Effect of Ramosetron on Stool Consistency in Male Patients With Irritable Bowel Syndrome With Diarrhea

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BACKGROUND & AIMS: Ramosetron, a serotonin (5-hydroxytryptamine)-3 receptor antagonist with high selectivity, reduced stress-induced diarrhea and defecation caused by corticotropin-releasing hormone in rats. However, there have been no clinical trials of its effect in patients with diarrhea and irritable bowel syndrome (IBS-D). We performed a randomized, double-blind, placebo-controlled trial to determine whether ramosetron reduces diarrhea in these patients.

METHODS: Our study included 296 male outpatients with IBS-D treated at 52 centers in Japan. Patients were given 5 mg oral ramosetron (n = 147) or placebo (n = 149) once daily for 12 weeks after a 1-week baseline period. The primary end point was increased stool consistency in the first month. Secondary end points included relief of overall IBS symptoms and increased IBS-related quality of life.

RESULTS: More patients given ramosetron (74, 50.3%) than those given placebo (29, 19.6%) reported improved stool consistency in the first month (P < .001). The relative risk and number needed to treat were 2.57 (95% confidence interval, 1.79–3.70) and 3.25 (95% confidence interval, 2.44–4.89), respectively. The ramosetron group had significantly higher monthly rates of relief of overall IBS symptoms and IBS-related quality of life than the placebo group.

CONCLUSIONS: Ramosetron (5 mg oral, once daily for 12 weeks) improved stool consistency in male patients with IBS-D, compared with placebo. These study results, along with the pharmacologic profile of ramosetron, indicate that increased stool consistency is the best end point for studies of ramosetron in patients with IBS-D. Clinicaltrials.gov No, NCT01225237.

Keywords: 5-Hydroxytryptamine (5-HT); Abdominal Pain; Abdominal Discomfort; Global Improvement.

See editorial on page 960.

Irritable bowel syndrome (IBS) is a representative functional gastrointestinal disorder that impacts patients’ lives, the medical economy, and modern society. IBS is very common in the general population, with an estimated prevalence of 10%–20% in North America and 2.9%–15.6% in Asia, and it considerably compromises health-related quality of life (HR-QOL) of the patients. Nonetheless, treatments for IBS are unsatisfactory, and only 22% of IBS patients receiving usual medical care have reported at least 50% reduction in bowel symptoms.

The Rome III criteria classify the IBS phenotype into 4 groups: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), mixed IBS, and unsubtyped IBS. However, this symptomatic phenotyping does not guarantee etiologic and pathophysiologic homogeneity of IBS. Some evidence suggests that 5-hydroxytryptamine ([5-HT], serotonin) has a crucial role in IBS-D pathophysiology. IBS-D patients have exaggerated colonic motility in response to colorectal distention. The distention-induced peristaltic reflex is mediated by 5-HT. The 5-HT secretion is exaggerated in IBS-D, but not IBS-C, patients. Abnormal neurotransmission of 5-HT via the 5-HT receptor 3 (5-HT3) has been reported in IBS-D patients. Use of 5-HT3 antagonist for IBS-D patients is logical consequence, and alosetron showed distinct efficacy on symptoms of IBS-D. Moreover, meta-analysis of a large patient cohort indicated that 5-HT3 antagonists achieve global improvement in IBS symptoms and relieve abdominal pain and discomfort.

Abbreviations used in this paper: BSFS, Bristol Stool Form Scale; CI, confidence interval; FAS, full analysis set; FDA, Food and Drug Administration; HR-QOL, health-related quality of life; 5-HT, 5-hydroxytryptamine; 5-HT3, 5-hydroxytryptamine receptor 3; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-QOL, irritable bowel syndrome quality of life; MCID, minimal clinically important difference; NNT, number needed to treat; RR, relative risk; SD, standard deviation.

