The clinical potential of ramosetron in the treatment of irritable bowel syndrome with diarrhea (IBS-D)

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Abstract: Irritable bowel syndrome (IBS) is a highly prevalent functional bowel disorder. Serotonin (5-HT) is known to play a physiological and pathophysiological role in the regulation of gastrointestinal function. In experimental studies, 5-HT₃ receptor antagonists have been reported to slow colon transit, to blunt gastrocolonic reflex, and to reduce rectal sensitivity. Alosetron and cilansetron, potent and selective 5-HT₃ receptor antagonists, have proven efficacy in the treatment of IBS with diarrhea (IBS-D). However, alosetron was voluntarily withdrawn due to postmarketing reports of ischemic colitis and complications of constipation, and cilansetron was never marketed. Currently alosetron is available under a risk management program for women with severe IBS-D. Ramosetron is another potent and selective 5-HT₃ receptor antagonist, which has been marketed in Japan, South Korea, and Taiwan. In animal studies, ramosetron reduced defecation induced by corticotrophin-releasing hormone and had inhibitory effects on colonic nociception. In two randomized controlled studies including 957 patients with IBS-D, ramosetron increased monthly responder rates of patient-reported global assessment of IBS symptom relief compared with placebo. Ramosetron was also as effective as mebeverine in male patients with IBS-D. In a recent randomized controlled trial with 343 male patients with IBS-D, ramosetron has proved effective in improving stool consistency, relieving abdominal pain/discomfort, and improving health-related quality of life. Regarding safety, ramosetron is associated with a lower incidence of constipation compared with other 5-HT₃ receptor antagonists and has not been associated with ischemic colitis. Although further large prospective studies are needed to assess whether ramosetron is effective for female patients with IBS-D and to evaluate its long-term safety, ramosetron appears to be one of the most promising agents for patients with IBS-D.

Keywords: diarrhea, irritable bowel syndrome, ramosetron, serotonin, 5-HT₃

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder with recurrent abdominal pain and/or discomfort and disordered defecation [Longstreth *et al.* 2006]. Although the prevalence of IBS varies among countries, global pooled prevalence in 80 separate adult studies is 11.2% [95% confidence interval (CI) 9.8–12.8%] [Lovell and Ford, 2012]. According to predominant stool pattern [Longstreth *et al.* 2006], IBS with diarrhea (IBS-D) accounts for 23.4% (95% CI 8.4%–42.6%) of patients with IBS [Lovell and Ford, 2012].

Although the pathogenesis of symptoms in IBS is incompletely understood, altered bowel motility,

visceral hypersensitivity, mucosal immune activation, increased mucosal permeability, enteric neuromuscular dysfunction, abnormal brain–gut interactions, alteration in the gut microbiome, and psychological disturbance have been hypothesized [Camilleri, 2005, 2012; Hasler, 2011]. Serotonin type 3 (5-HT₃) receptor antagonists have been reported to slow colon transit, to blunt gastrocolonic reflex, and to reduce rectal sensitivity and postprandial motility [Talley *et al.* 1990; Prior and Read, 1993; Bjornsson *et al.* 1998]. Thus more potent and specific 5-HT₃ receptor antagonists (alosetron and cilansetron) were developed and their efficacy has been well established in IBS-D [Andresen *et al.* 2008]. However,

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alosetron was voluntarily withdrawn due to post-marketing reports of ischemic colitis and complications of constipation, and cilansetron was never marketed. Currently alosetron is available under a risk management program for women with severe IBS-D [Tong *et al.* 2013].

Ramosetron, another potent and selective 5-HT₃ receptor antagonist [Hirata *et al.* 2007], has been marketed in Japan since 1996 and has been used as an antiemetic for patients with cancer [Rabasseda, 2002]. In animal studies, ramosetron showed control effects on stress-induced defecation disturbance and inhibitory effect on colonic nociception [Miyata *et al.* 1998; Funatsu *et al.* 2007; Hirata *et al.* 2008]. From these observations ramosetron has also been used as a new agent for IBS-D. This article will review the efficacy and safety of ramosetron in IBS-D and will address its clinical potential.

