A SPECIAL ARTICLE

Update on Treatment of Patients with Irritable Bowel Syndrome Using Gastrointestinal Serotonergic Agonists and Antagonists

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Irritable bowel syndrome (IBS) imposes substantial clinical and financial burdens on patients and society. Traditional agents for the management of IBS have been documented to have limited efficacy and poor tolerability. Insight into the critical role serotonin plays in gastrointestinal (GI) tract function has led to the development of GI tract–specific serotonin agonists and antagonists. Recent clinical trials have demonstrated that several of these agents provide global relief in patients with IBS and that they reduce the severity of individual symptoms in these patients.

BACKGROUND

Irritable bowel syndrome (IBS) is a chronic, functional, gastrointestinal (GI) motility disorder characterized by abdominal pain or discomfort associated with altered bowel habits (1). IBS is highly prevalent; it affects between 10% and 15% of the US population (1). The chronic symptoms of IBS negatively affect the psychological well-being, work productivity, and social functioning of patients and are associated with high direct (medical) and indirect (lost productivity) costs (2,3).

In the past decade, research has provided new insight into the underlying pathophysiology of IBS, resulting in the development of unique agents that target serotonin (5-hydroxytryptamine [5-HT]) within the GI tract. Serotonin is a key factor in normal GI functions, including motility, visceral sensitivity, and intestinal secretion. These three functions appear to be altered in patients with IBS (3,4)—a finding that has

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led to the development of drugs designed to target key serotonin receptors in the GI tract and to treat the multiple symptoms of IBS.

International working groups on GI disorders (such as the Rome Committee on the Design of Treatment Trials for Functional GI Disorders [FGIDs], the American Gastroenterological Association, and the American College of Gastroenterology [ACG] FGID Task Force) agree that efficacy in IBS trials should be evaluated on the basis of global relief of IBS symptoms (eg, abdominal pain/discomfort, bloating, and altered bowel habits) and improvement in overall well-being (5–7).

The efficacy of serotonergic receptor agonists and antagonists in providing global improvement of IBS symptoms has been shown in well-designed, randomized, placebo-controlled clinical trials that included primary efficacy measures assessing global symptom improvement (8–11). These agents are important additions to the treatment armamentarium for patients with IBS. The goal of this article is to provide a brief review of the role in therapy of available and emerging serotonergic receptor agonists and antagonists for the treatment of patients with IBS. An overview of safety issues for select agents is also presented.

USEFULNESS OF TRADITIONAL TREATMENT OPTIONS FOR PATIENTS WITH IBS

Traditional treatment options, such as increasing fiber intake, laxatives, and antidiarrheal agents, are important for relieving the individual symptoms of IBS—eg, fiber and laxatives for constipation, antidiarrheals for diarrhea (Table 1) (1,12,13) particularly for patients with mild symptoms. However, the degree of relief these therapies provide for patients with more severe symptoms is often inadequate. Additionally, traditional agents can elicit adverse effects that mimic or exacerbate IBS symptoms (bloating, abdominal discomfort, and flatulence from fiber; constipation from antispasmodics and antidepressants) (1).

According to the consensus recommendations published by the ACG FGID Task Force, the goal of IBS therapy is to provide global improvement for the multiple symptoms of IBS; treatment of single symptoms is a suboptimal approach (1). Studies of most traditional therapies for IBS either have not focused on global symptom relief or have not provided global improvement for the condition. The ACG Task Force concluded that, based on the available evidence, stool-bulking agents, antidepressants, and antidiarrheals are not more effective than placebo in alleviating the global symptoms of IBS and that data are insufficient to permit an effective appraisal of the efficacy of antispasmodic agents for this patient population (1).

ROLE OF SEROTONIN IN IBS PATHOPHYSIOLOGY

Serotonin, a neurotransmitter found primarily (95%) in the gut, is critical to the normal functioning of the GI tract. As a common link in the integrated bidirectional communication track between the central and enteric nervous systems (CNS and ENS) (known as the brain–gut axis) and the autonomic nervous system, serotonin helps to regulate sensory, motor, and secretory activities of the intestines (14). Serotonin is directly involved in initiating and maintaining peristalsis and in enhancing intestinal secretions. Serotonin, in conjunction with other neurotransmitters, also modulates the transmission of pain signals from the gut to the CNS; in this manner, it plays a key role in the perception of bowel activity and pain sensation (15). Although more than 14 subtypes of serotonin receptors have been identified, type 1 (5-HT_1), type 3 (5-HT_3), and type 4 (5-HT_4) receptor subtypes have been shown to play major roles in the regulation of GI tract function (14,15).

