Background: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder seen in primary care practice. The symptoms of IBS, including abdominal pain, discomfort, and abnormal bowel function, may be modulated by activity of the serotonin type 3 receptor (5-HT₃). The efficacy and tolerability of the 5-HT₃ receptor antagonist alosetron hydrochloride in nonconstipated female patients with IBS were evaluated in a double-blind, randomized, placebo-controlled trial.

Methods: Patients received either 1 mg of alosetron hydrochloride (n=309) or placebo (n=317) twice daily for 12 weeks, followed by a 4-week posttreatment period. Adequate relief of IBS pain and discomfort was the primary end point. Secondary end points included improvements in urgency, stool frequency, stool consistency, incomplete evacuation, and bloating.

Results: Seventy-one percent of patients were classified as having diarrhea-predominant IBS. Forty-three percent of alosetron-treated patients with diarrhea-predominant IBS reported adequate relief for all 3 months compared with 26% of placebo-treated patients (P<.001; percentage point difference=17; 95% confidence interval, 8.0-25.4). Improvement with alosetron compared with placebo was observed by the end of the fourth week of treatment and persisted throughout the remainder of treatment. Alosetron significantly decreased urgency and stool frequency and caused firmer stools within 1 week of starting treatment. Effects were sustained throughout treatment and symptoms returned following treatment cessation. No significant improvement in the percentage of days with sense of incomplete evacuation or bloating was observed compared with placebo during the first month of treatment. Constipation was the most commonly reported adverse event.

Conclusion: Alosetron hydrochloride, 1 mg twice daily for 12 weeks, is effective in relieving pain and some bowel-related symptoms in diarrhea-predominant female patients with IBS.

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Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders seen in primary care and gastroenterology practices. Irritable bowel syndrome primarily affects women, with prevalence estimates of 14% to 24% of women in the United States and Great Britain. It negatively affects patients’ daily activities and quality of life and contributes to significant increases in health care resource utilization.

The primary symptoms of IBS are recurrent abdominal pain and discomfort. Patients with IBS also experience abnormal bowel function, which presents primarily as diarrhea (diarrhea-predominant subtype), constipation (constipation-predominant subtype), or alternation between the 2 (alternating subtype). In addition, increased sense of urgency, bloating, and incomplete evacuation may be present.

The serotonin type 3 (5-HT₃) receptor antagonists represent valuable therapeutic compounds for the treatment of IBS. The 5-HT₃ receptors have been identified on sensory neurons of the gut and mediate reflexes that control gastrointestinal motility and secretion, bowel function, and perception of pain. In patients with IBS, 5-HT₃ receptor antagonists increase colonic compliance, slow colonic transit, and improve stool consistency. Previous studies with the 5-HT₃ receptor antagonist alosetron have shown that 1 mg twice daily is the most effective dose in female patients with IBS for improving IBS abdominal pain and discomfort and urgency. A comparison study with the smooth muscle relaxant mebeverine hydrochloride showed that alosetron provided greater relief of pain and some IBS bowel abnormalities. The efficacy of a 1-mg, twice-daily dose of alosetron hydrochloride in the treatment of IBS has recently been confirmed.
PATIENTS AND METHODS

PATIENTS

Female patients with IBS aged 18 years or older were eligible for enrollment if their symptoms fulfilled the Rome I criteria for IBS for at least 6 months. Patients underwent a 2-week screening evaluation to confirm sufficient level of pain and stool consistency before randomization. Institutional review boards at all sites approved the protocol, and all patients provided written informed consent.

Patients with IBS and a diarrhea-predominant bowel pattern or a bowel pattern that alternated between diarrhea and constipation (ie, alternators) were enrolled in this study. Since no objective criteria exist for subgrouping of IBS patients, physicians were asked to assess patients according to predominant pattern of bowel function based on the patient’s disease history. Physicians were provided with a guideline based on the percentage of time the patient had experienced diarrhea or constipation (if diarrhea or constipation was present for ≥75% of the time, a patient’s IBS was active, then the patient was classified as being diarrhea predominant or constipation predominant, respectively; otherwise the patient was classified as an alternator). Patients with constipation-predominant IBS were excluded from the study.