Mechanism of action and animal studies of ramosetron

The gut contains about 95% of the body's 5-HT [Gershon and Tack, 2007]. 5-HT plays important physiological roles in the regulation of gastrointestinal function [Beattie and Smith, 2008]. Receptors mediating the actions of 5-HT amount to about 14 different receptors (from 5-HT₁ to 5-HT₇ and its subtypes) that produce diverse effects on a wide range of targets [Peroutka, 1994; Beattie and Smith, 2008]. 5-HT₃ receptors are widely distributed in the central and peripheral nervous system [Farber *et al.* 2004]. Intraluminal stimuli stimulate the release of 5-HT from enterochromaffin cells located in the mucosa [Crowell, 2004; Smith *et al.* 2014]. When secreted, 5-HT can activate 5-HT₃ receptors located on intrinsic primary afferent neurons with submucosal terminals, thus initiating the peristaltic reflex and modulating intestinal secretion [Gershon, 1999; Cooke, 2000]. 5-HT also stimulates 5-HT₃ and 5-HT₄ receptors located on primary afferent neurons of both splanchnic and vagal fibers, thereby modulating both sensory and motor responses [Crowell, 2004].

In the animal studies, ramosetron demonstrated logical results that are consistent with expected effects of 5-HT₃ receptor antagonists. In rats, corticotrophin-releasing hormone (CRH) exogenously administered or released from the central nervous system by stress peripherally promoted the release of 5-HT which in turn stimulated defecation

through the 5-HT₃ receptor and ramosetron reduced the defecation by CRH in a dose-dependent manner [Miyata *et al.* 1998]. Ramosetron also inhibited defecation induced by emotional stress and retarded stress-stimulated colonic transit in rats [Funatsu *et al.* 2007]. Unlike existing antidiarrheal and spasmolytic agents, ramosetron, had inhibitory effects on colonic nociception in rats [Hirata *et al.* 2008]. Collectively, ramosetron appears to have the pharmacological action for IBS-D through targeting 5-HT₃ receptor.

Efficacy of ramosetron in IBS-D

5-HT₃ receptor antagonist has been well demonstrated as an effective drug class in the treatment of IBS-D [Andresen *et al.* 2008]. A meta-analysis in 2008 [Andresen *et al.* 2008] including 14 randomized controlled trials (RCTs) with 3024 patients receiving alosetron and 1116 receiving cilansetron compared with 3043 placebo or 304 mebeverine found 5-HT₃ receptor antagonists more effective than the comparators in achieving global improvement in IBS symptoms [pooled relative risk (RR) 1.60; 95% CI 1.49–1.72] and relief of abdominal pain/discomfort (pooled RR 1.30; 95% CI 1.22–1.39). Benefit was apparent for both agents, in patients of either sex. An old 5-HT₃ receptor antagonist widely used as an antiemetic, ondansetron, has showed benefits in patients with IBS in small trials [Steadman *et al.* 1992; Goldberg *et al.* 1996]. Recently, a large RCT of 120 patients with IBS-D showed that ondansetron of 4 mg for 5 weeks improves stool consistency, reduced urgency, frequency, and bloating, but does not reduce abdominal pain [Garsed *et al.* 2014].

Until now, four RCTs of ramosetron in the treatment of patients with IBS-D have been reported in the literature (Table 1) [Matsueda *et al.* 2008; Lee *et al.* 2011; Fukudo *et al.* 2014]. In two randomized, double-blind, placebo-controlled studies [Matsueda *et al.* 2008] of 957 male and female Japanese patients with IBS-D meeting Rome II criteria, ramosetron 5 µg and 10 µg once daily increased the monthly responder rate of patient-reported global assessment of relief of IBS symptoms compared with placebo (42.57–47%, 43.01%, and 26.92–27% for 5 µg, 10 µg, and placebo, respectively). Ramosetron also hardened stool form, decreased stool frequency, and increased the rate of days without bowel urgency. Although the relative potency of ramosetron is 7.5–22 times that of alosetron, the doses used in