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Unfortunately, ischemic colitis, a serious adverse effect of alosetron, has limited the use of this drug.\textsuperscript{15}

Ramosetron, a 5-HT\textsubscript{3} antagonist with high potential and selectivity,\textsuperscript{16} clearly reduced stress-induced diarrhea and defecation caused by corticotropin-releasing hormone in rats.\textsuperscript{17,18} Distinct benefits of ramosetron were previously observed in a global assessment of relief of overall IBS symptoms.\textsuperscript{19,20} However, several issues need to be addressed. First, the effect of ramosetron on stool form as a primary end point requires investigation. The United States Food and Drug Administration (FDA) proposed a study design for clinical trials focused on IBS,\textsuperscript{21} suggesting use of abdominal pain and stool consistency as a primary end point. The guidance permits trials of drugs that target only one of these end points if the mechanism of action of the drug applies to only one of these symptoms. Ramosetron primarily improves stool consistency and has been approved by regulatory authorities in Japan,\textsuperscript{20,22} Korea,\textsuperscript{23} and Thailand. The phase II,\textsuperscript{19} III,\textsuperscript{20} and open-labeled\textsuperscript{23} studies reported improvement in stool consistency as a secondary end point. As FDA recommended, it is necessary to examine whether ramosetron performs well on stool consistency as the primary end point. Other key efficacy end points should be assessed as secondary end points. Second, the effect of ramosetron on HR-QOL must be established. Only one published report shows that 5-HT\textsubscript{3} antagonists improve disease-specific HR-QOL in female IBS-D patients.\textsuperscript{24} Moreover, male IBS-D patients have been largely ignored in most clinical trials of 5-HT\textsubscript{3} antagonists in Western countries. Clinical trials in male patients are important for increasing medical knowledge about the effects of these drugs on IBS-D. Thus, this study examined the effects of ramosetron on stool consistency in male IBS-D patients, testing the hypothesis that ramosetron is superior to placebo in improving stool consistency, with a low incidence of serious adverse events. The effects of ramosetron on HR-QOL were also verified.

**Methods**

**Patient Population**

This study was conducted from October 2010–August 2011 at 52 centers with departments of gastroenterology in Japan. Male outpatients aged 20–64 years and diagnosed according to the Rome III criteria\textsuperscript{7} were eligible. The study protocol was designed in accordance with the Declaration of Helsinki and was approved by institutional review boards at all sites. All patients provided written informed consent before participating in study-related procedures.

Patients satisfying the inclusion and exclusion criteria were monitored during a 1-week baseline period in which data on severity of abdominal pain/discomfort and stool consistency were collected to ensure that patients met the criteria. Severity of abdominal pain/discomfort was assessed daily on a 5-point ordinate scale. Stool consistency was classified by using the Bristol Stool Form Scale (BSFS).\textsuperscript{7} Patients who had not used drugs or undergone examinations that could affect the evaluation of study drug efficacy within 10 days before randomization; who recorded all items in the patient diary for \( \geq 5 \) days during the baseline period; who had mean severity scores of abdominal pain/discomfort of \( \geq 0.7 \) during the baseline period; in whom no type 1 or 2 stool form, as scored by BSFS, was recorded during the baseline period; who had bowel movements for \( \geq 5 \) days, with a mean score of \( > 5 \) on BSFS during the baseline period; and who were not judged ineligible for the study according to the clinical laboratory test results received before the baseline period were randomized and successively administered treatment (Supplementary Material).

**Study Design**

This randomized, double-blinded, placebo-controlled, clinical trial comprised a provisional registration period, a 1-week baseline period, and a 12-week treatment period, similar to previous studies.\textsuperscript{19,20} After the baseline period, eligible patients were randomly assigned to 12-week oral treatments with placebo or ramosetron hydrochloride (5 µg once daily) before breakfast. Visits were scheduled at weeks 2, 4, 8, and 12 (or at discontinuation) to assess treatment efficacy, drug compliance, and occurrence of adverse events. Randomization was performed in a 1:1 ratio by using a block size of 4 with a Web-based randomization system. All patients, investigators, and sponsors were blinded until all observations and evaluations were completed, statistical analysis plans were finalized, and all data had been entered. All authors had access to the study data and had reviewed and approved the final manuscript.

**Data Collection**

During the baseline and treatment periods, patients recorded their IBS symptoms daily on paper diary cards at bedtime and electronically entered data into a database daily by using an interactive voice response system to support completion of data entry in the paper diary cards every day. This system of evaluating IBS symptoms has been previously reported as reliable and valid.\textsuperscript{19,20} In the diary, patients recorded BSFS types and stool frequencies and scored the severity of their abdominal pain/discomfort on the 5-point ordinate scale. Urgency and feelings of incomplete evacuation were assessed on a binary scale. Every 7 days during the treatment period, patients also assessed the degree to which they experienced relief of overall IBS symptoms, abdominal pain/discomfort, and improvement in abnormal bowel habits compared with the baseline period and graded them on a 5-point ordinate
scale. Patients were assessed for disease-specific HRQOL every 4 weeks by using the Japanese version of the IBSQOL measurement instrument (Supplementary Material).