Patients were excluded if they were pregnant, breastfeeding, or not using approved methods of contraception (if of child-bearing potential); if an unstable medical or other gastrointestinal condition existed; if there was a major psychiatric disorder or substance abuse within the previous 2 years; if an investigational drug was used within 30 days of the screening phase; or if a prohibited concurrent medication (likely to interfere with gastrointestinal tract function or analgesia) was used within 7 days before entering the screening phase.

STUDY DESIGN

Patients were randomized 1:1 to receive 12 weeks of oral treatment with either matched (appearance and taste) placebo or alosetron hydrochloride, 1-mg tablets twice daily taken before meals. Treatments were randomly assigned with equal allocation to alosetron and placebo using a blocked (block size of 4) randomization schedule generated from Glaxo Wellcome’s Random Codes System. The treatment phase was followed by a 4-week follow-up period. Laboratory evaluations, menstrual records, and assessments of fiber intake were collected at the 4- and 8-week treatment visits and at the 12-week (or final treatment) visit.

DATA COLLECTION

During the screening, treatment, and follow-up periods, daily and weekly symptom data were collected using an interactive telephone-based system previously described.

Pain and bowel function data were collected during the screening phase to ensure that patients had a suitable symptom level at study entry. Severity of pain and discomfort was assessed daily on a 3-point scale (0, none; 1, mild; 2, moderate; 3, intense; and 4, severe). Average daily baseline pain and discomfort scores during the 2-week screening period were required to be between 1.0 and 3.3 (inclusive) for patients to enter the treatment phase. Stool consistency data were monitored daily and scored as follows: 1, very hard; 2, hard; 3, formed; 4, loose; and 5, watery. Absence of stool was assigned a value of 0. During the screening period, average daily stool consistency scores of 2.5 or higher were required to exclude patients with hard stools and enroll patients whose predominant bowel abnormality was diarrhea. Routine laxative treatment was not permitted during the screening, treatment, or follow-up periods.

During the treatment and follow-up phases, patients were asked once every 7 days if they had obtained adequate relief of their IBS pain and discomfort during the previous 7 days. Patients also recorded their IBS symptoms (pain severity, urgency, stool consistency, stool frequency, bloating, and sense of incomplete evacuation) daily during the treatment and follow-up phases.

Patients who experienced no bowel movements for 4 consecutive days were required to stop treatment for up to 4 days. Patients were able to remain in the study and resume treatment only if bowel movements returned within the 4-day drug holiday.

STATISTICAL ANALYSIS

The primary efficacy end point was the proportion of patients with adequate relief of IBS pain and discomfort on at least 2 weeks per month (defined as a monthly responder). The sample size was chosen with 90% power at the α = .05 significance level to detect a 15–percentage point difference between treatment groups for the proportion of patients with adequate relief on at least 2 weeks per month, assuming a 40% response in patients receiving placebo and a 55% response for patients receiving alosetron hydrochloride, 1 mg twice daily. Two hundred forty-four patients per treatment group were necessary to detect such a difference. Therefore, a target sample size of 300 patients per treatment group (total target of 600 patients) was chosen to allow for a 20% dropout rate.

Efficacy analyses were by intention to treat and included all patients randomized to study treatment; safety analyses included all patients randomized to treatment except those who did not take at least 1 dose of study treatment. The handling of missing data was managed according to the last observation carried forward (LOCF) principle, whereby missing values were replaced with the last previous nonmissing value. The impact of this imputation scheme on treatment differences for adequate relief was assessed.

The proportion of patients with adequate relief was compared between treatment groups using a Mantel-Haenszel test stratified by clusters of centers. Centers were prospectively grouped into 5 geographic “clusters” to avoid the loss of centers with small numbers of subjects in tests stratified by center or tests of treatment-by-center interaction. Therefore, treatment-by-cluster interaction was assessed (using cluster as a surrogate for center) via ordinal logistic regression using the total number of months a patient was a monthly responder as the dependent variable and treatment, cluster, and treatment by-cluster interaction terms as independent predictors in the model.

Daily stool consistency scores and daily number of bowel movements were averaged at baseline (for the 2-week screening period) and for each week of the treatment and follow-up phases. In addition, the percentage of days that patients experienced a sense of urgency, incomplete evacuation, and bloating was calculated at baseline and for the same weekly intervals. Changes from baseline in the 2 treatment groups were compared using the van Elteren test stratified by clusters of centers.