Dysregulation in one or more serotonin-signaling components—5-HT synthesis, storage, release, reuptake, degradation, receptor activation—may result in alterations in GI physiology, such as increased or decreased GI motility, increased GI tract sensitivity, and altered intestinal secretions. These manifestations may lead to symptoms associated with GI motility disorders (16,17). Recent data have also suggested that IBS with diarrhea (IBS-D) is characterized by reduced serotonin uptake, whereas IBS with constipation (IBS-C) is characterized by impaired serotonin release (18).

GASTROINTESTINAL SEROTONERGIC AGONISTS AND ANTAGONISTS

An enhanced understanding of the role of serotonin in normal gut function has led to the development of sev-

A SPECIAL ARTICLE

(continued on page 75)

Table 1.
Traditional Treatment Options for IBS

Drug category	*Examples*	*Therapeutic rationale*	*Primary target symptoms*	*Tolerability concerns*
Bulking agents (1)	Wheat bran, corn fiber, calcium polycarbophil, psyllium	Accelerate intestinal transit, add fluid to stool mass, and create gel-like matrix in stool	Constipation, diarrhea	May increase intestinal gas, bloating, and abdominal discomfort
Osmotic laxatives (12)	Magnesium hydroxide, sodium phosphate, lactulose, sorbitol solution	Poorly absorbed ions or sugars that cause an influx of fluid and electrolytes into the intestine	Constipation	Diarrhea, dehydration, electrolyte disorders, volume overload
Stimulant laxatives (12)	Senna, bisacodyl, castor oil, aloe	Reduce water and electrolyte absorption by stimulating colonic neurons and irritating the colonic mucosa	Constipation	Dehydration, electrolyte disturbances, significant cramping, and diarrhea Should be avoided
Antidiarrheal agents (1)	Loperamide	Delay intestinal transit and may enhance resting internal anal sphincter tone	Diarrhea	May cause constipation: should not be used in patients with IBS-C; use with caution in patients with alternating IBS symptoms
Antispasmodic agents (1)	Hyoscyamine, dicyclomine	Anticholinergic effects, and decreased spontaneous activity of intestinal smooth muscle Decreased fluid and electrolyte secretion	Diarrhea, abdominal pain	Anticholinergic adverse effects at high doses (including urinary retention and constipation) Use with caution in patients with IBS-C
Antidepressants (1,13)	Desipramine, amitriptyline, trimipramine, doxepin, paroxetine, fluoxetine	Decrease gut sensitivity, decreasing experience of abdominal pain Antianxiety and antidepressant effects	Pain	Constipation, dry mouth, and dizziness are common adverse effects of tricyclic antidepressants Diarrhea, nausea, nervousness, and fatigue are common adverse effects of selective serotonin re-uptake inhibitors

IBS, irritable bowel syndrome; IBS-C, IBS with constipation.

(continued from page 70)

eral agents designed to target key serotonin receptors in the GI tract. Two agents are available, a third is in clinical trial development, and a fourth has been discontinued in the United States during the investigational stage. The following sections provide an update on the place of these drugs in the therapy of IBS and on important precautions that should be observed with their use (Table 2) (10,19–23).

Tegaserod

Tegaserod, a selective 5-HT_4 receptor agonist, is approved by the US Food and Drug Administration (FDA) for the treatment of women with IBS-C and of men and women with chronic idiopathic constipation. In several large, randomized, placebo-controlled clinical trials, patients with IBS-C who received tegaserod experienced significantly greater global symptom improvement (the primary efficacy variable, assessed according to the Subject's Global Assessment of Relief [SGA]) than did patients who received placebo. The SGA is a validated efficacy measure that captures patient response to therapy in relation to three areas: overall well-being, abdominal pain/discomfort, and altered bowel function (24). Patients who received tegaserod also had greater improvement in single IBS symptoms (such as abdominal pain and discomfort, stool consistency and frequency, and bloating) than did patients who received placebo (8,9,25,26).

In clinical trials, response to tegaserod treatment was noted as early as the first week of therapy, and efficacy continued for the duration of the studies (12 weeks) (8,9). Withdrawal and re-treatment trials have shown that, although patient symptoms do not reach baseline levels, symptoms rapidly return with discontinuation of tegaserod. Subsequent reintroduction of tegaserod yields response rates similar to those observed with initial treatment (27,28).