Efficacy and Safety End Points

The primary end point was monthly responder rates of improvement in stool consistency in the first month. Drug efficacy in the first month is critical for IBS-D patients because lack of efficacy during this period motivates patients to seek alternative therapies. Patients with weekly mean BSFS scores of $\geq 3$ to $\leq 5$ during the 1 week of the treatment period and a decrease of $\geq 1$ point in mean BSFS scores from the baseline period were defined as weekly responders. Patients who were weekly responders for at least 2 of the 4 weeks in 1 month were considered monthly responders. If more than 2 daily scores were missing during any week of the study period, the mean score for that week was defined as missing. Patients with missing mean BSFS scores were regarded as weekly nonresponders.

Secondary end points included monthly responder rates of global assessment of relief of overall IBS symptoms, relief of abdominal pain/discomfort, and improvement in abnormal bowel habits. Patients with scores of 0 or 1 at each weekly evaluation point were defined as weekly responders, and patients who were weekly responders for at least 2 of the 4 weeks in 1 month were considered to be monthly responders. Scales measuring IBS symptoms, including severity of abdominal pain/discomfort, BSFS, stool frequency, urgency and feeling of incomplete evacuation, and IBS-QOL, were established for the secondary end points. All adverse events were recorded during the intervention period.

Statistical Analysis

Statistical analysis was performed by using SAS Drug Development (version 3.4) and PC-SAS (version 9.1.3) (SAS Institute Inc, Cary, NC). Sample sizes were calculated to provide 90% power to detect a 19.2% difference in monthly responder rates of improvement in stool consistency during the first month between the 2 groups (18.9% and 38.1% for the placebo and ramosetron groups, respectively) that were based on a preliminary clinical study (Clinicaltrials.gov ID: NCT00918411, unpublished data) by using the $\chi^2$ test with a 2-sided significance level of .05.

In total, 260 patients (130 patients/group) were selected for randomization. Efficacy analyses included the full analysis set (FAS), which was as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects. The FAS included all patients who received at least 1 dose of the study drug during the treatment period and in whom $>1$ end point could be evaluated. To determine the robustness of the results, primary analyses were performed according to the per-protocol set. Safety analyses were performed for all patients who received at least 1 dose of the study drug during the treatment period.

Monthly responder rates of improvement in stool consistency during the first month are expressed as a percentage of responders, and 95% confidence intervals (CIs) are presented. The treatment groups were compared by using the $\chi^2$ test with a 2-sided significance level of .05. Relative risk (RR) and number needed to treat (NNT) were then calculated. Other monthly responder rate parameters were similarly analyzed. Weekly changes in the severity of abdominal pain/discomfort and stool frequency, percentage of days without urgency, and percentage of days without a sense of incomplete evacuation were evaluated by using the $t$ test. For comparing ramosetron with placebo, analysis of covariance was performed with the treatment groups as a factor and baseline scores as covariates to measure changes in the overall IBS-QOL and IBS-QOL subscale scores at each evaluation point from the baseline.

Results

Overall Study Population

Figure 1 shows a flowchart of patient progression. Analyses were performed by using data from 148 placebo-treated and 147 ramosetron-treated patients. Among these, 10 and 18 patients in the ramosetron and placebo groups, respectively, discontinued treatment prematurely. Reasons for premature discontinuation are listed in Figure 1 (also Supplementary Material).

The demographic and baseline characteristics of all randomized patients were comparable (Table 1). Treatment compliance was 97.5% and 98.4% in the ramosetron and placebo groups, respectively. No statistically significant difference in the demographic and baseline characteristics was observed between the groups. Therefore, the study data were not adjusted statistically.

Evaluation of the Primary End Point

Monthly responder rates of improvement in stool consistency in the first month (primary end point) were 50.3% (95% CI, 42.0–58.7) and 19.6% (95% CI, 13.5–26.9) in the ramosetron and placebo groups, respectively (difference, 30.7%; 95% CI, 20.4–41.1; $P<.001$; Figure 2). RR was 2.57 (95% CI, 1.79–3.70), and NNT was 3.25 (95% CI, 2.44–4.89). Monthly responder rates at all evaluation points were significantly higher in the ramosetron group than in the placebo group (Supplementary Figure 1).