Closed testing procedures were used to address multiple significance testing in the analysis.
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Because of the range of symptoms associated with IBS, evaluating efficacy of treatments can be challenging. In previous studies with IBS patients, we have introduced and validated the end point of adequate relief of IBS pain and discomfort. Changes in adequate relief correlate with changes in measures that are meaningful to diarrhea-predominant patients with IBS: improved pain severity scores, a greater percentage of pain-free days, fewer days with urgency, and fewer and firmer stools. Furthermore, the adequate relief end point is responsive to treatment and the responses are reproducible. Thus, adequate relief is a valid end point for measuring improvement in multiple IBS-relevant dimensions.

This randomized, placebo-controlled clinical trial evaluated the efficacy and tolerability of alosetron in nonconstipated women with IBS. The primary efficacy measure was adequate relief of IBS pain and discomfort, with secondary efficacy measures of improved urgency, stool frequency, stool consistency, bloating, and incomplete evacuation. We have also assessed efficacy in the subset of patients with diarrhea-predominant IBS. This subset comprised 71% of the study population.

**RESULTS**

**STUDY POPULATION AND DEMOGRAPHICS**

Six hundred twenty-six of 1417 patients screened were randomized from 104 sites within the United States. Site enrollment ranged from 1 to 19 patients per site and averaged 6 patients per site. Seventy-one percent of patients randomized were classified as having the diarrhea-predominant form of IBS. A flowchart of patients' progression through the study is presented in Figure 1. Screening failures resulted primarily from failure to meet the entry criteria for pain and stool consistency. Two hundred eighty patients had harder stools than allowed, 175 patients had pain below the severity criterion, and only 20 patients had pain exceeding the severity criterion.

A total of 237 (77%) of 309 and 247 (78%) of 317 randomized patients in the alosetron and placebo groups, respectively, completed the study. Seventy-two patients prematurely discontinued treatment in the alosetron group and 71 in the placebo-treated group. Reasons for premature discontinuation from the study are indicated in Figure 1.

General and IBS-specific characteristics for randomized patients were similar between treatment groups (Table 1). Patients were predominantly white and in their mid-40s.

**ADEQUATE RELIEF OF PAIN AND DISCOMFORT**

Forty-one percent of alosetron-treated patients in the intention-to-treat population reported at least 2 weeks
Table 2. Proportion of Diarrhea-Predominant Patients With Adequate Relief During the 3 Months of Treatment

<table>
<thead>
<tr>
<th>Month</th>
<th>Alosetron Hydrochloride Group (n = 224)</th>
<th>Placebo Group (n = 222)</th>
<th>Treatment Difference*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 (43.5-56.5)</td>
<td>39 (32.8-45.6)</td>
<td>11 (35.0-47.9)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>2</td>
<td>58 (51.4-61.4)</td>
<td>43 (36.7-49.8)</td>
<td>15 (5.2-23.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>3</td>
<td>60 (53.9-66.7)</td>
<td>41 (35.0-47.9)</td>
<td>19 (9.7-27.9)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Percentage point difference.

Figure 2. Percentage of diarrhea-predominant patients with adequate relief of irritable bowel syndrome pain and discomfort on a weekly basis during treatment with alosetron hydrochloride, 1 mg, or placebo twice daily. Asterisk indicates P < .05 compared with placebo; dagger, P < .001 compared with placebo.

Figure 3. Percentage of days with urgency in diarrhea-predominant patients with irritable bowel syndrome during treatment with alosetron hydrochloride, 1 mg, or placebo twice daily or during posttreatment follow-up. Asterisk indicates P < .01 compared with placebo; dagger, P < .001 compared with placebo.

study population, efficacy, hereafter, will be described for diarrhea-predominant patients only.

Forty-three percent of alosetron-treated diarrhea-predominant patients and 26% of placebo-treated patients were monthly responders for all 3 months of treatment (treatment difference of 17 percentage points; P < .001; 95% CI, 8.0-25.4). The proportion of monthly responders at each month was also significantly greater in the alosetron group compared with the placebo group for diarrhea-predominant patients (percentage point differences of 11, 15, and 19 for months 1, 2, and 3, respectively, Table 2). There was no evidence of differential treatment effects among clusters of centers.

