daily for 4 weeks.

The weekly responder rates for global IBS symptoms, abdominal pain/discomfort and abnormal bowel habits in the ramosetron and mebeverine groups significantly increased during the treatment period ($P < 0.001$). The severity scores of abdominal pain/discomfort and urgency, the stool form scores and the stool frequency recorded daily were reduced significantly in both

treatment arms, compared with the baselines ($P < 0.001$). There were no significant differences in the weekly responder rates (37% vs 38% at 4-week) and in the adverse event profiles between the ramosetron and mebeverine groups. Neither severe constipation nor ischemic colitis was reported. The authors concluded that the ramosetron 5 µg once daily was as effective as mebeverine 3 times daily in male patients with IBS-D.

Comment

IBS is the most common functional bowel disorder and is characterized by recurrent abdominal pain and discomfort with altered bowel habits.⁴ IBS may lead to impaired social and personal functions as well as deterioration in the quality of life of affected individuals. While the pathophysiology of IBS is still unclear, altered bowel motility, visceral hypersensitivity, immune activation, enteric neuromuscular dysfunction, abnormal brain-gut interactions, and alteration in the gut microbiome have been hypothesized.⁵ Although the concept of IBS has been established for several decades, current available therapies remain unsatisfactory and provide only symptomatic relief at best for many patients with IBS.

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Serotonin (5-HT) signaling in the GI tract is known to control a range of functions such as motility, sensation and secretion.^{1,2} Some evidence suggests that drugs regulating the 5-HT signaling are effective in patients with IBS.⁶⁻⁹ Alosetron, a 5-HT₃ antagonist, was first evaluated in the 1990s, and initial trial data suggested that it was a promising drug for the treatment of IBS-D, particularly in female patients. However, because of the serious adverse events, such as severe constipation and ischemic colitis, reported in IBS patients treated with alosetron, it is available only in the USA with a limited access program for women with severe IBS-D refractory to conventional therapy.¹⁰ Recently, ramosetron, one of the 5-HT₃ receptor antagonists, have been reported to be effective for patients with IBS-D in 2 clinical trials.^{11,12} The administration of ramosetron 5 µg once daily had beneficial effects on IBS symptoms of male patients with IBS-D, compared with placebo.

Lee et al³ assessed the efficacy of ramosetron compared with mebeverine, an antispasmodic agent, in male patients with IBS-D. Ramosetron had similar therapeutic efficacy to mebeverine and the adverse event profiles of the ramosetron group were comparable with those of the mebeverine.³

Since IBS is defined as abdominal pain or discomfort that is improved with defecation,¹³ the US Food and Drug Administration (FDA) requested to evaluate the 2 major IBS symptoms: abdominal pain and defecation in IBS trials. Abdominal pain intensity was recommended as the primary pain assessment and to be evaluated on a daily basis. For defecation component, the assessment of stool frequency was encouraged for IBS-C and stool consistency for IBS-D.^{14,15} In the present study, the primary efficacy parameter was the patient-reported relief of IBS symptoms, including abdominal pain/discomfort and abnormal bowel habits, and the secondary endpoints were the changes in each symptom score. The IBS symptom scores and stool consistency were recorded daily throughout the study periods, and the changes of weekly mean scores were analyzed. This study is considered as a well-designed clinical study that was amenable to the proposal of the FDA for IBS clinical trials.

However, the present study had several limitations. First, because this study was not a placebo-controlled trial, the exact efficacy of ramosetron over placebo was not evaluated. The FDA proposed that clinical studies need to be randomized and placebo-controlled to adequately assess IBS treatment benefits.^{14,15} Furthermore, mebeverine, the control agent in this study, showed no statistically significant benefit compared with placebo for global improvement of IBS symptoms in recent systematic

reviews.¹⁶⁻¹⁸ Thus, randomized placebo-controlled studies are necessary to estimate the exact effects of ramosetron in patients with IBS-D. Second, as the authors mentioned in discussion, because a tablet of ramosetron was taken once daily and a tablet of mebeverine was taken 3 times daily, the psychological effects might be greater in the patients who received mebeverine. Finally, this study was conducted for a short period and used only one dose of ramosetron. Further studies to evaluate the long-term effects of ramosetron and whether twice daily administration of a ramosetron 5 µg tablet has greater efficacy in patients with IBS-D are needed.

Although several limitations exist, the present study is a well-designed, randomized clinical trial to assess the efficacy and safety of 5 µg ramosetron in male patients with IBS-D. Ramosetron can be used safely for the relief of IBS symptoms in male with IBS-D. Further studies on whether ramosetron is effective for female patients with IBS-D are warranted.

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