Evaluation of Secondary End Points

All monthly responder rates of global assessment of relief of overall IBS symptoms (Figure 3A) and relief of abdominal pain/discomfort (Figure 3B) were significantly
higher in the ramosetron group than in the placebo group at all evaluation points.

Changes in the severity of abdominal pain/discomfort from baseline per week were $0.78 \pm 0.82$ (mean ± standard deviation [SD]) in the ramosetron group and $0.60 \pm 0.86$ in the placebo group at the last point. At week 5, a significant reduction was observed in the ramosetron group ($0.70 \pm 0.73$) compared with the placebo group ($0.48 \pm 0.75$, $P = .012$). BSFS scores were significantly lower in the ramosetron group (4.9 ± 0.8 at week 1 and 4.8 ± 1.0 at the last point) than in the placebo group (5.4 ± 0.7 at week 1 and 5.2 ± 0.8 at the last point, $P < .001$) throughout the treatment period (Figure 3C). Changes in stool frequencies from baseline per week were significantly greater in the ramosetron group.

### Table 1. Demographics and Baseline Characteristics of the Treatment Groups

| Patient background | Placebo  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>(n = 148)</td>
<td>(n = 147)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>40.2 ± 10.1</td>
<td>40.9 ± 10.6</td>
<td>.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of disease (mo)</td>
<td>164.4 ± 134.4</td>
<td>155.0 ± 134.2</td>
<td>.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of abdominal pain/discomfort</td>
<td>1.8 ± 0.7</td>
<td>1.72 ± 0.6</td>
<td>.22</td>
<td></td>
<td></td>
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<tr>
<td>Stool form (appearance)</td>
<td>5.7 ± 0.4</td>
<td>5.7 ± 0.4</td>
<td>.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool frequency</td>
<td>2.9 ± 1.4</td>
<td>2.9 ± 1.6</td>
<td>.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS-QOL-Japanese</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>67.3 ± 18.7</td>
<td>70.4 ± 16.0</td>
<td>.14</td>
<td></td>
<td></td>
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<tr>
<td>Dysphoria</td>
<td>57.9 ± 23.1</td>
<td>61.3 ± 21.2</td>
<td>.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference with activity</td>
<td>55.5 ± 22.5</td>
<td>58.6 ± 20.6</td>
<td>.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body image</td>
<td>84.4 ± 17.5</td>
<td>87.4 ± 14.5</td>
<td>.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health worry</td>
<td>70.4 ± 21.4</td>
<td>73.9 ± 19.2</td>
<td>.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food avoidance</td>
<td>59.7 ± 28.1</td>
<td>63.5 ± 26.8</td>
<td>.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social reaction</td>
<td>80.7 ± 19.4</td>
<td>82.1 ± 16.0</td>
<td>.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual concerns</td>
<td>86.1 ± 18.2</td>
<td>88.5 ± 16.5</td>
<td>.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship</td>
<td>71.7 ± 23.8</td>
<td>74.6 ± 21.1</td>
<td>.26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are expressed as means ± SD.
group (−0.47 ± 0.80 at week 1 and −0.57 ± 1.10 at the last point) than in the placebo group (−0.26 ± 0.61 at week 1, \( P = .014 \) and −0.27 ± 1.13 at the last point, \( P = .023 \)) (Supplementary Figure 2).

In analyses of IBS-QOL, greater improvements in HR-QOL were observed in the ramosetron group than in the placebo group (Figure 4). Significantly greater improvements in overall IBS-QOL scores were observed in the ramosetron group at weeks 4 (13.7, [12.0–15.4]), adjusted mean [95% CI]), 8 (15.9 [13.9–17.9]), and 12 (17.5 [15.4–19.6]) and at the last point (16.8 [14.7–18.8]) than in the placebo group (9.2 [7.5–10.8]), \( P < .001; \) (11.7 [9.7–13.7]), \( P = .003; \) (13.3 [11.1–15.4]), \( P = .007; \) (12.4 [10.4–14.4]), \( P = .003, \) respectively (Supplementary Figure 3).