We further assessed weekly response rates to evaluate onset and sustainability of the response. The percentage of diarrhea-predominant patients in the alosetron and placebo groups with adequate relief of pain and discomfort reported each week is shown in Figure 2. Alosetron provided significantly greater adequate relief of pain and discomfort than placebo. Significant benefit was achieved by the fourth week of treatment (P < .001) and was maintained throughout the remainder of treatment. Symptoms rapidly returned following cessation of treatment.

BOWEL FUNCTION

Alosetron also significantly decreased the percentage of days with urgency and number of stools per day and caused firmer stools compared with placebo. Figures 3, 4, and 5 show the effects of alosetron and placebo on urgency, stool frequency, and stool consistency for diarrhea-predominant patients, respectively. For each symptom, significant improvement with alosetron compared with placebo occurred during the first week of treatment and was sustained throughout the 12 weeks of treatment. At week 12, days with urgency was decreased by 12.6 percentage points (95% CI, 6.1-19.1), stool frequency was decreased by 0.5 stool per day (95% CI, 0.3-0.7), and stool firmness was increased by 0.6 point (95% CI, 0.4-0.7; see the “Patients and Methods” section for scale) relative to placebo. Alosetron had no significant effect on the percentage of days diarrhea-predominant patients experienced a sense of incomplete evacuation in the first month of treatment, but did improve the percentage of days patients experienced this symptom in months 2 (46.4% in the alosetron group vs 56.4% in the placebo group; P = .02) and 3 (45.0% vs 57.1%; P = .009). Alosetron did not signifi-

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cantly improve bloating at any time compared with placebo (data not shown).

SAFETY

Safety data were collected for all patients in the intention-to-treat population who took at least 1 treatment dose. One hundred eighteen (38%) of 309 patients in the alosetron group and 62 (20%) of 316 patients in the placebo group had drug-related adverse events as assessed by the study physicians (P<.001). Constipation was the most commonly reported drug-related adverse event in the alosetron-treated group and occurred in 77 (25%) of 309 patients in the alosetron group compared with 15 (5%) of 316 patients in the placebo group. However, the percentage of alosetron-treated patients who reported adequate relief at each week was similar whether or not constipation was also reported. Constipation tended to occur within the first month of therapy (median onset of 10 days following initiation of treatment and duration of 6 days). Of patients reporting constipation, 76% reported only a single episode (laxatives were not permitted by protocol). No other drug-related adverse event was reported with a frequency greater than 5%, and, with the exception of constipation, adverse event profiles between the alosetron-treated and placebo groups were similar. Incidence of serious adverse events were the same (2%) in the alosetron and placebo groups.

Forty-eight patients (16%) in the alosetron treatment group and 21 patients (7%) in the placebo group withdrew from the study because of adverse events. The adverse event associated with most of these withdrawals was constipation in alosetron-treated patients (32 [10%] of 309 of alosetron-treated patients withdrew because of constipation compared with 5 [2%] of 326 patients in the placebo group). Most patients (45/77) who developed constipation remained in the study. Laboratory values were not significantly affected by alosetron treatment. No drug-related serious adverse events or deaths were reported during treatment.

COMMENT

In this multicenter, randomized, double-blind, placebo-controlled study, treatment with alosetron significantly relieved abdominal pain and discomfort, decreased the percentage of days with urgency, decreased stool frequency, and produced firmer stools compared with placebo in women with diarrhea-predominant IBS. Beneficial effects of alosetron on percentage of days with incomplete evacuation were noted during the second and third months of treatment. Alosetron exerted no effect on bloating, and bloating may be of greater significance to constipation-predominant patients. These results confirm those of a previous study, which showed that alosetron improved pain, urgency, stool frequency, and stool consistency after 1 to 2 weeks of therapy in diarrhea-predominant women with IBS.

