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Ramosetron in Irritable Bowel Syndrome with Diarrhea: New hope or the same old story?

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Over the last decade, greater understanding of the pathophysiology of diarrhea-predominant irritable bowel syndrome (IBS-D) has resulted in exploration of newer treatment targets, including tryptophan hydroxylase inhibitor (LX-1031), newer M3 muscarinic antagonists (otilonium, darifenacin, solifenacin), oral carbon adsorbents (AST-120), mast cell stabilizers (disodium cromoglycate, ketotifen), and amino acids (glutamine)[1]. Only a handful of these have been approved (e.g., otilonium by European Medicine Agency), many are being used off-label, and a few are in an investigational pipeline. Thus, there is a significant unmet need for treatment of disorders associated with chronic diarrhea such as IBS-D.

This editorial addresses three questions: First, are 5-HT_3 antagonists as effective in males as in females with IBS-D, and what might be potential reasons for the differences? Second, are newer generation 5-HT_3 antagonists also rarely associated with ischemic colitis? Third, were the endpoints used in the most recent studies consistent with regulatory guidelines for drugs in development for the treatment of IBS-D?

Antagonism of serotonin (5-HT) type 3 receptor has been an established treatment strategy for chronic diarrhea related to IBS, [2, 3] with occasional application to other disorders mediated by serotonin such as carcinoid syndrome[4]. Over 90% of the body's 5-HT is located in the enterochromaffin cells in the mucosa of the GI tract, and these mucosal 5-HT receptors are involved in secretion, motility, and nociception. Initial studies showed that ondansetron decreased colonic transit in healthy volunteers[5]. Granisetron impeded the reflex activation of colonic motility in response to upper gastrointestinal stimuli, including mechanical or chemical stimuli, such as antral distension or intraduodenal lipid[6] or a meal[7]. These observations with older 5-HT_3 antagonists led to development of second generation, more potent and specific 5HT_3 receptor antagonists (alosetron and cilansetron), which were highly efficacious in global endpoints (e.g. adequate relief), specific symptoms[2, 3], quality of life, and reversing the restriction of daily activities[8]. However, these were either withdrawn

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from the market (alosetron) or never marketed (cilansetron) due to concerns of complications of severe constipation and reports of ischemic colitis (0.6 and 1.1 per 1000 patient-years respectively); these rates of complications were confirmed in the analysis of data in the risk management program[9]. However, the pathobiological mechanisms of the ischemic colitis are unclear[10, 11], and it is still not completely resolved whether the risk is entirely due to the medication or related to IBS *per se* (independent of serotonergic therapies), since several population-based studies demonstrated that a diagnosis of IBS increases the risk of developing ischemic colitis 2- to 4-fold (reviewed in[12]). Currently, alosetron is available under a risk management program for women with severe IBS-D who are not responding to other therapies. Therefore, despite the efficacy of these agents, their restricted use has resulted in an unmet clinical need.

In this issue of *Clinical Gastroenterology and Hepatology*, Fukudo et al. present results of a randomized, double-blind, placebo-controlled trial of ramosetron in 296 male IBS-D patients recruited across 52 centers in Japan[13]. Ramosetron, a tetrahydrobenzimidazole derivative, is a potent and selective 5-HT_3 receptor antagonist and has been marketed in Japan since 1996, predominantly as an antiemetic for patients receiving chemotherapy[14]. Ramosetron dose-dependently suppressed restraint stress-induced defecation disturbance in rats[15] and was also found to suppress corticotropin-releasing hormone [CRH (intracerebroventricular injection)] induced accelerated defecation[16]. Moreover, ramosetron significantly increased the threshold of pain induced by colonic distension in rats[17]. In a previous trial from Japan, involving both men and women with IBS-D, ramosetron, 5μg once daily, was found to be effective, based on patient reported global relief of IBS, and ramosetron was well tolerated[18]. In Japan, the male IBS population is of particular relevance because of the higher prevalence of IBS in males as compared to the females. In the current trial, which was also conducted exclusively in males, there was a sizeable (30.7%) difference in the responder rates (50.3% ramosetron vs. 19.6% placebo) for the improvement in stool consistency in the first month (primary outcome). Additionally, monthly responder rates at all evaluation points were significantly higher in the ramosetron group than in the placebo group. The ramosetron group achieved significantly higher responder rates for global relief of overall IBS symptoms and abdominal pain/discomfort at all evaluation points. Greater improvements in overall IBS quality of life scores were observed in the ramosetron group at week 4 and at the last time-point. Significantly more people in the ramosetron group (8.2%) reported “hard stools” as compared to the placebo group (1.3%). However, the incidence of constipation was not significantly higher (3.4% vs. 0.7%, relative risk: 5.07, 95% CI: 0.6–42.3). The authors state that, between the current study and the previous studies with ramosetron, a total of 901 IBS-D patients have been recruited, and no cases of ischemic colitis have been reported. This is consistent with a summary of 28–52 weeks of follow-up of 957 patients who participated in ramosetron treatment trials of 12 weeks’ duration; in these patients, no serious adverse events of severe constipation or ischemic colitis were reported for long-term treatment with ramosetron[19].