### Safety

Safety was evaluated in all 296 patients, with adverse events occurring in 46.9% and 51.7% of ramosetron and placebo patients, respectively (Table 2). The incidence of

### Table 2. Incidence of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 149)</th>
<th>Ramosetron (n = 147)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>77 (51.7)</td>
<td>69 (46.9)</td>
<td>.48</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
<td>.37</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
<td>.37</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>21 (14.1)</td>
<td>21 (14.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (0.7)</td>
<td>5 (3.4)</td>
<td>.12</td>
</tr>
<tr>
<td>Hard stool</td>
<td>2 (1.3)</td>
<td>12 (8.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>5 (3.4)</td>
<td>3 (2.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>5 (3.4)</td>
<td>3 (2.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>39 (26.2)</td>
<td>29 (19.7)</td>
<td>.21</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2 (1.3)</td>
<td>4 (2.7)</td>
<td>.45</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>25 (16.8)</td>
<td>20 (13.6)</td>
<td>.52</td>
</tr>
<tr>
<td>Investigations</td>
<td>21 (14.1)</td>
<td>13 (8.8)</td>
<td>.20</td>
</tr>
<tr>
<td>Increased serum alanine aminotransferase</td>
<td>7 (4.7)</td>
<td>3 (2.0)</td>
<td>.34</td>
</tr>
<tr>
<td>Increased serum bilirubin</td>
<td>3 (2.0)</td>
<td>3 (2.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>4 (2.7)</td>
<td>4 (2.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
<td>.37</td>
</tr>
</tbody>
</table>

NOTE: Data are expressed as numbers (%). Events with an incidence of ≥2% in the ramosetron group are listed. \( P \) values were calculated by using Fisher exact test.
hard stools was significantly higher in the ramosetron group (8.2%) than in the placebo group (1.3%, \( P = .006 \)). Ramosetron also induced constipation in 3.4% patients. However, the incidence was not significantly higher than that in the placebo group (0.7%). RR of constipation was 5.07 (95% CI, 0.60–42.86). All episodes of constipation and hard stools in the ramosetron group, assumed to be caused by the pharmacologic actions of ramosetron, were classified as mild and resolved early without using rescue drugs (Supplementary Material).

Discussion

Ramosetron is more potent and selective than other 5-HT\(_3\) antagonists.\(^{16}\) Previous reports have shown superior efficacy of ramosetron compared with placebo in male IBS-D patients,\(^{19,20}\) and the mechanism is believed to be inhibition of 5-HT\(_3\) receptor antagonism in the myenteric plexus and vagal afferent neurons.\(^{29}\) Ramosetron showed the same clinical effects as the anticholinergic drug mebeverine in an open-labeled trial.\(^{13}\) Moreover, the incidence of constipation was much lower in ramosetron-treated patients than in alosetron-treated or cilansetron-treated patients.\(^{22,23}\) Here, RR (95% CI) of constipation was 5.07 (0.60–42.86) in the ramosetron group, and no significant increase in constipation was observed. Conversely, meta-analysis of other 5-HT\(_3\) antagonists found RR (95% CI) of constipation to be 4.89 (3.6–6.56) and 2.92 (1.85–4.63) in alosetron-treated and cilansetron-treated patients, respectively.\(^{14}\) In the present study and previous trials,\(^{19,20,23}\) ramosetron was administered to 901 IBS-D patients in total. Among these, no ischemic colitis was reported. Meta-analysis of alosetron and cilansetron indicated ischemic colitis in 9 of 4337 patients (0.2%).\(^{14}\) Its high potential, high selectivity, clear efficacy, and lower incidence of serious adverse events suggest that ramosetron is the most promising therapeutic agent for IBS-D.

After failure to demonstrate efficacy in male IBS-D patients,\(^{10}\) alosetron was approved and indicated for limited use only in female IBS-D patients.\(^{13,22}\) Hence, most subsequent clinical trials of alosetron and cilansetron have been performed in female IBS-D subjects.\(^{14,24}\) Conversely, ramosetron has been approved only for male IBS-D patients in Japan,\(^{10,25}\) Korea,\(^{23}\) and Thailand, according to the results of a phase III trial that demonstrated no significant effect in female IBS-D patients,\(^{10}\) mainly because of its small sample size. The present data confirmed the clinical effect of ramosetron in male IBS-D patients, and it is natural to assume that ramosetron would be effective regardless of ethnicity. Furthermore, RR values for alosetron and cilansetron have been reported to be lower in studies including only women (1.23 [1.14–1.32]) compared with studies including both sexes or only men (1.39 [1.28–1.51]; RR ratio, 0.88 [0.79–0.99]).\(^{14}\) However, larger trials with both men and women are required to resolve these gender differences.