Most patients with IBS who present to physicians in Western countries are women, and a number of chronic visceral pain syndromes are more prevalent in women compared with men. The present study evaluated only women with IBS, because preferential efficacy with alosetron has been reported in these patients. Although the reasons for sex-dependent responses are unknown, sex-based differences in blood-brain perfusion patterns during colorectal distension have been noted in IBS patients, and sex-based differences in motility and sensitivity to luminal distension have been observed in healthy volunteers. Preliminary studies also show that the effect of alosetron on colonic transit is significantly greater in women with diarrhea-predominant IBS than in men. Evaluating the therapeutic potential of new drugs in IBS and other functional gastrointestinal disorders is challenging because of the range and multiplicity of symptoms and the variable and often high placebo response rates. Patients with IBS report that their lives are most directly affected by IBS pain, discomfort, and altered bowel function, although IBS affects a range of patients’ psychological and social functioning. In a recent survey of nonconstipated, female patients with IBS who participated in the present and previous phase 3 study, the most bothersome symptoms reported were abdominal pain and discomfort, urgency, and increased stool frequency. As shown in the present study, alosetron treatment significantly improved all 3 of these symptoms but had no impact on bloating.
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Assessing multiple symptoms and prospectively choosing a primary outcome measure that allows clinical efficacy to be based on patients’ integration of their symptoms were recently endorsed by the Rome II working group guidelines on functional gastrointestinal disorders. Use of adequate relief of abdominal pain and discomfort as the primary outcome measure in the present study follows the Rome II guidelines, since it provides a meaningful, patient-evaluated measurement of clinical improvement in multiple symptoms of IBS.

Assessment of the clinical relevance of the alosetron treatment effect is complicated by the fact that there is no “gold standard” to define “clinically important.” Alosetron was observed to produce significant improvement in adequate relief of pain and discomfort, urgency, frequency, and stool consistency. The magnitude of improvement on each end point was similar and...
showed an advantage over placebo comparable to that observed for other drugs acting in the gastrointestinal tract, such as histamine receptor antagonists for gastric ulcer.42

The specific mode of action by which alosetron modulates IBS symptoms is not yet fully understood. Antagonists to the 5-HT3 receptor have been reported to slow colonic transit, increase colonic compliance, and increase pain thresholds during colorectal distension.11,13,15,45-46 Using an intracolonic barostatically controlled balloon, alosetron was found to increase colonic compliance in diarrhea-predominant patients with IBS without changing the pressure perception threshold.12 Increases in compliance would be anticipated to allow distension of the lumen during passage of a gas bolus without increased wall tension, thus attenuating afferent impulse activation and reducing the perception of visceral pain.

Receptors for 5-HT3 are present in both the peripheral and the central nervous system. Specifically, they have been reported on the spinal and vagal innervation of the gut, the spinal cord, and multiple areas in the brain, with highest binding in the amygdala and hippocampus. The amygdala and hippocampus are involved in sensation and emotional or affective responses. Blockade of 5-HT3 receptors by alosetron may, therefore, modulate visceral sensation and autonomic responses in IBS by altering the encoding, transmission, and processing of sensory information at different levels of the brain-gut axis.15

As with any study, there are limitations in the present trial. Only female patients were evaluated in the present study, based on female preferential efficacy in an earlier report.17 Although patients with continuous severe pain were excluded from enrollment by imposition of an upper pain cutoff of 3.3 (between intense and severe) during the 2-week screening period, only 20 (1.4%) of 1417 patients were excluded from the study because of this criterion. Patients who had severe pain on several days during the screening period were not excluded by this criterion. Many more patients (175 [12%] of 1417) were excluded because of insufficient (ie, less than mild) pain, and thus the randomized population generally was representative of patients with moderate to severe IBS. As a screening requirement, achieving a minimum stool consistency score, rather than both a consistency and frequency score, was required. Because there are no formal objective criteria for constipation, imposition of entry criteria for both stool frequency and consistency would have been advantageous for excluding constipated patients during the screening period.

Constipation was the most frequent drug-related adverse event during alosetron treatment. Based on the increased colonic transit time observed after treatment with 5-HT3 receptor antagonists,11,43,47 constipation is not an unexpected consequence of alosetron treatment, especially since laxative use was not routinely permitted in the present study. However, the percentage of alosetron-treated patients who reported adequate relief at each week was similar whether or not constipation was also reported.

In summary, treatment with alosetron produced relief of abdominal pain and discomfort, as well as improvements in some IBS-associated bowel function disturbances, in women with diarrhea-predominant IBS.

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