Tegaserod was well tolerated in clinical trials. A pooled analysis of data from three 12-week clinical studies showed that the adverse effects reported more frequently in tegaserod than in placebo recipients were headache (15% and 12%, respectively) and diarrhea (9% and 4%, respectively) (23). Most cases of diarrhea occurred as a single episode during the first week of treatment, were mild, did not result in serious consequences, and resolved with continued therapy (23). Overall, 1.6% of patients in the studies discontinued tegaserod treatment because of diarrhea. A few instances (0.04%) of diarrhea were clinically significant, resulting in hospital admission, hypovolemia, hypotension, and the need for intravenous fluids (23).

An open-label, long-term safety study was conducted in 579 patients with IBS-C who received tegaserod 6 mg twice daily (bid) for one year. The most commonly reported adverse effects associated with tegaserod treatment were similar to those noted in the 12-week phase three clinical trials, including diarrhea that was mild and transient (did not result in dehydration or electrolyte imbalance and did not require hospital admission [10.1%]), headache (8.3%), abdominal pain (7.4%), and flatulence (5.5%) (29).

The incidence of abdominal surgery, including cholecystectomy, hysterectomy, and appendectomy, is greater among patients with IBS than among their non-IBS counterparts (30). During tegaserod phase three clinical development, a numeric imbalance was detected in the number of patients requiring abdominal surgery. In total, five of 2,965 patients who received tegaserod and one of 1,740 patients who received placebo required cholecystectomy (23). However, a blinded adjudication of data from 13 clinical trials (including 6,197 patients who received tegaserod) by an independent panel of experts revealed no significant difference in the incidence of abdominal or pelvic surgery among patients who received tegaserod or placebo (30).

Clinical trial and post-marketing surveillance data disclosed no reports of ischemic colitis (IC) among more than 14,000 patients (4,888 patient-years of tegaserod use) treated with tegaserod; however, IC developed in one patient who received placebo (1,152 patient-years) (31). Furthermore, post-marketing surveillance data suggest that the incidence of IC in IBS patients taking tegaserod is much lower than the background incidence of IC in the IBS population (eight cases per 100,000 patient-years [data on file; Novartis Pharmaceutical Corporation] compared with 43 to 49 cases per 100,000 patient-years (32–35), respectively). Despite the reporting of these cases, pharmacologic data (based on in vitro concentrations in isolated coronary arteries or in vivo exposure in anesthetized rats) do not indicate a vascular mechanism that could lead

Table 2.
Serotonin Agonists and Antagonists for IBS

Drug class	*Examples*	*Therapeutic rationale*	*Primary target symptoms*	*Efficacy in global symptom improvement*	*Tolerability concerns*
5-HT_3 receptor antagonists (19–22) (methylimidazole analogs)	Alosetron Cilansetron[a]	Reduce visceral sensitivity and colonic transit	Abdominal pain, diarrhea, urgency	Effective in providing global relief of IBS-D symptoms	Alosetron: Black box warning regarding serious consequences of constipation; ischemic colitis (reported during clinical trials and in post-marketing surveillance) Cilansetron: Constipation, ischemic colitis (reported during clinical trials and in post-marketing surveillance), flatulence
5-HT_4 receptor agonists (23) (aminoguanidine indoles)	Tegaserod	Reduce visceral sensitivity and increase GI transit and intestinal secretion	Abdominal pain/discomfort, bloating, constipation	Effective in providing global relief of IBS-C symptoms	Diarrhea, ischemic colitis (reported in post-marketing surveillance)
Mixed 5-HT_4 receptor agonists/5-HT_3 receptor antagonists (10) (benzamide derivatives)	Renzapride[b]	Increase colonic transit time	Abdominal pain/discomfort, constipation	Not yet determined	Diarrhea

[a]Regulatory activities suspended in the United States, pending in Europe.
[b]In development (phase 2 clinical trials).
5-HT, serotonin; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea.

to mesenteric or colonic ischemia with tegaserod (36–38). Nevertheless, a precaution describing the possibility of IC is included in the package insert for tegaserod (23). The package insert also states that tegaserod "should be discontinued immediately in patients who develop symptoms of IC, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain" (23). If a patient receiving tegaserod experiences new or worsening abdominal pain or

(continued on page 78)

(continued from page 76)

blood in the stool, tegaserod use should be discontinued and appropriate diagnostic tests, such as colonoscopy, should be performed (23).