IBS-QOL is a reliable and well-validated instrument for assessing HR-QOL in IBS patients.\(^{25}\) Although most linear end points have no established minimal clinically important difference (MCID) as a benchmark, MCIDs of IBS-QOL lie between 10 and 14.\(^{31}\) In this study, IBS-QOL scores of the ramosetron group improved beyond the MCID benchmark at all time points, whereas those of the placebo group did not always improve beyond the MCID benchmark. Regardless of the QOL measure, appropriate administration of 5-HT\(_3\) antagonists to IBS-D patients is likely to induce a clinically meaningful improvement.

This study has some limitations. In contrast with most IBS clinical trials from Western countries, only limited use of ramosetron was approved, and the present study was limited to men. However, even in Western countries, the prevalence of IBS in men is high.\(^{2}\) In the present study, inclusion criteria and responder definition on stool consistency and abdominal pain/discomfort were not exactly the same as those in FDA proposal.\(^{21}\) They may be considered in a future study (Supplementary Material).

In conclusion, the present data indicate that ramosetron is superior to placebo in improving stool consistency with a low incidence of adverse events in male IBS-D patients. The results also indicate that ramosetron improves HR-QOL in IBS-D patients. Thus, ramosetron is suggested to be the most promising agent among the currently available 5-HT\(_3\) antagonists for treating IBS-D.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.11.024.

References


**Supplementary Material**

**Methods**

**Patient population.** Male outpatients aged 20–64 years who were diagnosed according to the Rome III criteria were eligible. In brief, IBS was defined by recurrent abdominal pain/discomfort for at least 3 days/month in the last 3 months, which was associated with $\geq 2$ of the following: improvement with defecation, onset associated with a change in frequency of stools, and/or onset associated with a change in the form (appearance) of stools. Patients were eligible if they fulfilled the criteria for the last 3 months, with symptom onset at least 6 months before diagnosis. IBS-D was defined as having loose (mushy) or watery stools for $>25\%$ of the time and hard or lumpy stools for $<25\%$ of bowel movements. Organic diseases were excluded by using the BSFS$^1$ as follows: type 1, separate hard lumps like nuts (difficult to pass); type 2, sausage-shaped but lumpy; type 3, like a sausage but with cracks on its surface; type 4, like a sausage or snake, smooth and soft; type 5, soft blobs with clear-cut edges (passed easily); type 6, fluffy pieces with ragged edges (mushy stool); and type 7, watery, no solid pieces, and entirely liquid. Urgency and feelings of incomplete evacuation were assessed by using a binary scale (0, absent or 1, present). Relief of overall IBS symptoms and abdominal pain/discomfort were graded according to a 5-point ordinate scale (0, completely relieved; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened). Improvement in abnormal bowel habits was scored by using a 5-point ordinate scale (0, nearly normalized; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened).

**Results**

**Overall study population.** In total, 296 of 471 patients who provided written informed consent to participate in the study were randomized during the treatment period. Of those who dropped out of the study before randomization, 148 did not satisfy the inclusion or exclusion criteria, 20 withdrew consent, 2 were judged unable to be kept under observation, 1 was excluded for protocol violation, and 4 were excluded for other reasons. Of 296 patients who were randomized to the treatment groups, 147 patients were allocated to the ramosetron group and 149 to the placebo group. One patient in the placebo group was excluded from the FAS because no efficacy variable was measured after administration of the study drug.

An FAS was used in this study, as defined in the ICH E9$^2$ generated by the regulatory authorities and pharmaceutical industries of the European Union, United States, and Japan based on each party’s agreement. The FAS is designed to be as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects. In this study, 1 patient with no data after randomization was excluded from the analysis set. The patient was unable to participate in the study because of his busy schedule, and there was no relationship between discontinuation and the treatment itself. The decision to exclude this patient from the analysis set was taken before unblinding, according to the predefined procedure stipulated in the study protocol. Hence, exclusion of this patient from the analysis set caused no bias. Only 1 patient was reasonably excluded from the study. Therefore, the quality of this study as a whole is high, and drug efficacy was evaluated appropriately.