In the FDA guidance statement for clinical trial endpoints for IBS-D[20], it is recommended that the defecation component of the proposed primary endpoint can be evaluated by assessing stool consistency using Bristol Stool Form Scale. It is also recommended to have

abdominal pain intensity as a second primary pain assessment in IBS trials. However, the authors in the current article suggest that, if a drug is expected to act on either pain or defecation as its primary target, it is reasonable to use that as the primary endpoint, with the second symptom being a secondary endpoint. Fukudo et al. selected improvement in stool consistency as their primary outcome endpoint, which is reasonable given the demonstration of the effects of this class of medication on colonic transit, as described above. However, one could also make a good case for using improvement in pain as a primary endpoint in studies of the efficacy of a 5-HT_3 antagonist, as it can be expected to improve pain and nociception[7, 21]; a previous trial with ramosetron showed improvement in pain[18]. Moreover, 5-HT_3 receptors are located on visceral and central terminal of spinal afferents in animal models and play a role in visceral sensitivity[22, 23].

The evaluation of efficacy in males alone in this trial is noticeable. In another, dose-ranging, randomized, double-blind, placebo-controlled study in males with IBS-D, alosetron,1mg twice a day, resulted in adequate relief of pain and discomfort during weeks 5–12 of the treatment phase (53% in alosetron group vs. 40% in placebo). All doses (0.5, 1, 2, and 4mg) of alosetron showed significantly reduced stool consistency scores within 1 week, and these effects were maintained throughout the treatment until the first week following treatment. The stool frequency, bloating, or pain and discomfort free days did not improve statistically over placebo in any of the treatment groups[24]. Direct efficacy comparisons with 5-HT_3 antagonists among male and female gender have not been made; however, in trials of women with IBS-D, each of these symptoms improved with alosetron compared to placebo. We have found that treatment with alosetron resulted in a significantly greater retardation of small bowel and colonic transit in 15 females with IBS-D as compared to 15 males[25]. In this pharmacodynamic study, the individual transit profiles (Fig.) showed that 2 of 15 males had retardation of colonic transit at 24h that was equal to or greater than the mean change (1.45 geometric center units) in females observed. Moreover, in 4 of the males, there was a slowing of colonic transit at 24h that was equivalent to at least one geometric center unit; that is, the geometric center in the evaluation with alosetron treatment was at least one region more proximal than it was at baseline, suggesting that the medication was having an effect on colonic function in these individuals. Conversely, alosetron had no effect on colonic transit in 2 females.

The greater overall efficacy in women is plausibly due to differences in pharmacokinetics (e.g., differences in CYP1A2 activity)[26], gender-related differences in serotonin-mediated modulation of gut sensorimotor responses[25], differences in serotonin reuptake transported protein (SERT) polymorphisms among women and men with IBS[27], and differential central effects (inhibitory effects on limbic areas which are more abnormally activated in response to visceral events in women than in men)[28, 29]. Thus, it is plausible that ramosetron will have equal or greater efficacy in females.

One of the key hopes in the development of newer 5-HT_3 antagonists for IBS-D is development of an agent that would be less likely to cause serious effects from constipation and ischemic colitis. This will play a significant role in development and approval of a drug in this class. Although, a good portion of participants in this trial reported “hard stool” and “constipation” in comparison to the placebo, this did not reach significance, and the authors

report that constipation was mild and easy to manage in most participants. Considering the reported ischemic colitis incidence of ~1/1000 patient years, it is not possible to be sure that ramosetron will be safer than alosetron. Overall, a successful trial of a new 5-HT_3 antagonist for IBS-D is welcome news, but whether it holds a new promise for both safety and efficacy is yet to be fully established.

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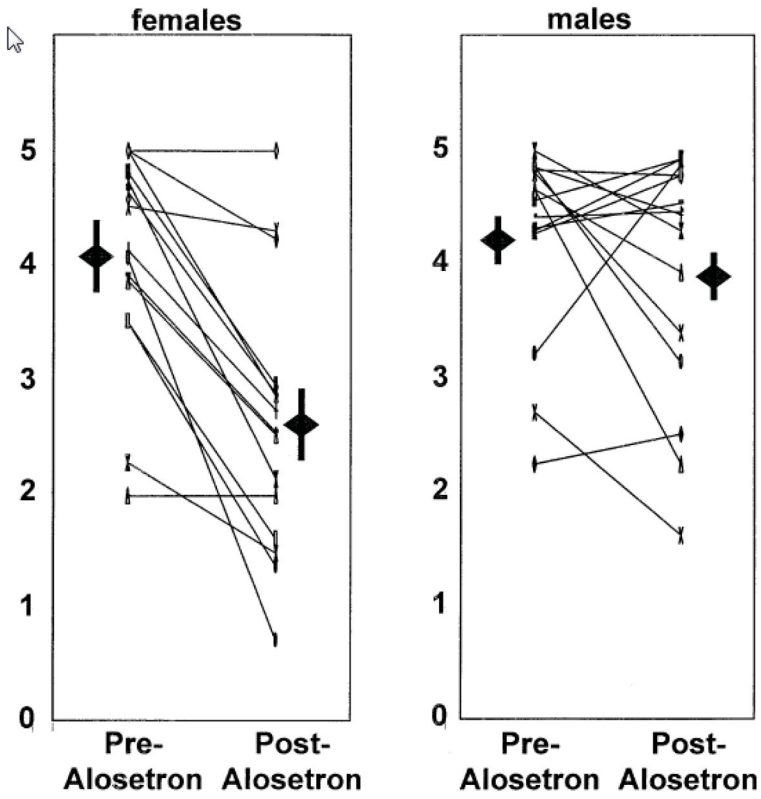

Figure.

Scatter plot of geometric centers of colonic transit at 24h pre- and post-alosetron in females and males with diarrhea-predominant irritable bowel syndrome. The range of geometric center is 0 for location of isotope at the ileocecal valve, and 5 for all isotope located in stool. Also shown are the mean + SEM for each data set.