Recent studies have reported the safety and efficacy of tegaserod treatment in patients with IBS with mixed or alternating bowel pattern (IBS-A) (39,40). Tegaserod (6 mg bid), compared with placebo, provided statistically significant improvement ($p < 0.001$) in the relief of IBS symptoms over a four-week treatment period for women with IBS-A (n = 324) and IBS-C (n = 337) (39). Tegaserod also significantly improved bowel movement frequency, stool consistency, and straining for patients with IBS-A and IBS-C ($p < 0.05$, compared with placebo). The most frequent adverse effects that resulted in discontinuation of study medication were diarrhea (1.1%) and headache (0.6%); no cases of IC were reported. In a randomized, double-blind, placebo-controlled study, tegaserod was safe and well tolerated in patients with IBS-A and IBS-C (40). Overall, 29.5% (n = 329) of patients treated with tegaserod and 25.7% (n = 331) treated with placebo experienced at least one adverse effect. Diarrhea was reported more frequently in patients with IBS-A (tegaserod, 12.1%; placebo, 1.8%) than in patients with IBS-C (tegaserod, 7.0%; placebo, 2.4%), but only a small percentage of patients discontinued tegaserod treatment because of this adverse effect (1.5% for IBS-A and 0.6% for IBS-C).

Alosetron

Alosetron, a 5-HT_3 receptor antagonist, was originally approved by the FDA in February 2000 for the treatment of patients with IBS-D. Large, double-blind, placebo-controlled clinical trials showed that alosetron (1 mg bid for 12 weeks) was significantly more effective than placebo in providing global improvement in patients with IBS-D and in improving single symptoms (eg, bowel urgency). Global improvement was measured by means of an IBS Global Improvement Scale, which asked participants to answer the following question: "Compared with the way you usually felt during the three months before you entered the study, are your IBS symptoms during the past four weeks substantially worse, moderately worse, slightly worse, not changed, slightly improved, moderately improved, or substantially improved?" *Responders* were defined as patients who rated their conditions as moderately or substantially improved (11,41).

In clinical trials, the most frequently reported adverse effects among patients who received alosetron, compared with patients who received placebo, included constipation (29% and 6%, respectively), abdominal pain/discomfort (7% and 4%, respectively), and nausea (6% and 5%, respectively) (20). In these trials, most instances of constipation were single episodes, occurred during the first month of treatment, and resolved spontaneously or when treatment was interrupted (20).

Ischemic colitis and other serious complications related to constipation were reported by patients who received alosetron during clinical trials and during post-marketing surveillance, causing this agent to be withdrawn from the market nine months after its introduction. In November 2002, alosetron was reintroduced to the market with a new, restricted indication: the treatment of women with severe diarrhea-predominant IBS who did not respond to conventional therapy (20). This patient population is defined as those with chronic IBS symptoms (symptoms that have lasted for six months or longer) and in whom anatomic and biochemical abnormalities have been excluded (20). A new dosage, 1 mg once daily (od), along with a risk management program (described in this section) were also included with its reintroduction to the marketplace.

The package insert for alosetron now carries a black box warning regarding serious GI adverse effects, including IC and serious constipation-associated complications. It further states that, in clinical trials, rare occurrences of complications arising from constipation (such as obstruction, perforation, impaction, and death) were noted in patients who received alosetron (at an incidence of one in 1000 patients) and that IC occurred at a cumulative incidence of two per 1000 patients over a three-month period and of three per 1000 patients over a six-month treatment period (20). More recent post-marketing surveillance data indicated that the post-adjudication rate of IC and the rate of serious complications were 1.1 and 0.66 per 1000 patient-years of alosetron use, respectively (42).

(continued on page 80)

(continued from page 78)

The risk management program for alosetron is designed to ensure that physicians and patients are aware of the serious nature of potential adverse effects and that they agree to follow the required steps to maximize safe use (20). Before prescribing alosetron, physicians must enroll in the physician prescribing program, sponsored by the manufacturer, which confirms their qualifications and explains responsibilities. To participate in this program, physicians must first sign and return the physician attestation form, which certifies that the physician is trained and experienced in the diagnosis and treatment of patients with IBS and is able to diagnose and manage IC and constipation-associated complications. On receipt of this signed form, the manufacturer sends out a prescribing program kit, which includes the medication guide for patients, the patient-physician agreement forms (which should be signed by the patient and the physician), prescribing program stickers (which contain an identification number issued to the individual prescribing physician), patient enrollment cards for a patient survey, and an educational CD-ROM (20). Physicians must affix a sticker to **all** (original and subsequent) prescriptions for alosetron; no refills or telephone, facsimile, or computerized prescriptions are allowed.