**Evaluation of the primary end point.** Regarding weekly responder rates, significant improvements were achieved in the ramosetron group compared with the placebo group at all weeks except at week 9 (Supplementary Figure 1). These results suggest a rapid and sustainable treatment effect of ramosetron on improvement of stool consistency in IBS-D patients.


**Evaluation of secondary end points.** Improvement in abnormal bowel habits (Supplementary Figure 2) was significantly higher in the ramosetron group than in the placebo group at all evaluation points.

At baseline, the percentage of days without urgency was 43.1% ± 30.8% and 39.8% ± 30.7% in the ramosetron and placebo groups, respectively. The percentage of days without urgency increased at week 1 (61.5% ± 31.7%) and at the last point (70.7% ± 33.4%) in the ramosetron group compared with the placebo group (at week 1: 50.4% ± 34.7%, \( P = .004 \); at the last point: 61.0% ± 36.6%, \( P = .018 \)). Similarly, at baseline, the percentage of days without incomplete evacuation was 45.0% ± 36.8% and 42.7% ± 38.4% in the ramosetron and placebo groups, respectively. The percentage of days without incomplete evacuation increased from week 5 (64.8% ± 36.7%) to week 9 (64.5% ± 37.6%) in the ramosetron group. This percentage was significantly higher than that in the placebo group (week 5: 51.8% ± 39.3%, \( P = .004 \); week 9: 54.8% ± 41.2%, \( P = .043 \)).

In IBS-QOL analysis, all subscale scores except those for sexual concerns (whose baseline was the highest of all 8 subscales) were significantly improved in the ramosetron group at week 4 (Supplementary Figure 3). Among the 8 subscales, scores for dysphoria, interference with activity, food avoidance, social reaction, and 1-point ordinate scales of improvement, or 7-point ordinate scales of improvement. In a phase III trial, ramosetron was superior to the placebo, with a difference in efficacy of 20% for global improvement of IBS symptoms, of 12% for adequate relief of abdominal pain/discomfort, and of 20% for improvement of abnormal bowel habits.

**Safety.** Other adverse events that had a frequency of >2% in the ramosetron group included headache, nasopharyngitis, gastroenteritis, anemia, hepatic dysfunction, increased serum alanine aminotransferase, and increased serum bilirubin. These adverse events are shown in Table 2 in main text. No death or serious/severe adverse events were observed in the ramosetron group. Almost all adverse events in the ramosetron group were mild and resolved spontaneously. Drug-related adverse events that had an incidence of >1% in the ramosetron group included abdominal distention, epigastralgia, constipation, hard stool, anemia, hepatic dysfunction, increased serum alanine aminotransferase, and increased serum bilirubin. All these drug-related adverse events were mild, except for 1 case of moderate epigastralgia.

**Discussion**

This study demonstrated the efficacy of ramosetron in improving stool consistency as a primary end point in male IBS-D patients. The results are in accordance with those of previous clinical studies involving ramosetron and also demonstrate the below points. First, our data indicated flexible drug development in IBS according to the characteristics of the drug. Global improvement measures, such as adequate relief or satisfactory relief of symptoms, are often used in IBS clinical trials; however, some arguments have been made regarding this method of assessment. Second, improvements in IBS-QOL scores due to ramosetron administration were clearly observed in male IBS-D patients. Although similar findings were recently reported with alosetron, subjects in that study were all female, and the study used a different QOL measure for IBS. Third, ramosetron is a readily available 5-HT<sub>3</sub> antagonist in East Asia and is associated with a low incidence of ischemic colitis or other serious adverse events. Fourth, although the clinical effects of ramosetron have not been clearly demonstrated in female IBS-D patients, the efficacy of this drug in male IBS-D patients provides a medical rationale for its use in other subsets of IBS-D patients. No new treatment has been approved for use in male IBS-D patients in Western countries since 2000. Thus, our findings support our main hypothesis regarding the superiority of ramosetron over the placebo in improving stool consistency, with a low incidence of serious adverse events. The findings support the additional hypothesis that ramosetron had positive effects on HR-QOL in male IBS-D patients.