the trials, 5 µg and 10 µg, are very low compared with the standard alosetron dose of 2 mg (equivalent to ramosetron 90–270 µg) [Hirata *et al.* 2007]. In the Korean multicenter, randomized, open-label, noninferiority comparative study [Lee *et al.* 2011] of 343 male patients with IBS-D meeting Rome III criteria, ramosetron 5 µg once daily increased the responder rates for global IBS symptoms, abdominal pain/discomfort, and abnormal bowel habits during the treatment period, which was as effective as mebeverine 135 mg three times daily. Severity of abdominal pain/discomfort, Bristol stool form scale score, and stool frequency were also improved in both groups compared with baseline. However, this study is limited because the exact efficacy of ramosetron over placebo was not evaluated. Furthermore, mebeverine, the control drug in this study, showed no statistically significant efficacy in global improvement of IBS [Darvish-Damavandi *et al.* 2010]. Recently, a multicenter, randomized, double-blinded, placebo-controlled clinical study of 343 male Japanese patients with IBS-D meeting Rome III criteria has been reported [Fukudo *et al.* 2014]. Ramosetron 5 µg once daily improved stool consistency in the first months (the primary end point) more than placebo (50.3% *versus* 19.6%, $p < 0.001$), and the number needed to treat was 3.25 (95% CI 2.44–4.89). In addition, monthly responder rates of global assessment of relief of overall IBS symptoms and relief of abdominal pain/discomfort were higher in the ramosetron group than in the placebo group at all evaluation points. Bristol stool form scale scores were lower and changes in stool frequencies from baseline per week were higher in the ramosetron group than in the placebo group. The percentages of days without urgency increased and of days without incomplete evacuation were significantly increased in the ramosetron group compared with placebo. Significantly greater improvements in overall health-related quality of life scores were observed in the ramosetron group than in the placebo group. In these trials, ramosetron has proved its efficacy in relieving symptoms in IBS-D.

Unlike the results of a phase II trial, a phase III trial demonstrated significant effects of ramosetron on relief of IBS symptoms at all evaluation points in male patients with IBS-D but not in female patients [Matsueda *et al.* 2008]. In female patients, it was only observed at month 2 (not at month 1 and month 3 and final point). However, these results are thought to be mainly due to the small sample size of female patients. Eighty

percent of the patients enrolled in this trial were male because IBS-D is more prevalent in men [Kumano *et al.* 2004]. Conversely, alosetron failed to demonstrate efficacy in male patients with IBS-D [Bardhan *et al.* 2000] and was indicated for only female patients in the USA. Later, alosetron has shown significant efficacy in relief of IBS pain/discomfort and stool consistency in male patients with IBS-D [Chang *et al.* 2005]. The lack of efficacy of alosetron in male patients was likely due to the small numbers of men enrolled. However, there are several factors contributing to differences in the treatment response of male and female patients with IBS. Alosetron has different pharmacokinetics by sex. Serum concentrations of alosetron were higher in women than in men for a given dose, resulting from a sex difference in clearance by metabolism [Koch *et al.* 2002] and systemic exposure to alosetron was higher in women due to lower cytochrome P450 enzyme 1A2 activity than in men [Koch *et al.* 2004]. In fact, the impact of alosetron on intestinal transit time in patients with IBS-D is significantly greater in women than men [Viramontes *et al.* 2001]. In addition, alosetron and ondansetron showed lower threshold of inhibiting migrating motor complex of murine bowel in female mice than in male mice [Bush *et al.* 2001]. Genetic polymorphisms at the serotonin reuptake transporter (SERT) protein promoter influence response to 5-HT₃ receptor antagonists in IBS-D [Camilleri *et al.* 2002]. Niesler and colleagues have shown that male patients with IBS-D have a reduced frequency of the 5-HTTLPR (ss) genotype compared with female patients (10% *versus* 19.4%) [Niesler *et al.* 2010]. In a recent study, the effect of ondansetron on the gut transit, however, did not differ between the SERT promoter polymorphisms [Garsed *et al.* 2014]. Likewise, it is not known whether differences in SERT protein polymorphisms between female and male patients contribute to the different clinical responses to 5-HT₃ receptor antagonists. In addition, there are important polymorphisms in tryptophan hydroxylase 1 and 5-HT₃ receptor which might be more relevant [Kilpatrick *et al.* 2011; Grasberger *et al.* 2013]. Another possible explanation for the greater efficacy of alosetron in women is due to sex-related differences in its central effects. Male and female patients with IBS differ in their brain response to a visceral stimulus and a condition [Berman *et al.* 2000; Naliboff *et al.* 2003]. Female patients show greater activation of affective and autonomic regions (ventromedial prefrontal cortex, infragenua cingulate, and amygdala).