Data from a randomized, double-blind, placebo-controlled 12-month study showed the long-term efficacy and safety profiles of alosetron in female patients with severe, chronic symptoms of IBS-D (the indicated patient population). In this study, patients were randomly assigned to receive alosetron 1 mg (n = 351) or placebo (n = 363) bid. Results showed that patients who received alosetron experienced a significantly greater rate of adequate relief from IBS-associated pain and discomfort than patients who received placebo and that they experienced satisfactory control of a variety of other GI symptoms (including urgency, stool frequency, stool consistency, and bloating). Similar findings were shown in a subset of patients with "more frequent urgency," which was defined as the presence of bowel urgency on 10 or more days of the 14-day screening period (43). Constipation was reported in 23% of patients who received alosetron and in 5% of the placebo group. Most episodes of constipation occurred during the first month of treatment. During the study period, a single constipation event was reported for every seven patients who received alosetron (43). No reports of IC or serious complications of constipation were reported during this study (43).

EMERGING SEROTONERGIC AGONISTS AND ANTAGONISTS

Renzapride

Renzapride is a mixed 5-HT_4 receptor agonist/5-HT_3 receptor antagonist in clinical trials for treatment of patients with IBS-C. Data from a phase 2 clinical trial (with 510 patients in the intention-to-treat population) suggest that renzapride (4 mg/d) improves abdominal pain/discomfort in patients with IBS-C to a greater extent than does placebo (56% vs 49%, respectively, at weeks five-12 of the study). In addition, patients who received renzapride experienced significant improvement in mean number of daily bowel movements and in stool consistency (10). Global IBS symptom improvement was not measured in this study. Renzapride was generally well tolerated in clinical trials. The adverse effects most frequently reported by patients who received renzapride, compared with placebo, were diarrhea (25.2% and 9.6% of patients, respectively) and headache (17.8% and 13.6%, respectively) (10).

A small study (N = 46) evaluating dose-ranging pharmacodynamic effects found that renzapride caused a clinically significant, dose-related acceleration of colonic transit in women with IBS-C (44). Improvements in stool form and ease of stool passage (but not of frequency) were significantly associated with the increase in colonic transit ($p < 0.05$ compared with placebo). No significant improvement was reported in relief of symptoms or of bowel function, which could be attributed to the small sample size aimed at pharmacodynamic, but not clinical, efficacy. A dose-escalating pilot study assessed the efficacy and tolerability of renzapride (2 mg od and 2 mg bid) in patients with IBS-C (N = 17) (45). Renzapride 2 mg bid, compared with placebo, increased overall GI motility, reduced abdominal pain, increased the number of pain-free days, and improved stool consistency. Renzapride was generally well tolerated; the most common treatment-related adverse effects were abdominal pain, headache, constipation, and diarrhea.

Regulatory submissions for renzapride are expected for 2006 (46).

Cilansetron

Cilansetron is a 5-HT_3 receptor antagonist that was evaluated for the treatment of patients with IBS-D. Results from two large, randomized, double-blind, placebo-controlled phase three trials showed that cilansetron, compared with placebo, was more effective in improving overall symptoms in patients with IBS-D (21,47). However, safety issues were associated with cilansetron use. The overall event rate for suspected IC during the clinical trials was 3.77 per 1000 patient-years, which was similar to that reported for alosetron (48). A new drug application for cilansetron was submitted to the FDA in June 2004, but additional clinical work was requested. In 2005, Solvay Pharmaceuticals decided to suspend activities in the pursuit of regulatory approval for cilansetron in the United States; a decision for continuing regulatory activity in Europe is pending.

CONCLUSIONS

In the past decade, insight into the underlying pathophysiology of IBS has led to the development and FDA approval of pharmacologic agents that target serotonin receptors in the GI tract. These agents have been effective in carefully designed, controlled clinical studies and are well tolerated in IBS patients. Lessons from early use of alosetron have led to appropriate-use programs for these agents designed to maximize their therapeutic usefulness while minimizing the potential for serious adverse effects. By keeping abreast of their potential benefits, of their place in therapy, and of precautions when using serotonin agonists and antagonists, primary care clinicians can maximize the treatment benefits for IBS patients and enhance patient satisfaction with therapy. ■

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