In other clinical trials of drug treatments for IBS, global assessment has been used as a primary end point. Typical measurement constructs for global assessment include adequate relief, satisfactory relief, 5-point ordinate scales of improvement, or 7-point ordinate scales of improvement. Previous clinical trials of ramosetron have demonstrated improvement in global assessment by using a 5-point ordinate scale. In a phase III trial, ramosetron was superior to the placebo, with a difference in efficacy of 20% for global improvement of IBS symptoms, of 12% for adequate relief of abdominal pain/discomfort, and of 20% for improvement of abnormal bowel habits.

In the present study, these clinical effects of ramosetron were suggested to be related to improvement of stool consistency. This is a scientifically logical conclusion that is based on the mechanism of action of ramosetron on 5-HT<sub>3</sub> receptors in the myenteric plexus. Ramosetron may relieve abdominal pain/discomfort by antagonizing the exaggerated motility of the lower gut and the increased tone of the smooth muscles of the gut in response to meals, distention, or stressors. Because 5-HT<sub>3</sub> in the myenteric plexus plays a key role in the generation of peristalsis and in diarrhea, using improvement in stool consistency as the primary end point is a rational approach.

According to FDA guidance, drugs for IBS should be specifically developed to treat the co-primary end points of abdominal pain and abnormal defecation. However, this guidance permits investigators to design trials with only 1 of these end points if the mechanism of action of the drug applies to only 1 of these symptoms. Demonstration of significant and clinically meaningful changes in the targeted single end point could serve as a basis for approval, as long as the other important symptom or sign did not worsen on treatment. These study data combined with the data of other studies
provide evidence that improvement in stool consistency can be used as a single primary end point or a co-primary end point with the evaluation of global assessment of relief of overall IBS symptoms in clinical trials of the 5-HT₃ antagonist for IBS-D patients.

The inclusion criteria and the definition of a responder on stool consistency in this study are almost consistent with the FDA guidance on IBS issued in 2010. However, in 2012, the FDA issued a revised guidance that modified the inclusion criteria to require at least 2 days per week with a BSFS of 6 or 7. The revised guidance also modified the responder definition to require at least a 50% reduction in the number of days per week with a type 6 or 7 BSFS. For abdominal pain or discomfort there were several differences from both the 2010 and 2012 guidance of FDA. The scale used in the study was a 5-point ordinate scale rather than 11 points as recommended by the FDA. The inclusion criterion used in this study was a weekly average of at least 0.7 on the 0–4 scale, whereas the inclusion criterion for both the 2010 and 2012 FDA guidance was an average of 3 or higher on a 0–10 point scale. The responder definition in this study for pain/discomfort was an average weekly pain/discomfort rating of 1 or less on a 0–4 scale, whereas the pain responder definition for the 2010 and 2012 FDA guidance was a 30% reduction in the average intensity of abdominal pain or discomfort. These facts do not undercut the importance of the findings, but it is suggested that the FDA moved the goal posts in the process of this study and that delicately modified protocol from the newest FDA guidance is also useful for drug development in the world.

IBS-QOL is a reliable and well-validated instrument for assessing HR-QOL in IBS patients. The reliability and validity of the Japanese version of IBS-QOL have been established. IBS-specific HR-QOL improvement was also demonstrated in a previous study in which alosetron was administered to female IBS-D patients. However, that study used IBSQOL, which differs from IBS-QOL. Regardless of the QOL measure, appropriate administration of 5-HT₃ antagonists to IBS-D patients is likely to induce clinically meaningful improvement.

References

Supplementary Figure 1. Weekly responder rate of improvement in stool consistency. Line graph: responder rate (%). Error bar: 95% CI. Thin line: placebo group (n = 148). Thick black line: ramosetron group (n = 147). *P < .01, **P < .001, compared with the placebo. P values were calculated by using the $\chi^2$ test.

Supplementary Figure 2. Monthly responder rate of improvement in abnormal bowel habits. Column height: responder rate (%). Error bar: 95% CI. Open column: placebo group (n = 148). Black column: ramosetron group (n = 147). $P$ values were calculated by using the $\chi^2$ test.

Supplementary Figure 3. Changes in all subscale scores of the Japanese version of IBS-QOL from baseline to week 4. Column height: the values adjusted by using the baseline value as a covariate. Error bar: 95% CI. Open column: placebo group (n = 148). Black column: ramosetron group (n = 147). *P < .05, **P < .01, ***P < .001, compared with the placebo. P values were calculated by using analysis of covariance, with the treatment groups as a factor and baseline score as a covariate.