Table 1. Clinical studies of ramosetron in irritable bowel syndrome with diarrhea.

Study	Design	N	Sex	Agents and dosing	Treatment duration	Primary end point and efficacy	Adverse events
Fukudo <i>et al.</i> [2014]	Randomized, double-blinded, placebo-controlled trial	296	Male	Ramosetron 5 µg or placebo	12 weeks	Monthly responder rates of improvement in stool consistency in the first month Ramosetron <i>versus</i> placebo 50.3% <i>versus</i> 19.6% ($p < 0.001$)	Ramosetron <i>versus</i> placebo - Hard stool (8.2% <i>versus</i> 1.3%, $p = 0.01$) - Constipation (3.4% <i>versus</i> 0.7%, $p = 0.12$) No ischemic colitis or severe constipation
Lee <i>et al.</i> [2011]	Randomized, open-label, parallel-group, non-inferiority comparative study	343	Male	Ramosetron 5 µg or mebeverine 135 mg three times daily	4 weeks	Weekly responder rate of patient-reported assessment of relief of IBS symptoms Ramosetron <i>versus</i> mebeverine 37% <i>versus</i> 38%	Ramosetron <i>versus</i> mebeverine - Constipation (2% <i>versus</i> 1%, $p = 0.372$) No ischemic colitis or severe constipation
Matsueda <i>et al.</i> [2008]	Randomized, double-blind, placebo-controlled trial	539	Mixed	Ramosetron 5 µg or placebo	12 weeks	Monthly responder rate of 'Patient-reported global assessment of relief of IBS symptoms' Ramosetron <i>versus</i> placebo 47% <i>versus</i> 27% ($p < 0.001$)	Ramosetron <i>versus</i> placebo - Hard stool (7.41% <i>versus</i> 0.74%, $p < 0.001$) - Constipation (5.19% <i>versus</i> 1.86%, $p = 0.063$) No ischemic colitis or severe constipation
Matsueda <i>et al.</i> [2008]	Randomized, double-blind, placebo-controlled trial	418	Mixed	Ramosetron, 1, 5, 10 µg, or placebo	12 weeks	Monthly responder rate of 'Patient-reported global assessment of relief of IBS symptoms' Ramosetron 5 µg <i>versus</i> 10 µg <i>versus</i> placebo 42.57% <i>versus</i> 43.01% <i>versus</i> 26.92% ($p < 0.05$)	Ramosetron 10, 5, 1 µg, and placebo - Hard stool (8.9%, 6.8%, 1.0%, and 0%) - Constipation (14.9%, 5.8%, 1.9%, 2.8%) No ischemic colitis or severe constipation

Alosetron decreases brain activity in response to rectosigmoid stimuli in structures of the emotional motor system (the amygdala, ventral striatum, hypothalamus, and infragenua cingulate gyrus), and this is associated with symptom improvement in nonconstipated patients with IBS [Mayer *et al.* 2002]. Thus, greater efficacy of alosetron in women with IBS may be due to its

inhibitory effect on the emotional regions of the brain which are more activated in women than in men with IBS in response to visceral stimuli. However, ramosetron is known not to act centrally because P-glycoprotein at the blood-brain barrier efflux ramosetron to circulating blood [Yamamoto *et al.* 2002]. Although sex-related differences in pharmacologic profile have not been

invested in ramosetron it might be natural to assume that ramosetron would also be effective in females like other 5-HT₃ receptor antagonists. However, further studies on whether ramosetron is effective in female patients with IBS-D are necessary to draw firm conclusions.

Safety of ramosetron in IBS-D

Severe constipation and ischemic colitis are possible serious adverse events that might be from the classic effects of 5-HT₃ receptor antagonist. According to a meta-analysis [Andresen *et al.* 2008] with 14 RCTs including 3221 patients receiving alosetron and 1116 receiving cilasetron compared with 3647 controls, 5-HT₃ receptor antagonists increased the risk of constipation (pooled relative RR 4.28; 95% CI 3.28–5.60) and the number needed to harm was 4.7. The risk of constipation was higher in the studies with alosetron (RR 4.89; 95% CI 3.6–6.56) compared with the studies with cilasetron (RR 2.92; 95% CI 1.85–4.63). Approximately 10–40% of the participants who developed constipation withdrew from the trials for this reason. However, most cases of constipation in these trials were considered mild to moderate in severity and no serious events as a result of constipation were reported. In this meta-analysis, nine cases (0.2%), all from the patients receiving alosetron, in the 5-HT₃ receptor antagonist treatment group had at least possible ischemic colitis and yielded an RR for ischemic colitis of 16.01 (95% CI 0.93–275; *p*=0.06). A recent study [Tong *et al.* 2013] evaluating 29,072 patients receiving alosetron under a risk management plan during the 9-year postmarketing period reported the cumulative adjudicated incidence rate of ischemic colitis (1.03 cases/1000 patient-years) and that of complications of constipation (0.25 cases/1000 patient-years). The incidence rate of ischemic colitis has remained rare and stable, while the incidence rate of complications of constipation has sharply decreased.

According to four RCTs [Matsueda *et al.* 2008; Lee *et al.* 2011; Fukudo *et al.* 2014] including 696 patients receiving ramosetron (5 µg once daily) compared with 526 placebo and 168 mebeverine (135 mg three times daily), the frequency of constipation with ramosetron (2.0–5.19%) seems lower than the 27.6% and 16.2% observed in the studies with alosetron and cilasetron [Andresen *et al.* 2008], respectively. However, it is worth noting that ramosetron has been evaluated for mostly men, only in Asian populations, and for relatively

short treatment periods. Thus, further studies with longer treatment duration and in the different populations are required to confirm if constipation is less in ramosetron than other 5-HT₃ receptor antagonists. In addition, severe constipation or ischemic colitis, which has been observed with alosetron, was not reported with ramosetron. However, considering the incidence rates of ischemic colitis (1.03 cases/1000 patient-years) and complications of constipation (0.25 cases/1000 patient-years), it is a little early to conclude that ramosetron is safer than alosetron. Furthermore, ondansetron also shows a low constipation rate (9%) without a report of ischemic colitis [Garsed *et al.* 2014]. The pathophysiological mechanism of ischemic colitis in patients treated with 5-HT₃ receptor antagonist is uncertain. In a phase II trial with ramosetron, the incidence rates of constipation and hard stool increased in a dose-dependent manner [Matsueda *et al.* 2008]. Although ramosetron has an affinity for the 5-HT₃ receptor more than three times that of alosetron, the usual dose of 5 µg is very low compared with the equivalent usual dose of alosetron. Likewise, the potency of ondansetron is 3–10 times lower than that of alosetron [Clayton *et al.* 1999]. From these observations, it could be suggested that careful dosing at a very low level might avoid adverse events, including serious complications of ramosetron in the treatment of IBS-D.

Conclusion

Although there has been advancement in the treatment of IBS, current available therapies remain unsatisfactory. While 5-HT₃ receptor antagonist is an approved target therapeutic agent with good efficacy in patients with IBS-D, it has been used in a limited number of patients due to its side effects and different clinical response between sexes. The 5-HT₃ receptor antagonist available in Asia, ramosetron, shows good efficacy in terms of stool consistency, abdominal pain/discomfort, and health-related quality of life. In addition, ramosetron is associated with a lower incidence of constipation compared with other 5-HT₃ receptor antagonists. Furthermore, ischemic colitis, which had been observed with alosetron, seems unlikely to be caused by ramosetron. Lastly, ramosetron would be effective in female patients as well as in male patients. Although further large prospective studies are needed to assess whether ramosetron is effective for female patients with IBS-D and to evaluate its long-term safety, ramosetron appears to be one of the most promising agents for patients with IBS-D.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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